Abbreviated Title: Vandetanib in Hereditary MTC
CC Protocol: # 07-C-0189 L
AstraZeneca Protocol #IRUSZACT0098
Version Date: 06/27/2017
NCT Number: NCT00514046

Title: Phase I/II Trial of Vandetanib (ZD6474, ZACTIMA) in Children and Adolescents with Hereditary Medullary Thyroid Carcinoma

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C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
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Investigational Agents:

Drug Name:	Vandetanib (ZD6474, Zactima)
IND Number:	77570
Sponsor:	Center for Cancer Research, NCI
Manufacturer:	AstraZeneca

Commercial Agents: None

TABLE OF CONTENTS

PRECIS

Background

- Hereditary medullary thyroid carcinoma (MTC), which is a rare calcitonin-producing tumor arising from the parafollicular C cells of the thyroid, is often a manifestation of multiple endocrine neoplasia (MEN) types 2A and 2B and can be detected in children as young as 5 years in MEN 2A and 1 year in those with MEN 2B.
- MEN results from an activating mutation in the RET proto-oncogene resulting in a constitutively activated receptor tyrosine kinase (RTK).
- Vandetanib is an orally bioavailable multi-RTK inhibitor that blocks the mutant RET gene product and has anti-tumor activity in adults with hereditary MTC.

Objectives

- To assess the activity of vandetanib in children and adolescents with hereditary MTC using RECIST (primary endpoint), tumor biomarkers and tumor-related diarrhea.
- To assess the safety and tolerance of vandetanib in children and adolescents at a dose equivalent to the recommended dose in adults.
- To assess the pharmacokinetics of vandetanib at steady state in children and adolescents.
- Secondary objectives include monitoring progression-free and overall survival, assessing RET, EGFR, VEGFR and somatostatin receptor expression in archival tumor tissue, assessing changes in DNA mutations in RET in tumor tissue vs. germ line in PBMC and after treatment; assessing gene expression and gains/losses of DNA in tumor tissue at baseline, during treatment and at the time of progression; establishment of pediatric MTC cell lines to assess the effects of vandetanib on RET activation and signaling pathways in sensitive and resistant cells lines *in vitro*.

Eligibility

- Children and adolescents 5 to 18 years of age (inclusive) with unresectable, recurrent or metastatic hereditary medullary thyroid carcinoma.
- Measurable disease by RECIST (Response Evaluation Criteria in Solid Tumors).

Design

- Vandetanib will be administered as a once daily dose, continuously (1 cycle = 28 days) at a dose of 150 mg/m^2/d.
- To ensure the safety of the adult dose in children and adolescents, a limited intra-patient dose escalation will be performed in the initial cohort of patients, with older patients (13-18 yrs) being studied before younger patients (5-12 yrs).
- Patients will be enrolled at a dose of 100 mg/m^2/d (180 mg/d in adults) for two 28 day cycles and escalated to 150 mg/m^2/d (270 mg/d in adults) on cycle 3, if dose-limiting toxicity was not observed at the lower dose. If the 150 mg/m^2/d dose level is tolerable on cycles 3 and 4, all subsequent patients will be enrolled at this dose level.
- Pharmacokinetics of vandetanib will be studied at steady state at the end of cycle 2 and trough levels will be obtained prior to the second dose on cycle 1, and on day 1 of cycles 2-5.
- Response of measurable tumors will be assessed by RECIST. Biomarker and clinical response will also be monitored. Twenty-one patients will be studied to determine if the

response rate in children and adolescents with hereditary MTC is consistent with the 28% objective response rate in adults.

1 INTRODUCTION

1.1 Study Objectives

1.1.1 PRIMARY OBJECTIVES

- To assess the activity of daily oral vandetanib in children and adolescents with hereditary medullary thyroid carcinoma (MTC) by measuring:
  - change in tumor size compared to baseline using RECIST (primary endpoint);
  - change in tumor biomarkers (calcitonin and CEA) compared to baseline; and
  - change in tumor-related diarrhea (frequency and consistency), compared to baseline.
- To assess the safety and tolerance of vandetanib in children and adolescents at a dose that is equivalent to the recommended dose in adults using a limited intra-patient dose escalation.
- To assess the pharmacokinetics of vandetanib at steady state (end of cycle 2) in children and adolescents with hereditary MTC.

1.1.2 EXPLORATORY OBJECTIVES

- To determine the progression-free survival and overall survival in children and adolescents with hereditary MTC treated with vandetanib.
- To assess the expression of RET, EGFR, VEGFR and somatostatin receptor by immunohistochemistry in archival tissue blocks from children and adolescents enrolled on this protocol.
- To assess gene expression by microarray prior to and during treatment with vandetanib.
- To screen for gains or losses of DNA sequences in tumor tissue using comparative genomic hybridization.
- To perform RET gene mutational analysis in tumor and peripheral blood mononuclear cells prior to treatment and in tumor at the time of disease progression on treatment with vandetanib to discover tumor-specific somatic mutations that may be responsible for drug resistance.
- To establish pediatric MTC cell lines and investigate the effects of vandetanib on cell proliferation, RET activation and signaling pathways *in vitro* in cell lines from patients with sensitive and resistance tumors.

1.2 Background and Rationale

1.2.1 HEREDITARY MEDULLARY THYROID CARCINOMA (MTC)

Medullary thyroid carcinoma (MTC) is a rare, calcitonin (CTN)-producing tumor that arises from neural crest derived parafollicular C cells of the thyroid gland. MTC accounts for <10% of thyroid cancers in the U.S., and hereditary MTC, which is usually bilateral and multicentric, accounts for 25% to 30% of MTC cases.[1,2]

Hereditary MTC is divided into three distinct clinical subtypes. Multiple endocrine neoplasia (MEN) 2A, or Sipple's syndrome, is the most common subtype, accounting for approximately 70% to 80% of patients with hereditary MTC. MEN 2A is characterized by MTC in 100% of affected individuals, by pheochromocytoma in 50%, and by primary hyperparathyroidism in 20%. MTC is usually the first manifestation of the syndrome. Patients typically present with a

thyroid nodule or neck mass by 15 to 20 years of age, but MTC can appear as early as 5 years of age.[1-3]

MEN 2B is less common than MEN 2A, accounting for approximately 5% of MTC cases. It is characterized by a clinically more aggressive form of MTC that is manifest at a younger age (second decade) and that occurs in 100% of affected individuals, by pheochromocytoma in 50%, and by characteristic dysmorphic features including distinctive mucosal neuromas on the tongue, lips, and subconjunctival areas, diffuse ganglioneuromas of the gastrointestinal tract, and marfanoid habitus. Hyperparathyroidism is not associated with MEN 2B.[1,3,4]

Familial MTC is the third clinical subtype of inherited MTC. It accounts for 10% to 20% of hereditary MTC cases and is defined by the presence of MTC in kindreds with four to 10 or more affected members and with objective evidence of the absence of adrenal and parathyroid gland involvement. This form of hereditary MTC is less aggressive and has an older age at onset, usually between 20 and 40 years, compared to MEN 2A and 2B.[5,6]

MTC is the most common cause of death in patients with MEN 2a, MEN 2b, or FMTC, and the tumor is relatively unresponsive to conventional doses of radiation therapy and to standard or novel chemotherapeutic regimens.[2,7-13] Surgery is the only standard treatment. Patients with MTC can be cured only by thyroidectomy, but only when it is performed at a time when the tumor is confined to the thyroid gland. Early recognition through genetic screening and detection of one of the characteristic mutations (see below) followed by prophylactic thyroidectomy has become the standard of care.[14,15] The timing and extent of the prophylactic surgery is determined by germline mutational analysis.[2,16,17] In three large series, patients who were detected by screening and who subsequently had prophylactic total thyroidectomy had 5 and 10 years survival rates approaching 100%.[7,8,18] However, genetic screening is only applicable to those with a family history of MEN or FMTC. There is no treatment (apart from complete surgical removal) that has been shown to be effective for recurrent or persistent MTC.[19]

In published series, which span many years, over half of patients with MEN 2A and 2B present with advanced (stage 3) or metastatic disease, and a majority of the patients with MEN 2B represent new mutations, that could not have been detected early by genetic screening.[7,8] MTC metastasizes to local and regional lymph nodes, lung, bone and liver. The survival in patients with advanced or residual local tumor or metastatic disease can be prolonged and even patients with metastatic MTC can remain asymptomatic and live for many years.[2,8] Survival in patients who are not cured by thyroidectomy and have persistent local or metastatic disease is 80% and 70% at 5 and 10 years, and 5-year survival rate for patients with stage 4 disease exceeds 50%.[7,8]

1.2.2 MTC Biomarkers

The primary secretory product of thyroid C cells and MTC is CTN, which is an excellent tumor marker that correlates well with tumor bulk.[20-22] Basal or stimulated CTN values are almost always elevated with MTC.[2,22] Similarly, elevated CTN values after surgery are generally the first sign of persistent or recurrent disease. The physiologic role of CTN remains unclear.[23] It may play a role in calcium regulation through its effects on 3 target organs: bone (resorption), kidney (calcium excretion), and gastrointestinal (GI) tract,[24] but an excess or deficiency of CTN does not appear to have a significant pathologic effect and some believe that it is vestigial and has no function. Extremely high levels (>30,000 pg/ml) of serum CTN can cause symptomatic, intractable diarrhea and are usually associated with metastatic MTC.[25]

MTC cells also secrete carcinoembryonic antigen (CEA) and several biogenic amines, in addition to CTN. As with CTN, CEA levels are generally proportional to tumor burden and, as a result, CEA is a useful, although nonspecific, tumor biomarker.[26]

1.2.3 GENETICS OF MEN 2 AND MTC

MEN 2 syndrome is an autosomal dominant inherited disorder that is caused by germline activating mutations in the *RET* (*RE*arranged during *T*ransfection) proto-oncogene, which has 21 exons.[26,27] MEN 2 mutations are localized in exons 10, 11, and 13 to 16 (see Table below). Missense mutations at one of six cysteine codons (609, 611, 618, 620, 630 at exon 10 and 634 at exon 11), which result in the substitution of any one of these extracytoplasmic cysteines by a different amino acid, are responsible for the majority of cases of MEN 2A (93–98%).[3,14] In more than 95% of cases, MEN 2B is associated with a point mutation in the methionine residue in exon 16 (codon 918) in the intracellular tyrosine kinase receptor domain of RET.[28] Mutations are de novo in about 50% of MEN 2B cases; therefore, many patients with MEN 2B lack a family history of the disease and thus would not otherwise be targeted to undergo early screening and prophylactic thyroidectomy. These MEN 2B patients often experience a delay in diagnosis until signs of mucosal neuromas or palpable thyroid tumors are obvious.

Domain	Exon	Codons	Syndrome
Cadherin-like			
Cysteine-rich	10	609, 611, 618, 620, 630	MEN 2A, FMTC
	11	634	MEN 2A, FMTC
Transmembrane			
Tyrosine kinase 1	13	768, 790, 791	MEN 2A, FMTC
	14	804, 844	MEN 2A, FMTC
Tyrosine kinase 2	15	883	MEN 2B
	16	918	MEN 2B

The RET protooncogene is located on chromosome 10 and encodes for a receptor tyrosine kinase module. The RET protein contains an extracellular ligand binding domain, a transmembrane region, and an intracellular tyrosine kinase region. The ligands known to interact with RET include Glial-derived neurotrophic factor (GDNF), neuturin, persephin, and artemin. There is also a family of membrane bound co-receptors termed GFRa-1, -2, -3, and -4. To activate RET, the ligand first binds with the requisite co-receptor, which then interacts on the cell membrane with the RET protein to cause receptor dimerization and initiation of intracellular signaling through the tyrosine kinase domains.[17] Because the mutations to RET in MEN and MTC are activating, the RET RTK is a potential direct therapeutic target in this disease.

1.2.4 VANDETANIB (ZD6474, ZACTIMA)

Mechanism of Action

Vandetanib is a small molecule receptor tyrosine kinase (RTK) inhibitor (see Table below) that potently inhibits vascular endothelial growth factor receptor-2 (VEGFR-2, KDR) tyrosine kinase activity (IC_{50} = 40 nM), and it also inhibits RET receptor tyrosine kinase (IC_{50} = 100 nM), Flt-4 (VEGF receptor-3: IC_{50} = 110 nM) and EGF receptor tyrosine kinases (IC_{50} = 500 nM).[29,30] Vandetanib also inhibits the kinase activity of RET oncoproteins (although its affinity for all of the known mutated forms of RET in MEN 2A and 2B has not been studied) and blocks *in vivo* phosphorylation and signaling of the RET/papillary thyroid carcinoma and RET/MEN2B activated oncoproteins.[29,31] Notably, RET/MEN2B phosphorylation and RET/ MEN2B-dependent MAPK activation were inhibited by vandetanib *in vivo* at tolerable doses. The growth of cells expressing the RET/PTC oncoprotein was also inhibited *in vitro* and *in vivo*.[29]

Vandetanib inhibition of VEGF receptor tyrosine

kinase activity and selectivity profile[32,33]

Kinase	Mean (± SE) IC_{50} (μM)*	Fold selectivity versus KDR†
KDR	0.04 ± 0.01	-
Flt-4	0.11 ± 0.02	2.7
RET	0.13	2.5
Flt-1	1.6 ± 0.4	40
EGFR	0.5 ± 0.1	12.5
PDGFRβ	1.1 ± 0.3	27.5
Tie-2	2.5 ± 1.2	62.5
FGFR1	3.6 ± 0.9	90
MEK	>10	>250
CDK2	>10	>250
c-Kit	>20	>500
ErbB2	>20	>500
FAK	>20	>500
PDK1	>20	>500
AKT	>100	>2500
IGF-1R	>200	>5000

* Data represent the mean ± SE of at least 3 separate determinations. IC_{50} values quoted as "greater than" denote the inability to reach an IC_{50} value with the highest concentration tested.

† Ratio for the IC_{50} obtained with a given kinase compared to that achieved versus KDR.

Vandetanib also has broad-spectrum antitumor activity *in vivo*, in a range of models (subcutaneous or orthotopically implanted human tumor xenografts or syngeneic murine tumors) and histological types (lung, colon, breast, prostate, ovarian, vulval).[33] Vandetanib has also been shown to inhibit tumor metastases in liver, lung and lymph nodes with a variety of tumors types.[33] Reduced CD31 (endothelial cell) staining and increased tumor cell necrosis has been observed in human tumor xenografts from mice treated chronically with vandetanib (once-daily, orally, for 24 days), consistent with inhibition of angiogenesis and tumor vascular permeability. This is supported by dynamic contrast-enhanced MRI 24 hours post-vandetanib demonstrating a dose-dependent reduction in tumor k_{trans}, consistent with a reduction in vascular permeability, in mice bearing human prostate tumor xenografts.[34]

Preclinical Toxicology

The preclinical safety evaluation of vandetanib revealed:

- Elevated plasma alanine transaminase (ALT), aspartate transaminase (AST), and GLDH activities; hepatocellular necrosis; and acute cholangitis were seen at the highest doses used in the rat 1-month and 6-month studies.
- Gastrointestinal tract toxicity (body weight loss, emesis, and diarrhea) was the dose-limiting in dogs, but there were no associated histopathological findings.
- Renal papillary necrosis was observed at the higher doses in the 1-month rat study, but this finding was not seen in the 6-month rat study or in any dog study.
- Histopathological and ultrastructural changes, consistent with the induction of phospholipidosis, were observed in rats at the 1- and 6-month studies. No histological evidence of phospholipidosis was observed in dogs in any study. Vandetanib has physiochemical properties, which have been shown to induce excessive accumulation of intracellular phospholipids.
- The muzzle region of the skin of rats receiving the higher doses of vandetanib in the 1- and 6-month studies showed dose-related acute folliculitis and epidermal microabscess formation.
- As expected from its antiangiogenic properties, vandetanib has shown significant effects on all stages of female reproduction in rats. These effects were characterized by the following:
    - decreased numbers of corpora lutea in the ovaries of rats.
    - increased estrus cycle irregularity and a dose-related increase in early intrauterine deaths, resulting in reduced number of live embryos and increased post-implantation loss.
    - embryofetal developmental toxicity in the rat, indicated by embryofetal loss, delayed fetal development, heart vessel abnormalities and precocious ossification of some skull bones.
- Vandetanib produced a dose-dependent increase in the femorotibial epiphyseal zone of hypertrophy in growing rats when dosed daily for 14 days (an observation consistent with an ability to inhibit VEGF signaling and also angiogenesis *in vivo*).
- Vandetanib elevated systolic and diastolic blood pressure in telemetered rats.

- Vandetanib shows evidence of phototoxicity potential
    - Vandetanib had no effect on male fertility in rats and no mutagenic or clastogenic potential.

Preclinical Pharmacology

The pharmacokinetics and metabolism of vandetanib was studied in animals after oral and intravenous (IV) administration in the rat and dog and revealed:

- The bioavailability after oral dosing was high (>90% in the rat and >33% in the dog). There was evidence of slightly lower bioavailability in the rat at higher doses (72 to 78%). The absorption was not rapid, with peak concentrations occurring 3-8 hours post dose. At higher doses in rats and dogs, C x T profiles were flat, indicating prolonged absorption.
- After an IV dose of 5 mg/kg in rats, the clearance rate was 30 L/kg and the terminal half-life was 16 to 31 h. After a single IV dose (5 mg/kg) in dogs, the clearance was 85 ml/min/kg and the half-life was 8 h. The volume of distribution was 45 L/kg.
- Plasma protein binding ranged from 83% in rats to 90% in human plasma. Vandetanib was shown to bind to both human serum albumin and human α-1- acid glycoprotein.
- Toxicokinetic monitoring in rats showed dose proportional increases between 1 and 10 mg/kg, but a less than proportional increase in exposure between 25 and 75 mg/kg. Administration to rats for 6 months at 5 mg/kg resulted in a 3-fold increase in exposure (accumulation). There was evidence of a small degree of accumulation in the dog (13%) in the 1-month toxicity study that was confirmed in the 9-month toxicology study.
- After ^{14}C-vandetanib administration to rats, radioactivity (parent drug + metabolites) was rapidly and extensively distributed, with the highest concentrations in the gastrointestinal tract, liver, spleen, adrenal glands and other glandular tissues.
- Two metabolites have been identified in samples from rats and dogs: the N-oxide of vandetanib and N-desmethyl vandetanib. These metabolites and a vandetanib glucuronide have been identified in humans. N-desmethyl vandetanib is primarily produced by CYP3A4 and N-oxide vandetanib by flavine-containing mono-oxygenase enzymes FMO1 and FMO3.
- Vandetanib had no inhibitory effect on the activity of human CYP1A2, 2C9, 2C19, or 3A4, but did inhibit 2D6 activity (k_i of 13 μg/ml).
- Urinary recoveries after ^{14}C-vandetanib in rat and dog ranged from 4-12% of the dose. The majority of the radioactivity was recovered in the feces. Studies in rat demonstrated both biliary excretion and enterohepatic recirculation of vandetanib-related material.

Clinical Trials

Vandetanib has been administered to over 500 adults who were enrolled in 16 clinical trials, including 2 phase I trials in cancer patients,[35,36] 6 phase I/pharmacokinetic studies in healthy volunteers, and 8 phase II trials in NSCLC, SCLC, breast cancer, multiple myeloma and MTC (see Section **1.2.5**).

The recommended adult dose of vandetanib is a fixed dose of 300 mg/d, administered continuously. The most common adverse events related to vandetanib are skin rashes, diarrhea, hypertension, and asymptomatic prolongation of the electrocardiogram QTc interval. These events are dose-dependent. At a dose of 300 mg/d, QTc prolongation resulting in dose reduction

has been seen in less than 15% of patients. No patient with QTc prolongation reported symptoms or developed cardiac arrhythmia that could be exclusively attributed to QTc prolongation or other cardiac arrhythmia.

In the U.S. phase I trial conducted in adult patients with refractory solid tumors, patients received once-daily oral vandetanib (50-600 mg) in 28-day cycles. Seventy-seven patients were treated at doses of 50 mg (n=9), 100 mg (n=19), 200 mg (n=8), 300 mg (n=25), 500 mg (n=8), and 600 mg (n=8). Adverse events were generally mild. The most common drug-related adverse events were diarrhea (n = 29), rash (n = 26), nausea (n = 15), hypertension (n = 14), fatigue (n = 14), anorexia (n = 10), acneiform rash (n = 9), and maculopapular rash (n = 8). Drug-related adverse events that led to treatment discontinuation were congestive cardiac failure, follicular rash, folliculitis and prolonged QT interval (all n = 1). The most common dose-limiting toxicities (DLT) were diarrhea (n=4), hypertension (n=4), and rash (n=3). The incidence of most adverse events appeared to be dose-dependent. In the 500 mg/day cohort, 3/8 patients experienced DLT and this dose was therefore considered to exceed the maximum tolerated dose. Once-daily oral dosing of vandetanib at 300 mg/d was generally well tolerated in patients with advanced solid tumors, and this dose was recommended phase II trials.[35]

In the largest monotherapy vandetanib study conducted to date comparing vandetanib to gefitinib,[37] the most frequent adverse events observed with vandetanib were diarrhea (55.4%, grade 3 or 4, 8.4%), fatigue (36.1%), rash (27.7%, grade 3 or 4, 4.8%), nausea (24.1%), and grade 1 QTc prolongation (20.5%). Approximately 10% of subjects who received vandetanib developed hypertension, the majority of which was CTC grade 1 or 2. Three subjects developed CTC grade 3 hypertension, and none were CTC grade 4. The median increase in systolic blood pressure for subjects who received vandetanib was 10 mmHg; the median increase in diastolic blood pressure was 6 mmHg.

An increased incidence of SAEs was noted in subjects who received vandetanib compared to those who received gefitinib (44.6% vs. 35.3%). Cardiac disorders (6.0% vs. 1.2%), gastrointestinal disorders (6% vs. 2.4%, mainly diarrhea), and respiratory disorders (13.3% vs. 8.2%) did occur more frequently in subjects receiving vandetanib. The cardiac events included a variety of terms without any apparent pattern. Respiratory events were primarily those that would be anticipated in subjects with advanced lung cancer. Three subjects receiving vandetanib developed pulmonary embolism and 3 subjects developed interstitial lung disease, but cases were confounded by such factors as smoking, reduced mobility, infection, lung cancer progression and previous chemotherapy or radiation therapy. One subject in each arm developed a serious skin disorder. One subject who received vandetanib developed a hematologic event, as did 2 subjects who received gefitinib. No subjects who received vandetanib developed serious hepatotoxicity.

Thirteen adverse events on study were followed by an outcome of death, 7 in the vandetanib arm (ARDS, pneumonia, pneumonitis, dyspnea, interstitial lung disease, respiratory failure and carcinomatous meningitis) and 6 in the gefitinib arm (breathlessness, bone pain, cellulitis, acute respiratory failure (2 cases) and pleural effusion).

There were 12 subjects with confirmed QTc prolongation. Of these, 6 occurred in the first 28 days, and 2 in the following 28 days. The remaining 4 occurred sporadically, with the longest time to occurrence of 323 days. There were 3 events of CTC grade 1 reversible dizziness in subjects with a confirmed QTc prolongation occurring within the first 4 weeks. Subjects with

dizziness had other events that might have caused dizziness and the events were not well correlated in time with the actual QTc prolongation. There were no other potentially relevant adverse events in subjects with confirmed QTc prolongation within the first 4 weeks, and no relevant adverse events in subjects whose first confirmed QTc prolongation occurred more than 4 weeks after randomization.

Evidence of an advantage for progression-free survival in NSCLC was seen with vandetanib 300 mg compared with gefitinib, and in the combination of vandetanib 100 mg and docetaxel compared to docetaxel alone. These progression advantages did not translate into a corresponding advantage for overall survival in preliminary data. These observations have led to phase III trials of vandetanib in NSCLC.[32,37]

In April 2011, the U.S. Food and Drug Administration (FDA) approved vandetanib for the treatment of advanced (metastatic or unresectable locally advanced) medullary thyroid cancer under the orphan drug designation at a recommended daily dose of 300 mg.

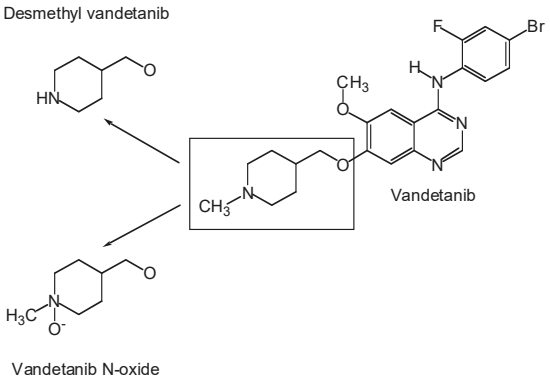
Human Pharmacokinetics and Metabolism

In healthy subjects, vandetanib absorption appeared to be relatively slow with a median t_{max} of 6 h (range, 4-10 h). From the C_{max}, plasma levels declined in a biexponentially with a terminal half-life of about 10 days. In population pharmacokinetic modeling, vandetanib was best described by a two-compartment, first order absorption, first order elimination with lag-time model, with a CL/F of 14 L/h and a volume of distribution of 4590 L. After single doses over the dose range 300-1200 mg, exposure appeared to increase in proportion to the dose. There was no effect of food on the either AUC or C_{max}. There was no pharmacokinetic interaction with the potent inhibitor of CYP3A4 itraconazole or with the 5HT3 antagonist ondansetron.

The recovery of [^{14}C]-vandetanib was slow and both biliary (44%) and renal (25%) routes of excretion were important in its elimination. Vandetanib and its N-desmethyl and N-oxide metabolites were detected in the systemic circulation. Vandetanib, the N-oxide, the N-desmethyl, and a glucuronide metabolite were identified in urine and feces.

The inhibitory activity of N-desmethyl and N-oxide metabolites of vandetanib, were examined in a growth factor stimulated HUVEC proliferation assay. N-desmethyl vandetanib retained similar potency against VEGFR and selectivity (versus EGF and bFGF) to the parent drug, whereas the N-oxide of vandetanib had relatively weak activity in cells (IC_{50} >3 μM) against the growth factor stimuli examined.

In patients,[35,36] the absorption of vandetanib appeared to be more variable and prolonged than in healthy subjects, with median t_{max} of 4-10 h and a larger range of 1-24 h. Population pharmacokinetic modeling showed a CL/F of 6.43 L/h, a volume of distribution of 6260 L, and an estimated terminal half-life of about 20 days. Over the dose range 100-600 mg, exposure appeared to increase in a dose-proportional manner. Trough levels indicate that a minimum of 28 days of daily dosing is required to achieve steady state plasma concentrations, with about a 10-fold (range, 3- to 30-fold) accumulation compared to a single dose.



1.2.5 PHASE I AND II TRIALS OF VANDETANIB IN CHILDREN AND ADULTS WITH MTC

A phase II single arm, open label trial of daily oral vandetanib at a dose of 300 mg is ongoing in adults with hereditary MTC (MEN 2a, MEN 2B, and FMTC).[26] Patients enrolled on this trial are required to have a characteristic germline RET mutation. The most common adverse events observed in the first 14 patients enrolled on the trial include diarrhea (11), rash (10), headache (9), dysphagia (8), and fatigue (8), dizziness (7), and urinary tract infection (7). Four SAEs were observed in 3 of the first 14 subjects that included a GI obstruction and GI hemorrhage in 1 subject (unrelated to study drug) and a grade 3 dysphagia (n=1) and grade 3 diarrhea (n=1) that were both attributed to study drug. Four subjects experienced QTc prolongation on study.

Response data are available in the 30 patients enrolled on the adult phase II trial. Seven (23%) of 30 have had an objective response (see the example in the Figure below), 3 have progressed and the remainder have stable disease (<30% decrease in tumor size). Reduction in tumor size is gradual (up to 2 years to achieve a PR) and responses have been durable. All patients have had a >50% reduction in CTN levels and 70% have had a >50% reduction in plasma CEA.

As on 7/16/08, five children have been enrolled on this trial, including 3 in older age group and 2 in the younger age group. One of the older patients had progressive disease after 2 cycles and was removed from the study. The other two older patients tolerated the 2 cycles at 100 mg/m^2/d and their dose was escalated to 150 mg/m^2/d on cycle 3. One of these two patients experienced dose-limiting diarrhea requiring a dose reduction. The two younger patients have been treated at the 100 mg/m^2/d dose and have tolerated it well. The patient experiencing progressive disease did not have the codon 918 mutation typical for MEN-2B. The remaining 4 patients have this mutation and the phenotypic features of MEN-2B. Three of the 4 have been restaged on treatment at least once and all have a >80% reduction in serum CTN, a >40% reduction in serum CEA and a 15 to 19% reduction in tumor size by RECIST.

1.2.6 STUDY RATIONALE

Vandetanib is a molecularly targeted RTK inhibitor that blocks the mutant RET oncoprotein, which is believed to play a key role in the pathogenesis of hereditary MTC. In adults with hereditary MTC, vandetanib at a dose of 300 mg/d has an objective response rate of 28% in a tumor that has been refractory to standard chemotherapy and radiation therapy, and the drug has been well tolerated. The purpose of this trial is to confirm this response rate in children and adolescents with hereditary MTC. This trial is likely to enroll a much higher fraction of patients with MEN 2B-related MTC than the adult trial, because the tumors occur at a younger age in MEN 2B and because most patients with this syndrome represent new mutations and, as a result, usually present with advanced (stage 3) or metastatic disease.

A phase I, dose finding component is built into this trial, because there are no completed phase I trials of this agent in children. The trial uses an intra-patient dose escalation design in order to ensure that all patients receive the equivalent dose to that used on the adult phase II trial (if it is tolerated) and that all patients are evaluable for the phase II portion of the trial. The dose escalation portion of the trial will be performed in the initial cohort of 3 to 6 patients who are 13 to 18 years old followed by the first 3 to 6 patients who are 5 to 12 years old. Two dose levels (100 and 150 mg/m^2/d) will be studied and the drug will be dosed based on body surface area in children and adolescents. The first dose level (100 mg/m^2/d) is equivalent to 60% of the adult MTD and the second dose level (150 mg/m^2/d) is equivalent to 90% of the adult MTD of 300 mg/d. In a recent review comparing the results of pediatric and adult phase I trials,[38] the MTD in

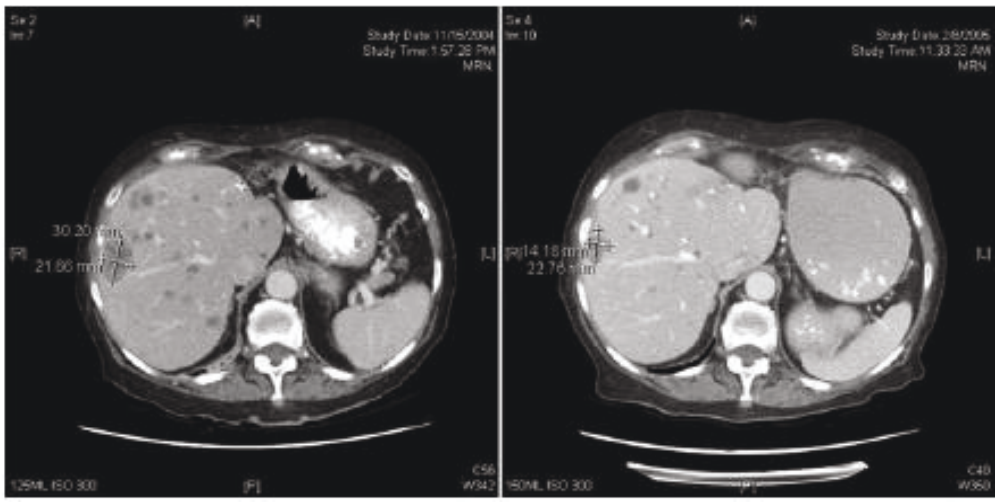


Figure 1
CT results showing medullary thyroid carcinoma in a patient with MEN2A. *Left*, baseline; *right*, after 3 months of treatment with ZD6474.

children exceeded the adult MTD for two-thirds of the agents, and in all but one case (all-*trans*-retinoic acid), the pediatric MTD was at least 60% of the adult MTD. These authors also evaluated the ratio of pediatric to adult drug clearance for a variety of agents in this meta-analysis and the median ratio was 1 (clearances were equivalent when normalized to BSA). Pharmacokinetic studies will be performed at steady state (end of cycle 2) on this trial.

The phase II portion of the trial was designed to have similar eligibility criteria and response criteria as the ongoing phase II trial in adults with hereditary MTC (Section **1.2.5**). Although objective radiographic response using RECIST is the primary endpoint, biomarker (CTN and CEA) and clinical response (diarrhea) will also be monitored. Because the drug has demonstrated activity in adults with the same cancer, the trial uses a single-stage design – without an early futility evaluation.

The trial includes several secondary objectives to document progression-free and overall survival, to assess expression of the molecular targets of vandetanib and somatostatin receptor in archival tumor tissue, and to assess gene expression, secondary genetic changes and RET mutational status in tumor tissue prior to the start of therapy and at the time of response and progression in selected patients who are over 12 years of age and who have easily accessible tumors for biopsy, and to establish pediatric MTC cell lines from biopsy or surgical specimens to study the effects of vandetanib on proliferation, RET activation and signaling pathways in cell lines from patients with clinically sensitive and resistant tumors. Although exploratory, these studies will be critical to assess the effect of treatment on signaling pathways in the tumor and to determine if somatic mutations to RET in the tumor are responsible for de novo or acquired resistance to vandetanib.

Dr. Frank Balis served as the Adjunct Principal Investigator on this trial until June 27, 2017. Dr. Balis designed and has led this phase I/II trial of vandetanib in children.

Update on trial status July 2012: Since initiation of the trial 16 patients were enrolled, 10 in the adolescent cohort (age 13-18 years) and 6 in childhood cohort (age 5-12 years). Vandetanib has been well tolerated without evidence of cumulative toxicity. One of 6 patients 5-12 years old enrolled at 100 mg/m^2/dose developed dose-limiting diarrhea. Of 8 adolescents 13-18 years old, who were eligible to receive vandetanib at 150 mg/m^2/dose, one developed dose-limiting diarrhea, one had a dose reduction for non dose-limiting diarrhea, and one patient had a dose

reduction for non-dose-limiting hypertension in presence of baseline bradycardia. Common non-dose-limiting toxicities included prolonged QTc interval, hypertension, diarrhea, rash and TSH elevation necessitating an increase in levothryroxine dosage in athyrotic patients who were previously on a stable dose. Patients received a median (range) of 27 (2-52) cycles. For subjects with M918T RET germline mutations (n=15) the confirmed objective partial response rate was 47% (95%CI, 34%, 60%). Durable responses were achieved in children and adolescents at 150 mg/m^2/d (n=2, duration 40-52 cycles), 100 mg/m^2/d (n=4, duration 20-44 cycles) and 67 mg/m^2/d (n=1, 48 cycles). While both dose levels were tolerated in the patients studied, the activity of vandetanib at the 100 mg/m^2 dose level combined with the better tolerability of vandetanib was recommended for pediatric patients with MTC.

Update on trial status Amendment J: This trial is closed to further accrual as an adequate number of subjects have been enrolled to allow us to meet the study objectives. Eleven subjects remain on study drug, which has been approved by the FDA for treatment of symptomatic or progressive MTC in adults with unresectable locally advanced or metastatic disease. All patients remaining on the trial have received vandetanib for more than 2 years. In conjunction with AstraZeneca, vandetanib will continue to be supplied to subjects on this study as long as they meet requirements for continued therapy. Vandetanib package insert recommendations and standard of care clinical practice will be followed in managing these patients. Data collection will be limited to serious adverse events and to data required to make a decision about continued treatment, such as response data, while drug accountability will be maintained.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 INCLUSION CRITERIA

- *Age*: Participants must be 5 to 18 years of age, inclusive. The first cohort of 3 to 6 participants enrolled on the trial will be at least 13 years of age.
- *Diagnosis*: Hereditary (MEN 2A or MEN 2B) medullary thyroid carcinoma (histologically confirmed) that is unresectable, recurrent or metastatic. Participants must have previously had a characteristic germline mutation in the RET proto-oncogene documented. Results of the germline mutation testing will be obtained from the referring institution.
- Participants must have measurable disease as defined in RECIST as the presence of at least one lesion that can be accurately measured in at least one dimension with longest diameter of at least 20 mm using conventional techniques or at least 10 mm with spiral CT scan. Superficial (easily palpable) lymph nodes will be considered measurable.
- Participants must be able to take one of the oral formulations of vandetanib. Administration of the liquid formulation via a nasogastric tube or gastrostomy is allowed.
- *Prior therapy*: There are no standard chemotherapy regimens known to be effective for MTC. Therefore, previously untreated participants are eligible if their tumor(s) are not surgically resectable.
  - Participants must be at least 4 weeks from prior surgical procedures and surgical incisions must be healed.
  - Participants must have had their last fraction of external beam radiation therapy at least 4 weeks prior to enrollment.

- Participants must have had their last dose of cytotoxic chemotherapy at least 28 days prior to enrollment, their last dose of biological therapy, such as biological response modifiers (e.g., cytokines), immunomodulatory agents, vaccines, differentiating agents, used to treat their cancer at least 7 days prior to enrollment, their last dose of a monoclonal antibody at least 30 days prior to enrollment, and their last dose of any investigational agent at least 30 days prior to enrollment.
- Participants must have received their last dose of short acting colony stimulating factor, such as filgrastim or sargramostim at least 72 hours prior to enrollment and their last dose of long-acting colony stimulating factors, such as PEG-filgrastim at least 7 days prior to enrollment.
- Participants must have recovered from the acute toxic effects of prior therapy to a grade 1 (CTCAE v.3.0) level prior to enrollment.

- *Performance Status*: Lansky (for participants 10 years of age or younger) or Karnofsky (for participants older than 10 years) performance score greater than 50 (**Appendix 1**: Performance Status Scales/Scores)
- Concomitant Medications:
  - Participants who have previously had a thyroidectomy should be on thyroid hormone replacement therapy.
- *Hematological Function*: The peripheral absolute neutrophil count must be at least 1,500/µL and the platelet count must be at least 100,000/µL within 72 hours prior to enrollment.
- *Coagulation*: PT and PTT must not be more than 1.5 x ULN within 72 hours prior to enrollment. PT and PTT should be drawn by venipuncture, rather than from a central venous catheter when feasible.
- *Hepatic Function*: Bilirubin must not be more than 1.5 x ULN and the AST and ALT must not be more than 2.5 x ULN within 72 hours prior to enrollment. AST and ALT may be up to 5 x ULN within 72 hours prior to enrollment in participants with hepatic metastases.
- *Renal Function*: Participants must have an age-adjusted normal serum creatinine (see Table) or a creatinine clearance of at least 60 ml/min/1.73 m^2.

	Maximum Serum Creatinine (mg/dL)	
Age (years)	Male	Female
5 to <10	1	1
10 to <13	1.2	1.2
13 to <16	1.5	1.4
16 and older	1.7	1.4

- *Birth Control*: Participants of child-bearing or child-fathering potential must be willing to use a medically effective form of birth control, which includes abstinence, while taking vandetanib and for 2 months after the last dose.

- Negative pregnancy test for women of childbearing potential.
- *Informed Consent*: Participants who are 18 years of age or legal guardians of participants who are younger than 18 years must sign an informed consent for the POB Screening Protocol prior to participating in studies required to determine eligibility for this trial. After confirmation of eligibility, participants or legal guardians of minor participants must sign an informed consent document for this trial, indicating that they are aware of the investigational nature of the proposed treatment, the risks and benefits of participating and the alternatives to participating.

2.1.2 Exclusion Criteria

- Pregnant or breast feeding females because the anti-angiogenic properties of vandetanib may be harmful to the developing fetus or nursing infant.
- Participants with pheochromocytoma as evidenced by elevated plasma free metanephrines.
- *Electrolytes*: Participants with a serum potassium less than 3.5 mmol/L or a serum calcium or magnesium below the lower limits of normal. Correction of these electrolyte abnormalities with supplements is allowed.
- Cardiac:
  - Participants with a history of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia, uncontrolled atrial fibrillation, left bundle branch block) that is symptomatic or requires treatment (except for controlled atrial fibrillation)
  - Participants with a history of congenitally prolonged QTc, a first degree relative with unexplained sudden death under 40 years of age, or a measured QTc (Bazett's correction) longer than 480 msec on ECG. ECGs should be performed after correction of electrolyte abnormalities. Participants with a prolonged QTc should have a repeat ECG at least 24 hour after the first, and the mean of the 2 QTcs should not exceed 480 msec.
  - Participants who experienced QTc prolongation with other medications requiring discontinuation of that medication
  - Participants receiving a medication that has a known risk of QTc prolongation (**Appendix 4**: Medications Known to Prolong the QT Interval or Induce Torsades de Pointes, Group 1) within 14 days (28 days for levomethadyl) of enrollment.
- *Hypertension*: Diastolic blood pressure above the 95% for age (**Appendix 2**: Normal Blood Pressure Range for Children) on at least 2 of 3 measurements with an appropriate-size cuff or patients who are currently taking anti-hypertensive therapy.
- Other clinically severe or uncontrolled systemic illness that could compromise the participant's ability to tolerate vandetanib or could compromise study procedures or endpoints.

2.1.3 Eligibility Criteria for Optional Biopsy to Obtain Tumor for Research

- *Age*: Participants must be older than 12 years of age
- *Tumor Location*: Easily accessible tumor site that is
  - Superficial
  - Extra-cavitary (i.e., not within the chest or abdominal cavity)
  - Sufficiently distant from vital structures to avoid direct damage from insertion of the biopsy needle
  - The biopsy must be taken from within a site that has NOT been previously radiated

- *Coagulation Studies*: Participant must have a platelet count >100,000/mcL and a normal PT and PTT within 72 hours of each biopsy
- *Anesthesia*: Must be able to perform the biopsy under local anesthesia.
- *Consent/Assent*: The parent/guardian must sign a separate biopsy consent and the participant must sign an assent describing the biopsy.

2.2 Screening Evaluation

2.2.1 General

- History and Physical Examination: including vital signs with blood pressure, documentation of palpable, measurable disease (longest diameter and location), and a description of signs and symptoms is required. Daily stool frequency over the prior 7 days and consistency (formed, loose or partially formed, watery) should be documented. A family history of endocrine neoplasia should also be recorded.
- Height, Weight and Body Surface Area: The BSA should be calculated from the average of 3 repeated measurements of weight and height on the same day by the standard formula in use at the NCI:

$$BSA = \frac{Weight\ \ (kg)^{0.425} \langle\ Height\ \ (cm)^{0.725}}{139.315}$$

2.2.2 Laboratory Evaluation

Pre-treatment blood tests should be performed within 72 hours prior to enrollment on the trial unless otherwise stated.

- Hematology: complete blood count, differential, platelet count, PT, PTT.
- Chemistries: ALT, alkaline phosphatase, bilirubin (total and direct), GGT, BUN, creatinine, electrolytes, calcium, magnesium, phosphorus, uric acid, total protein, and albumin.
- Thyroid Stimulating Hormone
- Plasma Free Metanephrine and nor-Metanephrine: Patients must be NPO 8 h prior to sampling. No acetaminophen, attention deficit disorder medications, caffeine, alcohol, or smoking within 24 hrs prior to the sample. Patient should be supine for 15 min after PIV placement and prior to sample being drawn. Draw sample into prechilled tubes and place on ice immediately. Values obtained within 8 weeks of trial entry and outside values are acceptable.
- Biomarkers: Serum calcitonin (CTN) and CEA. CTN and CEA should be measured during screening. Serum CTN should be drawn after a 12 hour fast and sent to the lab immediately at room temperature.
- Urine or Serum Pregnancy Test: required for females of childbearing potential.

2.2.3 Performance Score

Lansky (for participants 10 years of age or younger) or Karnofsky (for participants older than 10 years).

2.2.4 ECG with Calculation of QTc

Use Bazett's correction ($QTc = QT/RR^{0.5}$).

2.2.5 RADIOGRAPHIC EVALUATION

Scans should be performed within 28 days prior to enrollment of the study.

- CT scans of the neck, chest and abdomen
- MRI of the brain and neck
- ^{99m}Tc-Bone scan
- MRI of the knee to assess the growth plates. Open growth plates will be assessed with volumetric measurements prior to and during therapy until the growth plate is closed, as documented by MRI or plain x-ray.

2.2.6 TUMOR BIOPSY

Percutaneous core needle (16 or 18 gauge) biopsy of superficial (e.g., cervical lymph nodes) tumors (not within a body cavity) will be performed if it can be done under local anesthesia with minimal risk to surrounding vital structures (see Section **2.1.3** for complete eligibility criteria to participate in the part of the trial). A single tumor will be biopsied, and the number of needle passages to obtain a core biopsy of tumor tissue for research purposes will be limited to two. The biopsy will be used to document RET gene mutations and gene expression in the tumor at baseline and to establish pediatric MTC cell lines. Whole blood will also be obtained to assess RET germ line mutation status (see Section **3.5.2**). If a biopsy is required for clinical indications (e.g., to make or confirm the diagnosis), then the two additional passages to obtain a tumor specimen for research purposes will be obtained after the biopsy for clinical indications. If a tumor is resected, residual tissue remaining after processing for diagnostic tests will be processed for research studies as outlined in Section **3.5**.

Research specimen labels will include the protocol number (07-C-0189), the two digit participant's study number and NIH medical record number.

2.3 Registration Procedures

When registering a patient, information about all entry criteria (e.g., laboratory results) must be available to allow for verification of eligibility (see Section **2.1**). Dr. Brigitte Widemann 240-760-6203 must be contacted to discuss the patient prior to entry onto the trial.

The research nurse will register patients by FAXing the completed eligibility checklist to the Central Registration Office at (301) 480-0757 within 24 hours of signing consent.

3 STUDY IMPLEMENTATION

3.1 Study Design

3.1.1 OVERALL TRIAL DESIGN

This phase II trial is designed to determine whether daily oral vandetanib, which has activity in adults with hereditary MTC, is also active against hereditary MTC in children and adolescents. Vandetanib activity will be primarily assessed by response of measurable disease using RECIST, but change in biomarkers (calcitonin and CEA) and tumor-related symptoms (diarrhea) from baseline will also be monitored to assess drug effect (see Section **7.2**).

Vandetanib is administered to adults continuously in a fixed daily dose of 300 mg/d and has not been previously studied in children. In this trial, children will be dosed based on body surface area (BSA). The adult dose of 300 mg/d is equivalent to approximately 150 mg/m^2/d. In

addition, a limited intra-patient dose escalation study will be performed to assess the safety of the equivalent to the recommended adult dose of vandetanib in this pediatric population, which is likely to be less heavily pretreated with cytotoxic chemotherapy than children with other types of refractory cancers that are typically treated on pediatric phase I trials. Initially three adolescents 13-18 years will be enrolled and started on a dose of 100 mg/m^2/d (equivalent to an adult fixed dose of 180 mg/d). The dose will be escalated to 150 mg/m^2/d on cycle 3 in these three older patients if the lower dose was tolerable (no dose-limiting toxicity [defined in Section **3.1.4**] that was possibly, probably or definitely related to vandetanib) on cycles 1 and 2. The dose is escalated after 2 cycles because steady state levels are not achieved until at least 4 weeks of continuous daily dosing. If the first cohort of older (13-18 years) children tolerate the cycles 1 and 2 at a dose of 100 mg/m^2/d, then a cohort of three children who are 5-12 years of age will be enrolled and treated with 100 mg/m^2/d of vandetanib on cycles 1 and 2 and escalated to 150 mg/m^2/d on cycle 3 if they tolerated (no dose-limiting toxicity that was possibly, probably or definitely related to vandetanib) the lower dose on the cycles 1 and 2. If the 150 mg/m^2/d dose is tolerated for 2 cycles, then subsequent patients will be enrolled at the 150 mg/m^2/d dose level. Detailed pharmacokinetics of vandetanib will be performed in children and adolescents at steady state at the end of the second 28 day cycle of treatment (end of cycle 2).

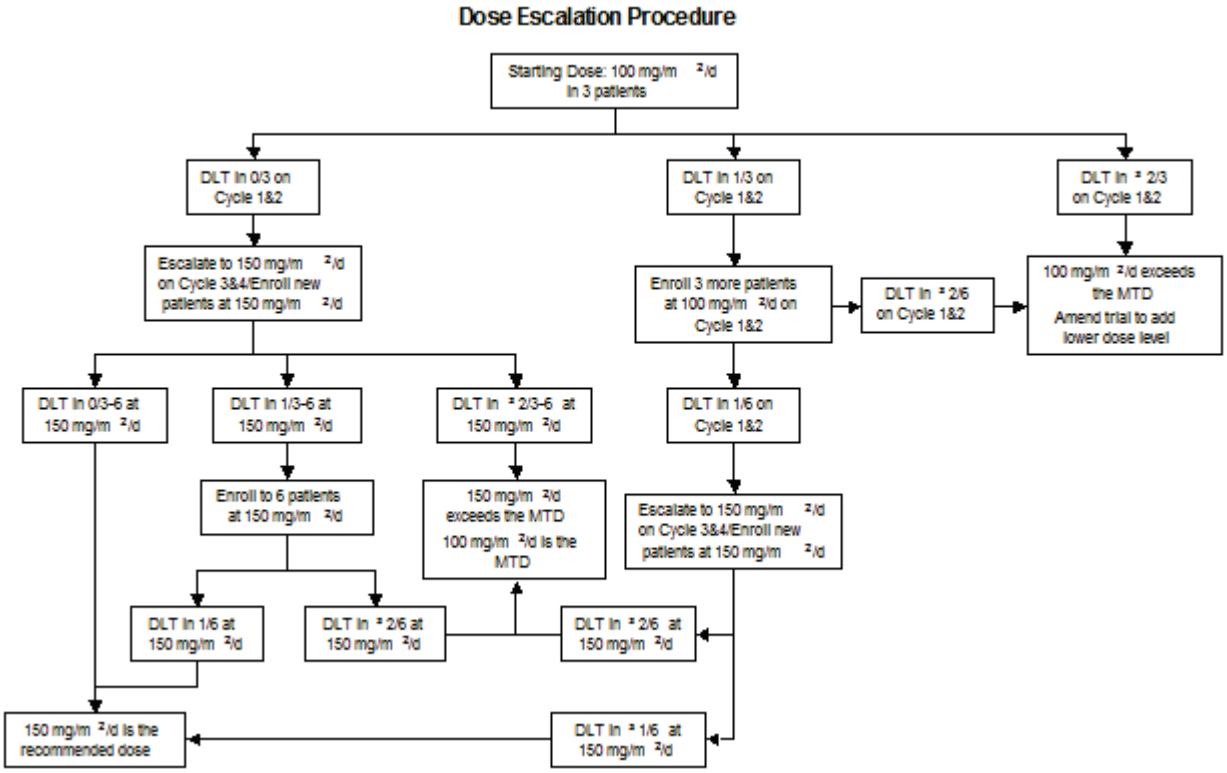
Patients will be staged to assess measurable disease by RECIST, biomarkers and disease-related symptoms prior to the start of therapy, after every 2 cycles x 4 (prior to cycles 1, 3, 5, 7 and 9), prior to cycle 13, and then after every 6 cycles (prior to cycles 19, 25, etc.). There will be no limit on the duration of therapy. The drug will be discontinued if there is evidence of tumor progression clinically or by RECIST or biomarkers (CTN or CEA) or there is intolerable toxicity that is not alleviated by dose reduction.

As of March 2014 (amendment J): Clinical restaging for all patients remaining on study receiving long term therapy will be performed as per **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy.

Secondary endpoints on this trial include progression-free and overall survival, assessment of target (RET, EGFR, VEGFR) expression and somatostatin receptor expression in archival tissue, RET mutational status in tumor vs. peripheral blood mononuclear cells at entry, and changes in gene expression and RET mutational status in tumor tissue with treatment at the time of tumor response and progression on treatment.

3.1.2 Dose Levels and Intra-Patient Dose Escalation

In order to ensure that children and adolescents can tolerate a dose that is equivalent to the 300 mg fixed dose used in adults, a limited intra-patient dose escalation will be performed in the initial subset of patients enrolled on this trial. The two dose levels that will be studied are 100 mg/m^2/d, which equivalent to 180 mg/d in adults (60% of the adult recommended dose), and 150 mg/m^2/d, which is equivalent to 270 mg/d in adults (90% of the recommended dose of 300 mg/d). These doses will be studied in older patients (13-18 yo) before being administered to younger patients (5-12 yo). The dose will not be escalated beyond 150 mg/m^2/d. Intra-patient dose escalation is permitted in patients who tolerate (do not experience a vandetanib-related DLT) the 100 mg/m^2/d dose level of vandetanib on cycles 1 and 2.



13-18 yo Cohort (see the algorithm):

- Initially, three 13-18 yo patients will be treated at the 100 mg/m^2/d dose level for two cycles. Those who do not experience a vandetanib-related DLT (see Section **3.1.4**) during cycles 1 and 2 (56 days) at the 100 mg/m^2/d dose level will have their dose escalated to 150 mg/m^2/d for their third and subsequent cycles.
- If 0/3 of 13-18 yo cohort experience a vandetanib-related DLT on cycles 1 and 2 at the 100 mg/m^2/d dose level, then these 3 patients will be evaluated for toxicity on their third and fourth cycles at the 150 mg/m^2/d dose level (patients who come off treatment before completing cycle 2 for reasons other than a vandetanib-related DLT can be replaced on the intra-patient dose escalation component of the trial). New 13-18 yo patients can be enrolled on the trial at the 150 mg/m^2/d dose level if none of the first 3 patients enrolled at the 100 mg/m^2/d dose level experienced a vandetanib-related DLT on cycles 1 and 2, but no more than 6 patients should be receiving the 150 mg/m^2/d dose until 3 patients have completed 2 cycles at this dose level.
- If 1/3 of 13-18 yo cohort experiences a vandetanib-related DLT on cycle 1 or 2 at the 100 mg/m^2/d dose level, then three additional 13-18 yo patients will be enrolled at the dose 100 mg/m^2/d level. If 1/6 of the expanded 13-18 yo cohort experience a vandetanib-related DLT on cycle 1 or 2 at the 100 mg/m^2/d dose level, then the 5 patients who tolerated the drug will be evaluated for toxicity on their third and fourth cycles at the 150 mg/m^2/d dose level (patients who come off treatment before completing cycle 2 for reasons other than DLT can be replaced on the intra-patient dose escalation component of the trial). Additional new 13-18 yo patients can be enrolled on

the trial at the 150 mg/m^2/d dose level if no more than 1 of the first 6 patients enrolled in the expanded cohort at the 100 mg/m^2/d dose level experienced a vandetanib-related DLT on cycles 1 and 2, but no more than 6 patients should be receiving the 150 mg/m^2/d dose until 3 patients have completed 2 cycles at this dose level.

- If 2 or more of the initial 3 to 6 13-18 yo patients experience a vandetanib-related DLT on cycle 1 or 2 at the 100 mg/m^2/d cohort, accrual to the trial will be suspended until the protocol can be amended to include a new lower dose level.
- If the 100 mg/m^2/d dose level is tolerable (0/3 or 1/6 with a vandetanib-related DLT) on cycles 1 and 2 in 13-18 yo population and none of the 3 to 6 patients experience a vandetanib-related DLT on 2 cycles at the 150 mg/m^2/d dose level, then subsequent 13-18 yo patients will be enrolled at the 150 mg/m^2/d dose level.
- If the 100 mg/m^2/d dose level is tolerable (0/3 or 1/6 with a vandetanib-related DLT) on cycles 1 and 2 in 13-18 yo cohort and one of the 3 to 6 patients experiences a drug-related DLT on 2 cycles at the 150 mg/m^2/d dose level, then additional 13-18 yo patients (if necessary) will be enrolled at the 150 mg/m^2/d dose level until there are 6 evaluable patients who have received 150 mg/m^2/d for 2 cycles. If 1/6 patients experience a vandetanib-related DLT at the 150 mg/m^2/d dose level, then subsequent 13-18 yo patients will be enrolled at the 150 mg/m^2/d dose level.
- If 2 or more of the initial 3 to 6 13-18 yo patients experience a vandetanib-related DLT at the 150 mg/m^2/d dose level, then all subsequent patients will be treated at the 100 mg/m^2/d dose without intra-patient dose escalation.

5-12 yo Cohort:

- If 0/3 or 1/6 of 13-18 yo cohort experience a vandetanib-related DLT on cycles 1 and 2 at the 100 mg/m^2/d dose level, then three 5-12 yo patients can be enrolled at this dose level. Those patients in the 5-12 yo patients who do not experience a vandetanib-related DLT during cycles 1 and 2 at the 100 mg/m^2/d dose level will have their dose escalated to 150 mg/m^2/d for their third and subsequent cycles.
- The dose escalation for the 5-12 yo cohort follows the same rules described above for the 13-18 yo patient cohort (see the algorithm above).
- If the 150 mg/m^2/d dose level is found to be intolerable in the 13-18 yo cohort (i.e., 2 or more patients experience vandetanib-related DLTs out of 3 to 6 patients), then the 5-12 yo cohort will be treated at the 100 mg/m^2/d dose level without intra-patient dose escalation to 150 mg/m^2/d.
- If 0/3 of 5-12 yo cohort experience a vandetanib-related DLT on cycles 1 and 2 at the 100 mg/m^2/d dose level, then these 3 patients will be evaluated for toxicity on their third and fourth cycles at the 150 mg/m^2/d dose level (patients who come off treatment before completing cycle 2 for reasons other than a vandetanib-related DLT can be replaced on the intra-patient dose escalation component of the trial). New 5-12 yo patients can be enrolled on the trial at the 150 mg/m^2/d dose level if none of the first 3 patients enrolled at the 100 mg/m^2/d dose level experienced a vandetanib-related DLT on cycles 1 and 2, but no more than 6 patients should be receiving the 150 mg/m^2/d dose until 3 patients have completed 2 cycles at this dose level.
- If 1/3 of 5-12 yo cohort experiences a vandetanib-related DLT on cycle 1 or 2 at the 100 mg/m^2/d dose level, then three additional 5-12 yo patients will be enrolled at the 100 mg/m^2/d dose level. If 1/6 of the expanded 5-12 yo cohort experience a vandetanib-

related DLT on cycle 1 or 2 at the 100 mg/m^2/d dose level, then the 5 patients who tolerated the drug will be evaluated for toxicity on their third and fourth cycles at the 150 mg/m^2/d dose level (patients who come off treatment before completing cycle 2 for reasons other than DLT can be replaced on the intra-patient dose escalation component of the trial). Additional new 5-12 yo patients can be enrolled on the trial at the 150 mg/m^2/d dose level if no more than 1 of the first 6 patients enrolled in the expanded cohort at the 100 mg/m^2/d dose level experienced a vandetanib-related DLT on cycles 1 and 2, but no more than 6 patients should be receiving the 150 mg/m^2/d dose until 3 patients have completed 2 cycles at this dose level.

- If 2 or more of the initial 3 to 6 5-12 yo patients experience a vandetanib-related DLT on cycle 1 or 2 at the 100 mg/m^2/d dose level, accrual to the trial will be suspended until the protocol can be amended to include a new lower dose level.
- If the 100 mg/m^2/d dose level is tolerable (0/3 or 1/6 with a vandetanibs-related DLT) on cycles 1 and 2 in 5-12 yo population and none of the 3 to 6 patients experience a vandetanib-related DLT on 2 cycles at the 150 mg/m^2/d dose level, then subsequent 5-12 yo patients will be enrolled at the 150 mg/m^2/d dose level.
- If the 100 mg/m^2/d dose level is tolerable (0/3 or 1/6 with a vandetanib-related DLT) on cycles 1 and 2 in 5-12 yo cohort and one of the 3 to 6 patients experiences a drug-related DLT on 2 cycles at the 150 mg/m^2/d dose level, then additional 5-12 yo patients (if necessary) will be enrolled at the 150 mg/m^2/d dose level until there are 6 evaluable patients who have received 150 mg/m^2/d for 2 cycles. If 1/6 patients experience a vandetanib-related DLT at the 150 mg/m^2/d dose level, then subsequent 5-12 yo patients will be enrolled at the 150 mg/m^2/d dose level.
- If 2 or more of the initial 3 to 6 5-12 yo patients experience a vandetanib-related DLT at the 150 mg/m^2/d dose level, then all subsequent patients will be treated at the 100 mg/m^2/d dose without intra-patient dose escalation.

As of Amendment J: The recommended dose of vandetanib has been established at 100 mg/m^2/day and the dose escalation portion of the study is complete. Eleven subjects remain on study receiving long-term (> 2 years) therapy with vandetanib. All subjects will remain on their current dose level, while dose reductions may be made in 30% increments based on investigator's judgment (with guidance from the vandetanib package insert) following evaluation of side effects and quality of life measures (See **Appendix 6**: Vandetanib Package Insert).

3.1.3 Definition of Maximum Tolerated Dose (MTD) or Recommended Dose

A MTD for vandetanib will be determined if DLT is observed in 2 or more patients at one of the 2 dose levels (100 and 150 mg/m^2/d) being evaluated in the limited, intra-patient dose escalation portion of the study. However, the purpose of this dose escalation is to ensure that the adult recommended dose of 300 mg/d (approximately equivalent to 150 mg/m^2/d) is tolerable in children and adolescents, and the dose will not be escalated beyond the 150 mg/m^2/d, even if no DLT is observed at this dose level. If 150 mg/m^2/d is tolerable in the two age-based cohorts, then this dose will be the recommended dose for children and adolescents with MTC.

If vandetanib-related DLT is observed in 2 or more of the 3 to 6 patients who are treated for 2 cycles with 150 mg/m^2/d, then the MTD will be 100 mg/m^2/d, if 5 or 6 of the first 6 patients from each of the 2 age-based cohorts do not experience a vandetanib-related DLT on their first 2 cycles at this dose level. If 2 or more out of the first 3 to 6 patients in a cohort experience a vandetanib-

related DLT at the 100 mg/m^2/d dose level on cycle 1 or 2, then accrual to the trial will be suspended until the protocol can be amended to include a new lower dose level.

At the MTD or recommended dose fewer than 33% of patients in each age-based cohort (13-18 yo and 5-12 yo) should experience DLT on the first two treatment cycles at that dose level.

3.1.4 Definition of Dose-Limiting Toxicity (DLT)

This study will utilize the CTEP Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for toxicity and Adverse Event grading and reporting. A copy of the CTCAE version 3.0 can be viewed or downloaded from the CTEP website (http://ctep.info.nih.gov/reporting/ctc_v30.html). An adverse event must be judged to be possibly, probably, or definitely related to vandetanib to be a dose-limiting toxicity.

Dose-limiting toxicity is defined as:

- Hematologic Dose-Limiting Toxicity (H-DLT):
  - Neutrophil count below 1,000/µL (grade 3) on 2 consecutive measurements drawn at least 72 hours apart OR a single neutrophil count below 500/µL (grade 4).
  - Platelet count below 50,000/µL (grade 3) on 2 consecutive measurements drawn at least 72 hours apart OR a single platelet count below 25,000/µL (grade 4). A platelet transfusion administered when platelet count is below 50,000/µL is dose-limiting thrombocytopenia, unless the transfusion is being administered for peri-operative coverage.
  - Grade 3 or 4 decrease in hemoglobin that can be corrected to at least 8.0 g/dl (grade 2) by transfusion of red blood cells is not a dose-limiting toxicity. However, grade 3 or 4 hemolysis is a dose-limiting toxicity if it is judged to be vandetanib-related.
  - Grade 3 or 4 leucopenia is not a dose-limiting toxicity.
  - Grade 3 or 4 lymphopenia is not a dose-limiting toxicity.
- **Non-Hematologic Dose-Limiting Toxicity (NH-DLT)**: NH-DLT is any grade 3 or higher non-hematologic toxicity, with the exception of:
  - Grade 3 nausea that is controlled by symptomatic treatment with anti-emetics (see **Appendix 4**: Medications Known to Prolong the QT Interval or Induce Torsades de Pointes to avoid agents that can prolong the QTc) within 48 hours.
  - Grade 3 vomiting that is controlled by symptomatic treatment with anti-emetics (see **Appendix 4**: Medications Known to Prolong the QT Interval or Induce Torsades de Pointes to avoid agents that can prolong the QTc) within 48 hours.
  - Any grade of diarrhea that is tumor-related (present at baseline and associated with elevated calcitonin levels) or grade 3 diarrhea that is related to vandetanib and is controlled by symptomatic treatment within 48 hours.
  - Grade 3 serum transaminase elevation (ALT/AST) that returns to grade 2 or less within 7 days. The drug may be held until the transaminase elevation subsides, but if the grade 3 transaminase elevation recurs when the drug is re-instituted, this will be considered dose-limiting toxicity.
  - Grade 3 electrolyte abnormalities that are asymptomatic and correctable to grade 2 or less within 48 hours.

- Grade 3 infection, with neutropenia, without neutropenia, or with unknown ANC
- Grade 3 febrile neutropenia (fever with ANC ≤1000/µL)

- **Hypertension (HTN)**: For pediatric patients, the ULN for blood pressure is defined as a diastolic BP at the 95th percentile from age and gender-appropriate normal values (see **Appendix 2**: Normal Blood Pressure Range for Children). Patients with a diastolic blood pressure >95% for age and gender should have blood pressure measurement repeated x2 with an appropriate size cuff, and hypertension (HTN) is defined as at least 2 (of 3) measurements exceeding the ULN. Dose-limiting hypertension is defined as:
  - A diastolic BP on at least 2 of 3 measurements that is more than 25 mm Hg above the ULN for age and gender.
  - A diastolic BP on at least 2 of 3 measurements that is above the ULN but not more than 25 mm Hg above the ULN and that does not return to within the normal range after 14 days on single agent antihypertensive therapy.
  - Grade ≥4 (CTCAE v.3) hypertension.
- **QTc Prolongation**: Participants with QTc prolongation should have serum electrolytes (including calcium and magnesium) measured. If serum electrolytes are outside the normal range, the abnormality should be corrected before determining whether a patient has dose-limiting QTc prolongation. Dose-limiting QTc prolongation is defined as:
  - A single QTc value ≥550 msec OR an increase of ≥100 msec from baseline, OR
  - Two consecutive ECG measurements, which are within 48 hours of one another and which meet either of the following criteria:
    - QTc ≥500 msec but <550 msec OR
    - A ≥60 msec but <100 msec increase in the QTc from baseline QTc to a QTc value ≥480 msec.

3.1.5 Criteria for Starting Second and Subsequent Treatment Cycles

Patients who complete a treatment cycle (28 days) may receive another cycle if:

- Disease Status: The patient does not have radiographic or clinical evidence of progressive disease (see Section **7.2**) for cycles prior to which the patient is re-staged, or in the opinion of the investigator the patient is benefiting from the therapy with vandetanib as evidenced by stable or decreased tumor-related symptoms such as diarrhea or pain or stable or decreased tumor biomarkers (CEA, CTN) for cycles that are not proceeded by restaging.
- Toxicity: Patients who experienced dose-limiting toxicity in the previous cycle should have the dose modified (see Section **3.3**).
- Criteria for discontinuation of protocol treatment or off-study criteria (see Section **5**) have not been met.

As of Amendment J: All patients who continue on the trial receiving long term therapy may continue to receive additional cycles until clinical data warrants stopping for unacceptable

toxicity or progression of disease, as determined by the principal investigator. **There is no limit on the number of cycles that a patient may receive.**

3.1.6 Evaluation of Response to Vandetanib

The primary objective of this trial is to assess the activity of vandetanib in children and adolescents with MTC. Patients are required to have measurable disease at study entry according to the RECIST. Measurable disease will be quantified on physical exam for palpable tumors in the neck and by CT scan or MRI scan. Lesion detected on bone scan will be considered to be non-target lesions by RECIST. Patients will be evaluated for response after every 2 cycles x 4 (prior to cycles 1, 3, 5, 7, and 9) and then after every 4 cycles X 1 (prior to cycle 13) and then every 6 cycles (prior to cycle 19, 25, 31, etc) using the same method (type of scan) used to document the size target lesions at baseline (prior to treatment). RECIST criteria to assess response are summarized in Section **7.3.1**. If a response (PR or CR) is achieved for by RECIST, a confirmatory restaging should be performed 4 weeks later. Patients will be considered evaluable for response if they have at least one on treatment restaging performed (after cycle 2). Patients removed from study for clinical disease progression prior to the post-cycle 2 evaluation will also be considered evaluable for response.

Patients participating on the dose escalation portion of the trial will receive a lower dose (100 mg/m^2/d) for the first 2 28-day treatment cycles. Those who are eligible for dose escalation (no vandetanib-related DLT on cycles 1 and 2) may continue on treatment at the 150 mg/m^2/d dose level starting on cycle 3 and beyond as long as the sum of the longest diameters of target lesions has not increased by more than 40% compared to baseline and no new lesions have appeared, in order to ensure that these patients have an opportunity to receive the equivalent to the adult recommended dose (150 mg/m^2/d) of vandetanib.

If CEA or CTN levels are elevated prior to the start of treatment, these biomarkers will be measured after every 2 cycles x 4 (prior to cycles 1, 3, 5, 7 and 9), prior to cycle 13, and then every 6 cycles (prior to cycle 19, 25, 31, etc). Criteria for defining biomarker response are in Section **7.3.2**. If a response (PR or CR) is achieved for CTN or CEA, a confirmatory level should be drawn 4 weeks later. The frequency and consistency of bowel movements will also be monitored on treatment in patients presenting with MTC-related diarrhea.

As of Amendment J: All patients remaining on trial in long term therapy will be evaluated for clinical response status according to **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy.

3.2 Drug Administration

Vandetanib is administered orally, once daily continuously. Patients can receive the liquid formulation through a nasogastric tube or gastrostomy. A cycle of vandetanib is defined as 28 consecutive days starting with the first day of treatment (day 1). The dose of vandetanib is determined from the patient's body surface area using the dosing nomogram below. The BSA should be recalculated prior to each treatment cycle and the dose should be adjusted if necessary based on the nomogram. Treatment will be administered in an outpatient setting.

As of Amendment J: For all patients remaining on trial in long term therapy, refer to **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy.

Dose Level [mg/m^2]							
100	BSA [m^2]	0.50-0.62	0.63-0.87	0.88-1.12	1.13-1.37	1.38-1.75	>1.75-
	Dose [mg]	50	75	100	125	150	200
150	BSA [m^2]	0.50-0.75	0.76-0.91	0.92-1.16	1.17-1.50	1.51-1.83	>1.83
	Dose [mg]	100	125	150	200	250	300

Vandetanib is supplied as 10 mg/ml suspension and 50 and 100 mg tablets. A combination of tablets and suspension can be used. For example, a dose of 75 mg could be one 50 mg tablet plus 2.5 ml of suspension.

Vandetanib is supplied as a 10 mg/ml suspension and 50 and 100 mg tablets. Vandetanib should be stored at room temperature in the original pack until use.

Patients will receive their assigned dose of vandetanib once daily at the same time of the day (An every other day dosing schedule can be used to achieve lower dose levels in patients requiring a dose reduction, see Section **3.3.1**). Vandetanib absorption is not affected by a meal,[39] so it need not be administered in the fasted state. The tablet should be swallowed whole. If a patient misses a scheduled dose of vandetanib and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. If more than 6 hours have passed since the scheduled dosing time, the patient should not take the missed dose but should wait and take the next regularly scheduled dose.

If the patient vomits within 15 minutes of taking vandetanib, then another dose can be administered. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses should be given.

Patients or their guardians will document missed vandetanib doses, and vandetanib toxicities on the study calendar.

3.3 Dose Modifications for Vandetanib-Related DLT

As of Amendment J: For dose modifications for all patients in long term therapy, refer to **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy.

3.3.1 Dose-Limiting Toxicity

- Vandetanib should be held for any dose-limiting toxicity (see Section **3.1.4**). For DLTs that include a duration in the definition, such as a neutrophil count below 1,000/µL (grade 3) on 2 consecutive measurements drawn at least 72 hours, the drug will be held after the toxicity becomes dose limiting (e.g., after the second ANC <1,000/µL).

- If vandetanib-related DLT resolves to grade ≤1 or baseline in ≤14 days of drug free period, vandetanib may be restarted at a reduced dose.
- If the vandetanib-related DLT does not resolve to grade ≤1 or baseline in ≤14 days of a drug free period the patient should discontinue protocol therapy and be monitored until the toxicity resolves.
- The cycle duration remains 28 consecutive days in patients who have dose interruptions.

- The NCI Principal Investigator should be consulted for all dose reductions.
- Patients who experience a DLT (Section **3.1.4**) that is possibly, probably, or definitely related to vandetanib should have a 30% dose reduction of their dose of vandetanib (e.g., from 300 mg/d to 200 mg/d) for the remainder of the current course and for the subsequent ≥2 cycles of treatment. All dose reductions must be at least 30% of the administered dose rounded down to the nearest 25 mg (e.g., for patients receiving 150 mg/d, a 30% reduction would be a decrease in the dose by 45 mg to 105 mg/d, which is rounded down to 100 mg/d).
- Patients who experience DLT after a dose reduction can have additional dose reductions according to the guidelines above. An every other day dosing schedule can be used to achieve lower dose levels if the calculated daily dose is <50 mg/d.
- Once the dose-finding (phase I) portion of the trial is completed and the MTD is established in the two age groups, patients who have a dose reduction for a non-life-threatening DLT (diarrhea, nausea, vomiting, constipation, anorexia, weight loss, fatigue or skin rash) and who tolerate ≥2 cycles at the reduced dose can have their dose re-escalated to the prior dose level. The toxicity type that was previously dose-limiting at the higher dose level must not have exceeded grade 1 at the reduced dose level in order to re-escalate the dose. The dose will not be escalated above the MTD.

3.3.2 WOUND HEALING

- For patients who require **elective surgery**, vandetanib should be held for 2 weeks prior to the procedure and for 2 weeks after surgery. The treatment should resume only after the surgeon has determined that the wound is healed. Patients should have restaging studies performed prior to restarting the treatment or within a month of restarting treatment.
- For patients who require **emergency surgery or who experience a significant injury**, the vandetanib should be held for at least 2 weeks and only resumed when the wounds are judged to be healed. If the vandetanib is held for 4 or more weeks, then restaging studies should be performed prior to restarting the treatment.

3.4 Vandetanib Pharmacokinetic Studies

- A pretreatment sample will be drawn prior to the start of therapy (prior to cycle 1).
- A single trough sample will be drawn 24 hours after the first dose of Vandetanib on cycle 1.
- A single trough sample will be drawn 24 hours after the last dose of Vandetanib on cycle 1 (before the first dose on cycle 2).

- A detailed pharmacokinetic (PK) evaluation of vandetanib will be performed for each patient at the end of treatment cycle 2 (cycle 2, day 28±5 days). See **Appendix 3**: `Pharmacokinetic Worksheet for Vandetanib` for details of sample collection, handling, shipping, and PK Worksheet.
- Patients who have their dosing of vandetanib interrupted for toxicity during cycle 1 or 2 will have the PK sampling performed on a subsequent cycle. At least 42 days of continuous dosing is required to ensure that patients are at steady state at the time of the PK study.
- On cycle 2, day 28±5 days, 2 mL blood samples will be collected in tubes containing lithium heparin and mixed thoroughly prior to the dose and then 1, 2, 4, 6, 8, 10, and 24 hours after the dose. Trough samples (24 h after the previous dose) should be drawn on the first day of cycles 4 and 5 for patients who undergo a dose escalation on cycle 3. Plasma will be separated by centrifugation at 1,000 g for 10 min at room temperature within 30 min of collection, and the plasma sample should be taken off immediately and stored frozen in a plain plastic tube at -20°C or -70°C. Samples will be shipped frozen (see **Appendix 3**: `Pharmacokinetic Worksheet for Vandetanib`). The label on the tube should contain the following information:

  Study number

  Vandetanib PK

  Day number

  Cycle number

  Nominal time point (hours post-dose)
- Plasma concentrations of vandetanib will be determined in human plasma samples using solvent extraction followed by reverse phase high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS). Samples spiked with [$^{13}C,d_3$]-vandetanib internal standard are extracted into methyl-t-butyl ether at a basic pH. Extracts are evaporated to dryness, reconstituted in HPLC eluent and subjected to HPLC using an Inertsil ODS3 column. Vandetanib is detected using a Perkin Elmer Sciex quadrupole mass spectrometer using a turboionspray source (multiple reaction monitoring in positive ion mode). Concentrations are determined by reference to a calibration curve prepared over a range of 5 to 1000 ng/mL vandetanib in 100 µl aliquots of heparinized human plasma. This method will be performed at Bioanalytical Systems Inc (BASi), West Lafayette, Indiana, US.

3.5 Vandetanib Pharmacodynamic Studies

3.5.1 RET, VEGFR, EGFR, and Somatostatin Receptor Expression in Archival Tumor Tissue

When available, paraffin embedded tumor from diagnostic biopsies or prior surgical resections will be obtained and examined for the expression of RET, VEGFR and EGFR (and the phospho-forms of these proteins) and somatostatin receptor by immunohistochemistry (IHC). In the event that a biopsy or surgical procedure is performed for clinical indications or research purposes

while a patient is on this study, tumor may also be obtained and examined for expression of these targets by IHC. Pathology report should accompany each specimen and the specimen should be labeled with the patient ID number.

Tumor should be shipped to:

Brigitte Widemann, MD
10-CRC, 1-3750, MSC 1101
10 Center Drive
Bethesda, MD 20892-1206
Phone: 301-496-7387
Page 301-496-1121
Email widemanb@mail.nih.gov

3.5.2 Gene Expression and RET Gene Mutational Status in Tumor

Participants over the age of 12 years with superficial tumors (e.g., cervical lymph nodes metastases) that are not located in a body cavity and that are accessible to percutaneous core needle (16 or 18 gauge) biopsy with minimal risk to surrounding vital structures will be asked to voluntarily undergo a core needle biopsy of the tumor under local anesthesia prior to the initiation of treatment and at the time of documented tumor progression by RECIST (see Section **2.1.3** for eligibility). In those who have a partial response (by RECIST), residual superficial tumors will also be biopsied while the participants are in partial remission.

- A portion of the biopsy will be processed for histologic and immunohistochemical evaluation by Dr. Maria Merino in the Laboratory of Pathology
- A portion will be snap frozen in OCT and sent to:

  Paul Meltzer, M.D.

  Bldg. 37/Rm. 6138

  Phone: (301) 496-5266

  Email: pmeltzer@mail.nih.gov

- A small portion will be placed into RPMI media to establish a cell line and sent to:

  Maya Lodish, M.D.

  Bldg. 10/Rm. 1-3216 (East labs)

  Phone: (301) 451-7175

  Email: lodishma@mail.nih.gov

- A 5 ml blood sample in EDTA (purple top tube) should also be obtained and sent with the frozen tumor sample to Dr. Meltzer.

Research samples will be used to evaluate gene expression by microarray and to assess secondary genetic changes (gains or losses of DNA sequences) by comparative genomic hybridization (CGH) in the tumor, and to sequence and identify mutations in the RET gene and compare these mutations to germ line mutations in nucleated peripheral blood cells. These studies of the RET mutation status in peripheral blood and tumor will not be used to determine protocol eligibility or inform clinical decisions on the trial. They will be used for research

purposes only. Information about the development of somatic mutations in tumors that lead to resistance to vandetanib is not currently available in adults. Identification of such mutations in the active site or the drug binding site of the RET RTK in even one patient would provide valuable information to understand the mechanism of resistance to vandetanib and to identify new RET inhibitors that could circumvent the resistance. Pediatric MTC cell lines will be used to assess the effects of vandetanib on cell proliferation, RET activation, and cell signaling pathways in cell lines from patients with clinically sensitive and resistant tumors.

If a biopsy is required for clinical indications (e.g., to make or confirm the diagnosis), then the two additional passages to obtain a tumor specimen for research purposes will be obtained after the biopsy for clinical indications. If a tumor is resected, residual tissue remaining after processing for diagnostic tests will be processed for research studies as above.

Research specimen labels will include the protocol number (07-C-0189), the two digit participant's study number and NIH medical record number.

If archival tissue blocks in paraffin are available, a core sample may be taken from the block for extraction of DNA and sequencing of the RET gene to assess mutation status in the tumor and for CGH.

3.6 Study Calendar

As of Amendment J: See **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy for Evaluations of all patients receiving long term therapy.

OBSERVATION	Prior to Cycle[†%]	During Cycle 1 only	During Cycle 2	Post Study
History & Physical	1-9 then 13, 16[++],19, 22[++], 25, etc.	Weekly	Midcycle[+]	X
Assessment of toxicity	1-9 then 13, 19, 25, etc	Weekly	Midcycle[+]	X
BP Monitoring	1-9 then 13, 16[++],19, 22[++] 25,, etc	Days 1, 2, 3, 7[§], then Weekly	Midcycle[+]	X
Performance status (document changes only)	1-3 then 5, 7, 9, 13, 19, 25, etc.			X
Height, Weight, Body Surface Area	1-9 then 13, 19, 25, etc			
Urinalysis	1-9 then 13, 16[++], 19, 22[++], 25, etc			X

OBSERVATION	Prior to Cycle[†%]	During Cycle 1 only	During Cycle 2	Post Study
Urine/Serum pregnancy test*	1-9 then 13, 19, 25, etc			
CBC, differential, platelets	1-9 then 13, 16^{++}, 19, 22^{++}, 25, etc	Weekly	Midcycle[+]	X
PT, PTT	1-3 then 5,7,9,13, 19, 25, etc.			X
Electrolytes, glucose, BUN and Creat	1-9 then 13, 16^{++}, 19, 22^{++}, 25, etc	Weekly	Midcycle[+]	X
Ca^{+2}, Mg^{+2}, PO_4^{-}, uric acid	1-9 then 13, 16^{++}, 19, 22^{++}, 25, etc	Weekly	Midcycle[+]	X
LDH, AST, ALT, bilirubin[&], Alk Phos	1-9 then 13, 16^{++},19, 22^{++}, 25, etc	Weekly	Midcycle[+]	X
Total protein, albumin, GGT	1-9 then 13, 16^{++}, 19, 22^{++}, 25, etc			X
Plasma free metanephrine and nor-metanephrine Vitamin D 25-OH	Cycle 1, then every year (at NIH)			
Thyroid Stimulating Hormone (TSH), Free thyroxine (T4), Free-T3	Cycle 1-3, 5, 7, 9, 13, 16^{++}, 19, 22^{++}, 25 etc			X
Pharmacokinetic monitoring	Cycle 1	24 h after 1st dose	Cycles 2, 3, 4, 5 (trough)[^]	

OBSERVATION	Prior to Cycle[†%]	During Cycle 1 only	During Cycle 2	Post Study
Serum calcitonin and CEA[¶]	Cycle 1, 2, 3, 5, 7, 9, 13, 19, 25 etc			X
ECG	1-9 then 13, 16[++], 19, 22[++], 25, etc	Day 3, 7, then Weekly		X
CT neck, chest, abdomen	Cycle 1, 3, 5, 7, 9, 13, 19, 25, etc			X
MRI neck	Cycle 1 then as clinically indicated			X
MRI brain[¢]	Cycle 1 then annually or as clinically indicated			
Bone scan[@]	Cycle 1 then annually or as clinically indicated			X
MRI of the knee to assess the volume of the growth plate[£]	Cycle 1, 3, 5, 7, 9, 13, 19, 25, etc. until closed			

OBSERVATION	Prior to Cycle[†%]	During Cycle 1 only	During Cycle 2	Post Study

[%] After cycle 3, evaluations can be done at NIH as travel permits and if possible at home

[†] All pre-treatment labs must be completed within 72 hours of starting vandetanib for cycle 1

[§] Day 7 ± (2 days)

[+] Mid-cycle = day 14 (± 3 days)

[&] If total bilirubin elevated, check direct bilirubin

* Urine/serum pregnancy test in females of childbearing potential

[^] On day 28 ± 5 of cycle 2 obtain samples pre-dose and then 1, 2, 4, 6, 8, 10, and 24 h post dose. A single trough sample should be obtained on day 1 of cycles 2 and 3. Only patients who have their dose escalated to 150 mg/m^2/d after cycle 2 trough should have samples obtained on day 1 of cycles 4 & 5.

[¢] On treatment MRI brain scans will be performed only if the baseline scan was positive and then as clinically indicated. Neck MRI is optional if disease can be adequately followed on CT.

[@] If baseline bone scan is positive then subsequent bone scans will be obtained.

[£] On treatment MRIs will be performed only if the growth plates were open on the baseline MRI and can be discontinued after growth plates are fused.

[++] Every other visit – when staging is not done – patients may be seen by their local physician to have these studies completed. Records are to be sent to the NIH. Once the patient has completed Cycle 13, the visit schedule may be broadened to allow a +/- 4 week window.

Patients may be seen by their local physician in order to complete the necessary requirements for the study, including history and physical examinations, blood pressure monitoring, performance status, urinalysis and routine laboratory tests (blood counts and chemistries), when they are not seen by a study investigator. Whenever possible, restaging studies and biomarkers should be performed at the NIH.

3.6.1 General

- Blood Pressure: Should be monitored and recorded prior to the first dose of vandetanib, on day 1, and then on day 2, day 3, day 7 (± 2 days) and weekly with physical exams during cycle 1. In addition, blood pressure should be monitored and recorded at least every 2 weeks during cycle 2, and then prior to each cycle on cycles 3 through 9, then every 3 cycles (+/- 28 days) (13, 16, 19, 22, etc). See Section **6.1** for management of elevated diastolic BP.
- Physical Examination: A physical examination should be performed weekly during cycle 1. Then prior to and at the midpoint (day 14 ± 3 days) during cycle 2. Then prior to each cycle for cycles 3 through 9, then every 3 cycles (+/- 28 days) (13, 16, 19, 22, etc).
- Height, Weight, and BSA: Recorded prior to each treatment cycle for cycles 1 through 9, then prior to cycle 13, and then every 6 cycles (19, 25, etc).

- PERFORMANCE STATUS: Record any changes to performance status prior to each treatment cycle for cycles 1 through 3, and then prior to cycles 5, 7, 9, and 13, and then every 6 cycles (19, 25, etc) (**Appendix 1**: `Performance Status Scales/Scores`).

3.6.2 LABORATORY

- HEMATOLOGY: Complete blood count, differential and platelet count weekly (more frequent monitoring may be performed if the ANC <1,000/µL or platelet count <50,000/µL) for cycle 1, and then prior to and mid cycle for cycle 2. Then prior to each treatment cycle for cycles 3 through 9, then every 3 cycles (13, 16, 19, 22, etc). PT and PTT are monitored prior to each cycle for cycles 1 through 3, and then prior to cycles 5, 7, 9, and 13, and then every 6 cycles (19, 25 etc).
- CHEMISTRIES: Weekly BUN, creatinine, electrolytes (including Ca, Mg, PO_4), LDH, AST, ALT, alkaline phosphatase, bilirubin (total and direct if total is elevated), calcium, magnesium, phosphorus, glucose, and uric acid during cycle 1, then prior to and midcycle (day 14 ± 3) for cycle 2. And then prior to each cycle for cycles 3 through 9, then every 3 cycles (13, 16, 19, 22, etc), and at off study evaluation. GGT, total protein and albumin are monitored prior to cycles 1 through 9 then every 3 cycles (13, 16, 19, 22, etc).
- THYROID STIMULATING HORMONE (TSH) AND FREE THYROXINE (T4), FREE T3: Prior to every cycle on cycles 1-3, then prior to cycle 5, 7, 9, then every 3 cycles (13, 16, 19, 22, etc).
- BIOMARKERS: Serum CTN and CEA prior to cycles 1, 3, 5, 7, 9, and 13, and then every 6 cycles (19, 25, etc). Serum calcitonin should be drawn after a 12 hour fast and sent to the lab immediately at room temperature.
- URINALYSIS: Perform prior to every treatment cycle for cycles 1 through 9, then every 3 cycles (13, 16, 19, 22, etc).
- SERUM/URINE PREGNANCY TEST: Prior to every cycle in females with child bearing potential for cycles 1 through 9, then cycle 13, and every 6 cycles (19, 25, etc).
- Plasma Metanephrines and nor-Metanephrines and Vitamin D 25-OH: Prior to cycle 1 and then every year (at NIH).

3.6.3 ECG WITH CALCULATION OF QTC

Prior to cycle 1 and on days 3 and 7 and then weekly during cycle 1. Then prior to all subsequent cycles for cycles 2 through 9, then every 3 cycles (13, 16, 19, 22, etc). See Section **6.2** for management of QTc prolongation. Use Bazett's correction ($QTc = QT/RR^{0.5}$).

3.6.4 TUMOR MEASUREMENTS AND RADIOGRAPHIC EVALUATION

- The longest diameter of palpable tumors should be measured prior to each treatment cycle.
- CT scans of the neck, chest and abdomen prior to cycles 1, 3, 5, 7, 9, and 13, and then every 6th cycle (19, 25, 31, etc). For patients who demonstrate a PR or CR, the response should be confirmed by repeating the scans after the next cycle.
- MRI of the brain (if positive at baseline) annually or as clinically indicated. MRI of the neck (optional if disease can be adequately followed by CT) prior to cycles 1, and then as clinically indicated.

- ^{99m}Tc-Bone scan (if positive at baseline) prior to cycles 1 then annually or as clinically indicated.
- MRI of the knee to assess the volume of growth plates **only** in patients with open growth plates on the pretreatment MRI. Scans will be performed prior to cycles 1, 3, 5, 7, 9, 13 and then every 6th cycle (19, 25, 31, etc), until growth plates are fused.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1.1 Other Anti-cancer Agents

Patients may not receive other forms of cancer chemotherapy, radiation therapy, immunotherapy or investigational agents while enrolled on this trial and receiving vandetanib.

4.1.2 Complementary and Alternative Therapies

All complementary or alternative therapies including herbal preparations, vitamins, and supplements should be discussed with the PI or an Associate Investigator. All agents will be recorded on the electronic case report forms.

4.1.3 Thyroid Replacement Therapy

Patients who are receiving thyroid replacement therapy at the time of enrollment onto the study should be maintained on thyroid replacement therapy. The dose should be adjusted to maintain the TSH within the normal range. Patients who have an elevated TSH at enrollment and who are not on thyroid replacement therapy should be started on replacement therapy and maintained on a dose that suppresses TSH into the normal range.

4.1.4 Anti-Hypertensive Therapy

Please refer to Section **6.1.2** for information on the use of enalapril for the management of vandetanib-related hypertension.

4.1.5 Agents that Prolong the QTc

Please refer to **Appendix 4**: Medications Known to Prolong the QT Interval or Induce Torsades de Pointes prior to starting any new supportive care drug to ensure that it does not cause prolongation of the QTc. Agents in Group 1 cannot be administered concurrently with vandetanib. Participants requiring one of these agents should be removed from the treatment with vandetanib.

Drugs in Group 2 of **Appendix 4**: Medications Known to Prolong the QT Interval or Induce Torsades de Pointes are allowed during the study, at the discretion of the Investigator, if considered absolutely necessary (no alternative is available). In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes.

5 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

5.1.1 Criteria for removal from Protocol Therapy

- **Toxicity:** Patients who develop a vandetanib-related DLT (Section **3.1.4**) that does not recover to grade ≤1 in ≤14 days will discontinue protocol therapy. See Sections **6.1** to **6.3**

for criteria on discontinuation of vandetanib for hypertension, QTc prolongation, and skin toxicity.

- **Concurrent use of agents that prolong the QTc:** Vandetanib use must be discontinued if one of the QTc prolonging agents in Group 1 of **Appendix 4**: `Medications Known to Prolong the QT Interval or Induce Torsades de Pointes` is started.
- **Progressive Disease:** Patients with clinical or radiographic evidence of progressive disease will discontinue vandetanib (see Section **7.2**). If possible, tumor progression should be documented radiographically. Patients with progression of both CTN and CEA, should have a radiological evaluation to determine whether there is measurable evidence of tumor progression by RECIST.

Patients participating on the dose escalation portion of the trial will receive a lower dose (100 mg/m^2/d) for the first 2 28-day treatment cycles. Those who are eligible for dose escalation may continue on treatment at the 150 mg/m^2/d dose level starting on cycle 3 and beyond as long as the sum of the longest diameters of target lesions has not increased by more than 40% compared to baseline and no new lesions have appeared, in order to ensure that these patients have an opportunity to receive the equivalent to the adult recommended dose (150 mg/m^2/d) of vandetanib.

- Other Medical Reason:
    - The development of a concurrent serious medical condition that might preclude or contraindicate the further administration of vandetanib.
    - It is deemed in the best interest of the patient. In this instance the Principal Investigator should be notified and the reasons for discontinuation of vandetanib should be noted in the patient's medical record.
    - Serious protocol violation, such as non-compliance, as determined by the Principal Investigator.

5.1.2 OffStudy Criteria

- Patient or guardian withdrawal of consent. Reasons must be noted on the patient's medical record.
- Lost to follow up.

[Overall survival is an endpoint on this trial. Patients will remain on this trial to be monitored for this endpoint.]

The NCI Central Registration Office should be notified when a participant is taken off study.

5.1.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

5.2 Post-Treatment Evaluations

5.2.1 Follow-Up Evaluations

Once a patient develops progressive disease, annual contact with the patient or health care provider will be attempted to obtain survival data.

5.2.2 Off-Study Visit

The following tests or procedures should be performed, if possible, immediately prior to the time a patient comes off study regardless of the reason, unless the test or procedures have been performed within the past two weeks.

- Physical examination
- Performance status
- Assessment of clinical toxicity/adverse events
- Complete blood count with differential and platelet count
- Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus, uric acid, ALT, total and direct bilirubin, alkaline phosphatase, and albumin.
- Serum CTN and CEA drawn after a 12 hour fast and sent to the lab at room temperature.
- Radiographic evaluation of measurable or evaluable disease.

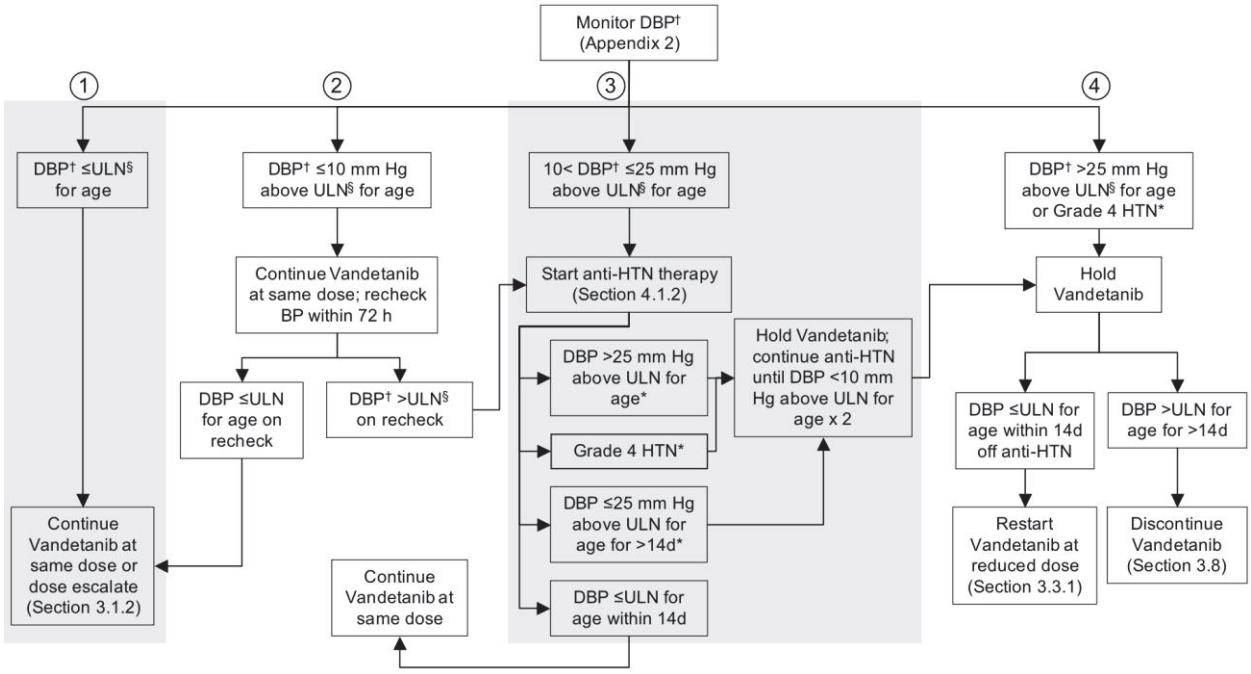
6 SUPPORTIVE CARE ISSUES

As of Amendment J: All patients remaining on trial in long term therapy will be monitored and managed according to **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy.

6.1 Management of Hypertension (HTN)

6.1.1 HTN Management Algorithm

If the diastolic BP is found to be elevated above the 95th percentile for age and gender (**Appendix 2**: Normal Blood Pressure Range for Children) at any point during treatment, the measurement should be repeated twice more with an appropriate size cuff. The diastolic BP will be considered to be elevated if at least 2 of the 3 diastolic BP measurements exceed the 95th percentile.



† Elevated diastolic blood pressure (DBP) measurements should be repeated x 2 to confirm the elevation
§ ULN (Upper Limit of Normal) is a diastolic BP at the 95th percentile from age and gender-appropriate normal values (Appendix 2)
* If DBP >25 mm Hg above ULN for age (verified) or grade 4 HTN at any time, holdVandetanib. Antihypertensive agents can be used to control hypertension as clinically indicated after Vandetanib is held.

- Refer to **Appendix 2**: Normal Blood Pressure Range for Children for age and gender normal blood pressure ranges in children and adolescents.
- **Arm 1 of algorithm:** If diastolic blood pressure ≤95% for age and gender, continue vandetanib at the same dose or dose escalate (Section **3.1.2**)
- **Arm 2 of algorithm**: If diastolic blood pressure ≤10 mm Hg above the ULN for age and gender, continue vandetanib at the same dose and recheck the DBP within 72 h.
    - If the DBP is ≤95% for age and gender on recheck, continue vandetanib at the same dose or dose escalate (Section **3.1.2**).
    - If the DBP remains above the ULN for age and gender on recheck, then start antihypertensive therapy (Section **6.1.2**) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.
- **Arm 3 of algorithm:** If diastolic blood pressure is 11 to 25 mm Hg above the 95% for age on ≥2 of 3 measurements, start single agent anti-hypertension therapy (see Section **6.1.2**), continue vandetanib at the same dose, and monitor blood pressure at least every 3 days.
    - If the diastolic blood pressure drops to ≤95% for age within 14 days, continue vandetanib at the same dose and continue concurrent single agent anti-hypertensive therapy.
    - If the diastolic blood pressure remains elevated ≤25 mm Hg above the 95% for age for more than 14 days after the institution of single agent anti-

hypertensive therapy, hold vandetanib, monitor blood pressure at least every 3 days, and follow Arm 4 of the algorithm from the point that vandetanib is held. The antihypertensive therapy should be continued until the DBP <10 mm Hg above the ULN for age and gender.

- If the diastolic blood pressure drops to ≤95% for age within 14 days and the antihypertensive therapy can be discontinued, restart vandetanib at a reduced dose (Section **3.3.1**).
- If the diastolic blood pressure remains >95% for age for more than 14 days, discontinue vandetanib (Section **5**).
  - If the diastolic blood pressure increases to >25 mm Hg above the 95% for age despite anti-hypertensive therapy or the participant develops grade 4 hypertension (CTCAE v.3), hold vandetanib, but continue the anti-hypertensive agent until the diastolic blood pressure is <10 mm Hg above the 95% for age on 2 measurements at least 3 days apart. Monitor the blood pressure at least every 3 days and follow Arm 4 of the algorithm from the point that vandetanib is held.
    - If the diastolic blood pressure is ≤95% for age within 14 days off of anti-hypertensive therapy, restart vandetanib at a reduced dose (Section **3.3.1**).
    - If the diastolic blood pressure is >95% for age for more than 14 days, discontinue vandetanib (Section **5**)

- **Arm 4 of algorithm:** If diastolic blood pressure is >25 mm Hg above the 95% for age or the participant develops grade 4 hypertension (CTCAE v.3), hold vandetanib and monitor blood pressure at least every 3 days. Anti-hypertensive therapy can be used until the diastolic blood pressure is <10 mm Hg above the 95% for age on 2 measurements at least 3 days apart.
  - If the diastolic blood pressure drops to ≤95% for age within 14 days off of anti-hypertensive therapy, restart vandetanib at a reduced dose (Section **3.3.1**).
  - If the diastolic blood pressure is >95% for age for >14 days, discontinue vandetanib (Section **5**)
- The cycle duration remains 28 consecutive days in patients who have dose interruptions.

6.1.2 Single Agent Anti-Hypertensive Therapy

- Participants with a persistently (>72 h) elevated DBP that is ≤10 mm Hg above the 95% for gender and age (ULN, **Appendix 2**: Normal Blood Pressure Range for Children) or with ≥2 of 3 DBP measurements on a single day that are 11-25 mm Hg above the ULN should be started on enalapril at a dose of 2.5 mg PO once daily for children weighing <50 kg and 5.0 mg PO once daily for children weighing ≥50 kg.[40]
- Blood pressure should be monitored 4 hours after the first dose (day 1), 24 hours after the first dose, and then every 48 hours until the DBP is ≤ULN x 2 measurements.
- If the DBP remains elevated at ≤25 mm Hg above the ULN after 7 days of enalapril, the dose of enalapril can be doubled, if the participant has not experienced enalapril-related toxicity at the starting dose.

- If the DBP remains elevated at ≤25 mm Hg above the ULN after 14 days of enalapril, then the vandetanib should be held (see Section **6.1.1**).
- If the DBP increases to >25 mm Hg above the ULN on ≥2 of 3 measurements at any time during enalapril treatment or the participant develops grade 4 hypertension at any time, then the vandetanib should be held. Antihypertensive therapy should be continued until the DBP is <10 mm Hg above the 95% for age and gender on 2 measurements at least 3 days apart (see Section **6.1.1**).

6.2 Management of QTc Prolongation

If a QTc value is ≥550 msec OR the QTc increases by ≥100 msec from baseline, vandetanib must be held and an ECG repeated at least twice weekly until the QTc interval is ≤480 msec. After resolution of the QTc prolongation to ≤480 msec, vandetanib may be restarted at a reduced dose (see Section **3.3**) after discussion with the protocol PI. Once the vandetanib is restarted at a lower dose, ECGs should be performed weekly for the first 8 weeks and then every 4 weeks thereafter. If the QTc does not return to ≤480 msec in ≤14 days, vandetanib should be discontinued.

If a QTc value is ≥500 msec but <550 msec, OR the QTc increases by ≥60 msec but <100 msec from baseline and the QTc is ≥480 msec, then a repeat ECG should be performed within 48 hours to confirm the QTc prolongation. Vandetanib should continue to be taken until the second ECG is performed. Then:

- If the repeat QTc meets the criteria above again, vandetanib should be held and an ECG repeated at least twice a week until the QTc is ≤480 msec. After resolution of the QTc prolongation to ≤480 msec, vandetanib may be restarted at a reduced dose (Section **3.3**) after discussion with the protocol PI. Once the vandetanib is restarted at a lower dose, ECGs should be performed weekly for the first 8 weeks and then every 4 weeks thereafter. If the QTc does not return to ≤480 msec in ≤14 days, vandetanib will be discontinued.
- If the repeat QTc does not meet the criteria above, vandetanib should be continued and ECG monitoring should be performed as outlined in Section **3.6**.

6.3 Management of Skin Toxicity

Vandetanib must be held when any CTCAE grade 3 or 4 vandetanib-related skin toxicity occurs. For grade 3 or 4 allergic skin reactions, vandetanib should be discontinued. For non-allergic reactions, treatment may be resumed at a lower dose (Section **3.3**) if the toxicity recovers to grade ≤1 or baseline within 14 days of discontinuing the drug. If the skin toxicity does not resolve to grade ≤1 or baseline in ≤14 days, vandetanib should be discontinued.

Agents that can be used to manage skin rashes include mild to moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams. If a patient develops a skin rash, the following actions are recommended for the management of this toxicity:

- For a grade ≥2 vandetanib-related rash, symptomatic treatment with topical creams or systemic anti-histamines should be provided.
- For grade ≥3 vandetanib-related rash (non-allergic), vandetanib should be held until recovery to grade ≤1. After recovery, vandetanib may be restarted at a reduced dose

(Section **3.3**) after discussion with the protocol PI. If the rash does not resolve to grade ≤1 in ≤14 days OR the rash is an allergic rash, vandetanib will be discontinued.

6.4 Management of Gastrointestinal Toxicity

Electrolytes should be closely monitored in the event of persistent vomiting or diarrhea. Vandetanib should be held in patients who develop electrolyte abnormalities from vomiting or diarrhea until the electrolyte abnormalities are corrected because of the risk of QTc prolongation and subsequent arrhythmias.

6.4.1 Nausea or Vomiting

Nausea and vomiting may be controlled with antiemetic therapy. There is a risk that the use of 5HT-3 antagonists may prolong QTc interval; therefore, these agents are prohibited. The dose of vandetanib may be repeated once if emesis occurs within 15 minutes of taking the dose.

6.4.2 Vandetanib-Related Diarrhea

Diarrhea that occurs after initiation of vandetanib is likely to be treatment-related and should be treated symptomatically to avoid dose modification or interruption. Diarrhea due to vandetanib has been successfully managed in adults with anti-diarrheal agents such as loperamide. Because diarrhea may be a component of MTC with elevated CTN, no dose modifications will be made for pre-existing cases of diarrhea. If grade 3 diarrhea that cannot be controlled by symptomatic treatments within 48 h or grade 4 diarrhea develops, or diarrhea worsens by one grade level (grade 3 to grade 4) while on vandetanib and is not alleviated by symptomatic treatment within 48 h, vandetanib should be held until diarrhea resolves to grade ≤1 or baseline. Once the diarrhea resolves, vandetanib may restarted at a reduced dose (Section **3.3**). Dose reduction should only occur if the investigator believes the diarrhea is related to vandetanib.

6.5 Management of MTC-Related Diarrhea

Patients who are receiving symptomatic treatment for diarrhea at study entry can continue the treatment while on study. If CTN levels are elevated at study entry in these patients and the levels drop by >50% on vandetanib therapy, an attempt should be made to taper or discontinue the symptomatic anti-diarrheal therapy.

Adults with MTC and CTN-related diarrhea had improvement in diarrhea on vandetanib, so symptomatic treatment for MTC-related diarrhea should not be started after study entry for at least 2 weeks to determine whether vandetanib can alleviate the diarrhea.

Patients should not be treated with short- or long-acting octreotide while on study because it may have an independent therapeutic effect on the biomarker endpoints (CTN and CEA).

7 DATA COLLECTION AND EVALUATION

7.1 Data Collection

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security

standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Clinical data will be shared with AstraZeneca as outlined in the CTA.

As of Amendment J: For all patients remaining on study on long term therapy after > 2 years of treatment with vandetanib, only Unanticipated Events and response data will be captured in C3D. In addition, safety evaluations required for continued treatment with vandetanib will be collected, but not entered into C3D.

7.1.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, X-rays. In the case of foreign language documents received from LMD or health care institutions, a certified NIH Translation Office translation may be accepted as a source document (but is not required).

The investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source documents.

7.1.2 Case Report Forms

Data may be entered from the source documents directly into eCRFs in C3D for each patient enrolled in this study.

As of Amendment J: For all patients remaining on study on long term therapy after > 2 years of treatment with vandetanib only SAEs and response data will be captured in C3D.

The principal investigator or research nurse will review the eCRFs for completeness and accuracy. Independent audits may also be conducted by NCI personnel to ensure completeness and accuracy of data in C3D.

In addition to the eCRFs the following forms will be completed:

- Eligibility checklist prior to enrollment (FAXed to the Central Registration Office).
- PK worksheets (**Appendix 3**: Pharmacokinetic Worksheet for Vandetanib) at the end of cycle 1.

7.1.3 Data Quality Assurance

The CRAs will monitor each patient's data set throughout the study. Source document review will be made against entries on the eCRF and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after eCRFs are completed by the CRA, review of the data will be conducted by a research nurse or physician at the NCI POB.

All data are coordinated through:

Claudia Derse-Anthony, R.N.
10 Center Drive, Room 1C244
Bethesda, MD 20982
Office Phone: (240) 760-6102

7.2 Genomic Data Sharing Plan

There is no GDS plan for this protocol. Patients on this study are co-enrolled in protocol 12-C-0178, *Longitudinal Assessment and Natural History Study of Children and Young Adults with MEN2A or MEN2B with or without Medullary Thyroid Carcinoma*, where genomic data sharing and analysis are conducted.

7.3 Response Criteria

7.3.1 RECIST

Baseline documentation of "Target" and "Non-Target" lesions

- All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
    - The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions or unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Confirmation of Response

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum 8 weeks from study entry.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest

measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/ Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Response

Duration of overall response:	The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
Duration of stable disease:	Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. To be considered clinically relevant, the duration of stable disease must be ≥8 weeks.

Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression.

7.3.2 Biomarker Response Criteria

See Section **3.6** for calcitonin (CTN) and CEA sampling time points. Only patients with average pretreatment CTN and CEA levels that are >2 times the ULN are evaluable for response. Response criteria for CEA and CTN are:

- **Complete Response (CR):** Normalization (≤ULN) of CEA or CTN level following treatment, confirmed with a repeat CEA/CTN level at least 4 weeks apart.
- **Partial Response (PR):** A ≥50% decrease in the CEA or CTN level relative to the baseline level, confirmed with a repeat CEA/CTN level at least 4 weeks apart.
- **Progression (P):** A ≥50% increase in the CEA or CTN relative to the prior value on 2 consecutive measurements at least 4 weeks apart (e.g., if the last prior CTN value was 1,000 pg/ml, consecutive values of 1,500 pg/ml and then 2,250 pg/ml at least 4 weeks later would represent progression). The patient must have been taking vandetanib for 4 weeks prior to the first measurements and must have continued to take the drug through the time that the second measurement was drawn.
- **Stable (S):** <50% increase or decrease in CTN or CEA level relative to the baseline level.

To be assigned a status of biomarker PR or CR, changes in serum tumor biomarker level must be confirmed by repeat measurement, which should be performed ≥4 weeks after the criteria for PR or CR are first met.

For stable disease, follow-up CEA/CTN levels must have met the stable disease criteria at least once after study entry at a minimum interval defined as 12 weeks.

Each patient's **best CEA response and best CTN response** will be calculated from the average (of 2) baseline measurement and lowest measurement during treatment (confirmed by a second measurement ≥4 weeks later). Responders are those subjects with a best biomarker response of CR or PR.

7.4 Toxicity Criteria

This study will utilize the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE-3) for toxicity and Adverse Event grading and reporting. A copy of the CTCAE-3 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_30).

8 Statistical Considerations

8.1.1 Patient Accrual

Patients of both genders, from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria outlined in Section **2.1**. There is no clinical information that suggests differences in vandetanib metabolism, disposition or MTC response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. This phase II trial of vandetanib will be conducted in children and adolescents (5-18 year olds) with hereditary MTC, which is a very rare condition. A similar trial has been conducted in adults with MTC. Efforts will be made to extend the accrual to a representative group from this population, but with a rare disease and with a planned accrual of 21 patients, a balance must be

struck between completing the trial in a timely fashion on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully. We anticipate that accrual to this trial can be completed in 2 to 3 years.

8.1.2 Statistics and Feasibility

The primary objective of this trial is to determine whether the RET inhibitor, vandetanib, which is active against hereditary MTC in adults, has equivalent anti-tumor activity in children and adolescents with hereditary MTC. The primary endpoint is objective response (CR or PR) measured with RECIST (see Section **7.3.1**). Because the agent is already known to be active in hereditary MTC, the trial will follow a single stage design (no early analysis for futility). The response rate in adults is 5/18 (28%; lower one-sided 95% CI bound = 10%). This trial is designed to determine whether the response rate in children and adolescents with hereditary MTC exceeds 10% and may be consistent with a response rate as high as 30%. With a planned sample size of 21 evaluable patients (see Section **3.1.6**), using a one-sided 0.1 alpha level exact binomial test, the trial would have 80% power to rule out a 10% response rate in favor of a 30% response rate. In practice, 5 responses in 21 patients would marginally rule out 10% as a response rate, and also may be consistent with a response rate of approximately 40%.

Biomarker (CTN and CEA) and clinical response rate will be reported with their associated exact 95% CIs. Only a subset of enrolled subjects will be evaluable for biomarker response or clinical response as defined in Sections **7.3.1** and **7.3.2**. The mean pretreatment CTN and CEA levels and mean nadir CTN and CEA levels across all patients enrolled on the trial will be calculated.

There are no phase I data for vandetanib in children. Therefore, the safety and tolerability of doses that are equivalent to the recommended doses in adults will be assessed initially in adolescents (13-18 yo) and then in children (5-12 yo). This will be done using an intra-patient dose escalation design, which will ensure that all patients receive the dose equivalent to the one used in the adult phase II trial (if that dose is tolerable in children), and therefore ensure that all patients are evaluable for the phase II component of this trial. The design of the limited dose escalation portion of this trial is described in detail in Section **3.1.2**. Because of the rare nature of this disease, the patients in the dose escalation phase are included in the 21 evaluable patients who are to be enrolled to evaluate response. Patients who are enrolled on the dose escalation portion of the trial and who do not complete the first 2 cycles for reasons other than a vandetanib-related DLT can be replaced on the intra-patient dose escalation portion of the trial, but they will remain potentially evaluable for the phase II portion of the trial.

The pharmacokinetics of vandetanib will be studied in children and adolescents with hereditary MTC at steady state (end of cycle 2) after at least 42 days of continuous dosing. At steady state, the AUC for the dosing interval (0 to 24 h) is equivalent to the $AUC_{0-\infty}$ after a single dose. Pharmacokinetic parameters to be derived include the AUC_{0-24h}, the peak and trough plasma concentrations, the time to peak concentration, and the CL/F. The relationship of CL/F to age and gender will be assessed as will the relationship of AUC_{0-24} to pharmacodynamic outcomes (toxicity, response).

Evaluations of other objectives will be done in an exploratory fashion:

- To determine the progression-free survival and overall survival in children and adolescents with hereditary MTC treated with vandetanib. Kaplan Meier curves will be constructed, and descriptively reported, including appropriate confidence intervals.
- To assess the expression of RET, EGFR, VEGFR, and somatostatin receptor by immunohistochemistry (IHC) in archival tissue blocks from children and adolescents enrolled on this protocol. IHC data will be scored and the findings will be reported descriptively. In those patients who have pre-treatment (diagnostic or research) samples, the difference in the scored values will be compared by a marginal homogeneity test or McNemar's test for paired categorical data, depending on the availability of data.
- To assess gene expression by microarray prior to and during treatment with vandetanib, appropriate data will be collected and analyzed by individuals with experience doing this evaluation. This will be considered an exploratory analysis.
- To perform RET gene mutational analysis in tumor and peripheral blood mononuclear cells prior to treatment and in tumor at the time of disease progression on treatment with vandetanib. Any novel gene mutations identified will be reported and, if possible, evaluated with respect to an association with disease progression using exploratory techniques. Kaplan-Meier analysis or other methods to relate genotype to clinical endpoints will be used in an exploratory fashion.
- To perform comparative genomic hybridization on tumor tissue DNA to globally screen for gains/losses of DNA. This will be considered an exploratory analysis.
- To study the effects of vandetanib on proliferation of pediatric MTC cell lines established from patients with clinically sensitive and resistant tumors and to study the drug's effects on RET activation and signaling pathways in the drug exposed cell lines. Standard cell survival analyses will be used to quantify the effect of various drug concentrations on cell proliferation compared to an untreated control. The effect of the drug on signaling pathways will be correlated to the IC_{50} of vandetanib in each cell line. This will also be considered an exploratory analysis.

Stopping Rule: If one grade ≥3 adverse event that is related to a core needle biopsy to obtain a research specimen occurs in a patient on this trial, then no further biopsies will be performed to obtain research samples.

8.2 Data Safety and Monitoring Plan

Vandetanib has been approved by the US Food and Drug Administration (FDA) for treatment of MTC and currently has a well established toxicity profile. Therefore, only unexpected ≥ grade 2 adverse events at least possibly related to study drug or any ≥ grade 3 or adverse events observed in patients enrolled on the trial will be recorded by the Principal and Associate Investigators, and attribution of these events to vandetanib will be determined at the end of each treatment cycle in each subject. The clinical research team (PI, adjunct PI, research nurses, data managers) will meet on a regular basis when patients are being actively treated on the trial to discuss each patient in detail and ensure that all events are graded appropriately, and that the attribution to study drug is correct. Decisions about dose level (escalation) and enrollment will be made based on the toxicity data from prior patients.

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of

clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients will be randomly selected and monitored at least biannually or as needed, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

This trial will not require monitoring by a DSMB.

8.3 Sample Storage, Tracking and Disposition

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

Research specimen collection, labeling, and initial processing is outlined in Sections **3.4** and **3.5**. Specimens will initially be stored in monitored freezers (-70°C or -20°C) or refrigerators (4°C) in the Pharmacology & Experimental Therapeutics Section (PETS) Laboratory, POB, NCI on 1 West (CRC). Samples will be tracked using the PETS pharmacokinetics FileMaker database. Samples will be identified using a unique patient number (study number). Specimens will be distributed to the following labs for assay:

- Plasma samples for pharmacokinetic analysis of vandetanib and its metabolites will be shipped in batches to AstraZeneca for analysis by HPLC-MS/MS. The PI will instruct AZ to destroy the residual samples after all pharmacokinetic samples have been assayed and the analysis of the PK data has been completed.
- Slides from archival tissues blocks will be requested from each patient's referring medical team. These slides will be transferred to Dr. Maria Merino-Neumann in the Laboratory of Pathology for immunohistochemical staining (RET, VEGFR, EGFR, somatostatin receptor). Stained slides, which will be labeled with the patients study number, will be stored in the Lab of Pathology until the trial is completed. If unstained slides are available after planned studies are completed, these may be used for future research after getting an exemption form OHSR or approval from the IRB.
- Cell lines generated from biopsy or surgical specimens will be maintained *in vitro* in tissue culture indefinitely.
- Snap frozen biopsy specimens and a blood specimen will be transferred to Dr. Paul Meltzer's lab for gene expression and RET mutation analysis. These specimens will be labeled with the patient's study number. Dr. Meltzer will retain residual specimens, which may be used for future research after getting an exemption form OHSR or approval from the IRB.

The study will remain open and status of the trial (and specimens) will be reported to the NCI IRB until all samples have been analyzed, reported, destroyed, stripped of all identifiers and unlinked from the protocol database, or transferred to another protocol. Unintentional loss or destruction of any samples will be reported to the NCI IRB as part of annual continuing reviews.

Any use of samples not outlined in Section **3.4** or **3.5** will require an exemption from OHSR or prospective NCI IRB review and approval.

9 COLLABORATIVE AGREEMENTS

9.1 Clinical Trial Agreement (00720-07)

A Clinical Trial Agreement (CTA) has been established between the CCR and AstraZeneca.

10 HUMAN SUBJECTS PROTECTION

10.1 Rationale for Subject Selection

Subject accrual in regard to gender, and racial and ethnic groups is described in Section **8.1.1**. The study population is limited to patients 18 years and younger because there is a separate phase II trial of vandetanib in adults with hereditary MTC. There is a younger age limit of 5 years because it is very unlikely that patients younger than 5 years with MEN 2A or 2B will have recurrent or refractory MTC.

10.2 Participation of Children

This trial is designed to determine whether the response rate of hereditary MTC to vandetanib in children and adolescents is equivalent to the response rate in adults with the same condition. There is currently no experience with vandetanib in children, so the tolerability of the adult equivalent doses in children, the toxicity spectrum in children and the pharmacokinetics in children are also being studied. Therefore, children and adolescents will be enrolled onto this research trial. This trial will be conducted by pediatric oncologists who have extensive experience in performing investigational drug trials in children. Patients enrolled at the POB, NCI will be cared for in the POB outpatient clinic or day hospital. When patients require hospital admission, they will be cared for on the 1NW Pediatric Unit by the POB staff.

10.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 Risks and Benefits

The primary risk to patients participating in this research study is from toxicity of vandetanib. In adults, vandetanib has been relatively well tolerated. The most common adverse events have been rash, diarrhea and asymptomatic QTc prolongation, which are reversible and generally can

be alleviated by dose reduction. Because the drug has not been previously administered to pediatric patients, the protocol provides for detailed and careful monitoring of all patients to assess for toxicity. The starting dose is based on the results of previous adult phase I trials of vandetanib and planned dose escalation will not exceed the dosing range which demonstrated clinical benefit and which was well tolerated in adults. Toxicity data from the first dose level will be collected and reviewed in real time to ensure that there were no severe (dose-limiting) toxicities prior to escalating to the second dose level (intra-patient dose escalation on cycle 3); and adolescents (13-18 yo) will be studied before introducing the drug to children (5-12 yo). The benefits of this molecularly-targeted agent in hereditary MTC have been demonstrated in adults. The objective response rate (PRs) by RECIST is approximately 30% and the majority of patients have substantial reductions in serum calcitonin levels, which is felt to contribute to MTC-related diarrhea.

The protocol incorporates percutaneous core needle biopsies of superficial tumors with minimal risk to surrounding vital structures in order to obtain tumor specimens for research purposes in participants over the age of 12 years who meet the eligibility criteria in Section **2.1.3**. These research specimens would be used to assess the effect of vandetanib (*in vivo*) on gene expression in tumors that partially respond to the agent and, more importantly, to assess the mutational status of the RET gene mutations in the tumor (compared to germ line mutations) at the onset of treatment and at the time of progressive disease. Pediatric MTC tumor cell lines will also be established to study the effects of vandetanib on the tumor *in vitro*. New mutations that account for drug resistance provide valuable information for the development of new agents to circumvent drug resistance. These types of studies have been critical to understanding and overcoming resistance to imatinib, another RTK inhibitor.[41,42] There would be no immediate direct benefit to the subject who undergoes a biopsy on this trial. The most likely site for biopsies would be superficial lymph nodes in the neck. In a small series (n=15) describing the use of ultrasound-guided cutting needle biopsy (16 or 18 gauge) in pediatric neck masses, 100% of the biopsy attempts yielded a tissue core from the target organ, including 12 lymph node masses.[43] Thirteen of these 15 patients had the biopsy successfully performed under local anesthesia (topical anesthetic cream and local injection of local anesthetic). There were no complications from the biopsies, but potential risks from the procedure include infection, local spread of tumor, pain, bleeding, and damage to structures in proximity to the biopsy site.

10.5 Risks/Benefits Analysis

Children and adolescents will be entered on this trial. A primary risk to patients participating in this research study is from toxicity of vandetanib, an investigational agent. In adult patients, doses of up to 300 mg daily (approximately equivalent to 150 mg/m^2/d) have been well tolerated. The pediatric starting dose on this trial is 100 mg/m^2/d, which is 40% below the adult recommended dose and the dose will be escalated 150 mg/m^2/d on cycle 3 only in patients who have demonstrated that they can tolerate the 100 mg/m^2/d dose in the initial dose escalation portion of the trial. The primary objective of this trial is to determine the activity of vandetanib in children and adolescents with hereditary MTC, and thus all patients entered will be treated with therapeutic intent and response to the therapy will be closely monitored. The potential benefits from this therapy are disease stabilization or shrinkage and a reduction in symptoms caused by the MTC, such as diarrhea. Therefore, the phase I/II component of this protocol involves greater than minimal risk to children, but presents the prospect for direct benefit to individual child-subjects (Category 2).

The biopsies being performed to obtain tumor samples for research purposes will not provide immediate direct benefit to the participants but will potentially provide value data regarding the mechanisms of resistance to vandetanib. The identification of a new somatic RET mutation in a tumor from a single patient would be significant if the mutation results in drug resistance. The four categories of research in minor subjects that can be approved by an IRB are listed below and on the OHSR website at http://ohsr.od.nih.gov/irb/Attachments/5-12_Children.htm

Category 1: Research that does not involve greater than minimal risk to children.

Category 2: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child-subject.

Category 3: Research involving greater than minimal risk and no prospect of benefit to the individual child-subject. In order to approve research in this category, an IRB must determine that the risk of the research represents no more than a minor increase over minimal risk; that the intervention or procedure presents experiences to the child-subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations; and the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for understanding or amelioration of the disorder or condition.

Category 4: Research not otherwise approvable under one of the above categories but the IRB determines that the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. In these cases the IRB will forward the research for review by the Deputy Director for Intramural Research (DDIR). If he/she agrees, the study will be forwarded to the Secretary of HHS who may approve the research after consultation with a panel of experts. The panel must determine that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and that the research will be conducted in accordance with sound ethical principles.

Category 3 allows for research that has no prospect of direct benefit to the individual child-subject if the IRB determines that the risk of the research (tumor biopsy) represents no more than a minor increase over minimal risk. The description of this category suggests that the IRB determine that the risk or "experience" of the procedure is "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations". The statement raises the concept of *relative risk* – indicating that what is acceptable (a minor increment over minimal risk) is in part determined by the subjects prior life experiences and that in a child with cancer who has undergone surgery, frequent blood draws, chemotherapy, or radiation, the proposed biopsy of a superficial tumor lesion may be commensurate with their life experiences and be considered a minor increase over minimal risk. If the IRB determines that the risk of the biopsies is greater than a minor increment over minimal risk (Category 4), the research is still approval but must be reviewed and approved by the NIH DDIR and then sent to the Secretary of DHHS for an ad hoc committee review.

A stopping rule has been included to discontinue performing biopsies for research samples if a single grade ≥3 adverse event related to the biopsy procedure occurs on this trial.

10.6 Consent and Assent Process and Documentation

Effective with amendment J, the protocol was closed to accrual. The information below regarding two consents is no longer applicable, but is being retained for historical purposes. Because not all patients enrolled on this trial will be eligible to have a biopsy to obtain a research specimen, we have written 2 consents for this trial – one of the treatment portion and one for the biopsy to obtain a tumor specimen for research purposes. We have also written an assent form for the biopsy. The treatment consent will explain the investigational nature and research objectives of this trial, the procedures (other than the biopsy) and treatment involved and the attendant risks and discomforts and benefits, and potential alternative therapies. These issues will also be carefully explained to the patient's parents or guardian (or the patient if he/she is 18 years old), and a signature will be obtained on the informed consent document prior to entry onto the study. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial and verbal assent will be obtained for participation in the treatment portion of the trial. The parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given verbal assent. Senior investigators from the Pharmacology & Experimental Therapeutics Section of the POB will lead this discussion. For those patients with a superficial tumor that can be safely biopsied, the investigator will also explain the purpose, risks, and lack of direct benefit from participating in the series of biopsies, and the optional nature of the procedure will be explained (i.e., refusing participation will not impact on their eligibility to participate in the treatment component of the trial). A signature will be obtained on a separate written consent and assent forms prior to performing the biopsies. The investigators are requesting a waiver from the IRB to allow only one parent to sign the treatment informed consent form to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. The parent who signs the consent for a minor must be a legally recognized parent or guardian. Both parents must consent to the biopsy for research purposes, unless there is only one legal guardian. If one of the parents did not accompany the child to the NIH, then consent will be obtained by phone. The biopsy consent form will be sent (FAX, e-mail or overnight shipping) to the parent who is not present prior to the telephone discussion. The child and the parent who came with the child to the NIH will be included on the call. The parent present at the NIH will sign for the absent parent if that parent agrees to the biopsy after the telephone conference call. A witness at the NIH will also be included on the call and sign the consent as a witness.

10.6.1 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We are requesting waiver of informed consent for those individuals who have been lost to follow-up or who, prior to the approval of Amendment L, have been taken off study before reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
   a. Analysis of samples and data from this study involves no additional risks to subjects.

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between a minor's enrollment and their age of majority, it is possible that more than a few subjects may be lost to follow up. A significant reduction in the number of samples analyzed could impact the quality of the research.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only plan to request a waiver of consent for those subjects who have been lost to follow-up or who, prior to the approval of Amendment L, have been taken off study before reaching the age of majority.

11 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

All data collection and reporting will be coordinated through:

Claudia Derse-Anthony, R.N.
10 Center Drive, Room 1C244
Bethesda, MD 20982
Office Phone: (240) 760-6102
Email: derseanthonycp@mail.nih.gov

This trial of the investigational agent, vandetanib, will be performed under an investigator IND held by the study PI, Dr. Brigitte Widemann. The Investigator IND is cross-filed on the IND held by the drug manufacturer, AstraZeneca. AstraZeneca will supply vandetanib for this trial. The Study PI and IND holder for this trial is responsible for reporting directly to FDA any adverse experiences that are associated with the use of vandetanib and that are both *serious* and *unexpected* (see definitions below) in an expedited fashion (see Section **11.3**) and for filing annual reports on the progress of the trial to the FDA (see Section **11.3**). The study PI will simultaneously provide AstraZeneca with a copy of all submissions (IND Safety Reports and Annual Reports) to the FDA. Expedited reporting of deaths on study and adverse events to the NCI IRB is described in Section **11.2**.

11.1 Definitions

11.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **7.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **11.2, 11.3, 11.4.**

As of Amendment J: For all patients remaining on study on long term therapy after > 2 years of treatment with vandetanib only unanticipated problems will be collected and documented.

11.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, package insert, or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

11.1.5 Serious adverse event:

Any adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.1.6 Disability:

A substantial disruption of a person's ability to conduct normal life functions.

11.1.7 LIFE-THREATENING ADVERSE DRUG EXPERIENCE:

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.1.8 PROTOCOL DEVIATION (NIH DEFINITION)

Any change, divergence, or departure from the IRB-approved research protocol.

11.1.9 NON-COMPLIANCE (NIH DEFINITION)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

11.1.10UNANTICIPATED PROBLEM

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.2 NCI-IRB and Clinical Director Reporting

11.2.1 NCI-IRB AND NCI CD EXPEDITED REPORTING OF UNANTICIPATED PROBLEMS, AND DEATHS

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations, except as noted above
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

11.2.2 NCI-IRB REQUIREMENTS FOR PI REPORTING AT CONTINUING REVIEW

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;

- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

11.2.3 NCI-IRB REPORTING OF IND SAFETY REPORTS

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

11.3 IND Sponsor Reporting Criteria

An investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a or equivalent, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

- All Grade 5 (fatal) events (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- All other serious adverse events including deaths due to progressive disease must be reported within one business day

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov and to the CCR PI and study coordinator.

11.3.1 REPORTING PREGNANCY

11.3.1.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form "Describe Event or Problem".

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

11.3.1.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months after the last dose of Vandetanib.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 3 months after the last dose should, if possible, be followed up and documented.

11.4 Safety Reporting Criteria to the Pharmaceutical Collaborators

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

The Sponsor will notify AstraZeneca (SAE Fax line, 302-886-1528 or email: AEMailboxClinicalTrialTCS@astrazeneca.com) in a **written** IND Safety Report (MedWatch, Form 3500A) of any adverse experience *associated* with the use of vandetanib that is both *serious* and *unexpected* as soon as possible and in no event later than 15 calendar days after initial receipt of the information.

The Sponsor will also notify AstraZeneca **by email:** AEMailboxClinicalTrialTCS@astrazeneca.com **)** of any *unexpected* fatal or life-threatening experience associated with the use of vandetanib as soon as possible but in no event later than 7 calendar days of initial receipt of the information. A Fax cover page should accompany the MedWatch form that is sent to AstraZeneca indicating the following:

- Vandetanib Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca reference number

The Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Any event or hospitalization that is unequivocally due to progression of disease, as determined by the PI, will not be reported as an SAE, however should be communicated to AstraZeneca.

Serious adverse events that do not require expedited reporting to the FDA will be reported to AstraZeneca quarterly in the form of a spreadsheet generated from the CCR C3D Oracle Clinical database.

For the purposes of this study any detrimental change in a patient's condition from the time written informed consent is given until 28 days after the last dose of study treatment should be considered an AE.

All dose-limiting toxicities (see Section **3.1.4**) that are possibly, probably, or definitely related to vandetanib and all serious adverse drug experiences (see Section **11.1**), including oncology related events that meet the criteria for a serious adverse drug experience, whether related to vandetanib or not, will be reported to Dr. Brigitte Widemann by telephone within 24 hours of being made aware of the event:

Brigitte Widemann, M.D.
Pediatric Oncology Branch
National Cancer Institute
10 Center Drive, MSC 1104
Bldg. 10 CRC, Rm. 1-3750
Bethesda, MD 20814-1104
Phone: 240-760-6203
E-mail: widemanb@mail.nih.gov

12 PHARMACEUTICAL INFORMATION

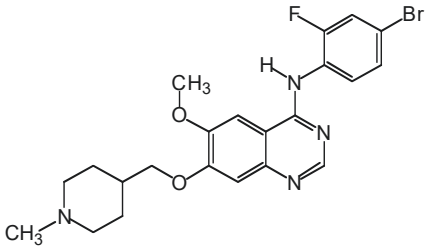
12.1 Vandetanib (IND #77570)

12.1.1 Chemical Information

Chemical name (IUPAC): N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine

Other Names: ZD6474, vandetanib, ZACTIMA

Chemical Structure:



Molecular Formula: $C_{22}H_{24}BrFN_4O_2$

Molecular Weight: 475.36

12.1.2 Mechanism of Action

Vandetanib is a potent inhibitor of the tyrosine kinase activity of kinase insert domain-containing receptor (KDR), an endothelial cell receptor for vascular endothelial growth factor (VEGF), and also possesses activity against epidermal growth factor receptor (EGFR). Vandetanib is being developed clinically for its antiangiogenic properties, but it also inhibits the enzymatic activity of RET-derived oncoproteins with an IC_{50} of 100 nM. RET inhibition is the basis for the use of vandetanib in MTC.

12.1.3 SOURCE

This trial of vandetanib for children and adolescents with MTC is being performed under an Investigator IND to be held by the protocol PI. The vandetanib for the trial was being supplied to the NCI by AstraZeneca. Effective 2016, Genzyme is supplying vandetanib for the study.

12.1.4 FORMULATION AND PREPARATION

The 50 and 100 mg tablets contain vandetanib, calcium hydrogen phosphate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate with a film coating containing methylhydroxypropylcellulose, polyethylene glycol 300 and titanium dioxide.

The oral solution will be used as needed until supplies are exhausted. The oral solution comes as 15 mL of 10 mg/mL vandetanib in 25 mL oral solution bottles. The bottles are sealed with ethylene tetrafluoroethylene (ETFE) copolymer coated chlorobutyl stoppers secured with screw on caps. Each bottle is intended for single use only.

12.1.5 STABILITY AND STORAGE

The tablets and bottles should be stored at room temperature in the original pack until use.

Documentation indicating Vandetanib was destroyed will be sent to AstraZeneca.

12.1.6 ADMINISTRATION PROCEDURES

Vandetanib is administered orally, once daily continuously. A cycle of vandetanib is defined as 28 consecutive days starting with the first day of treatment (day 1). The dose of vandetanib is determined from the patient's body surface area using the dosing nomogram (Section **3.2**). Treatment will be administered in an outpatient setting. Tablets and oral solution can be combined to accurately dose patients (e.g., a dose of 75 mg could be one 50 mg tablet plus 2.5 ml of the 10 mg/ml oral solution).

12.1.7 DISPENSING VANDETANIB

Vandetanib will be dispensed by the CC Pharmacy and documented according to CC Pharmacy SOP for drug accountability. Vandetanib will be dispensed every 6 cycles to patients who meet criteria for continued therapy according to **Appendix 5**: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy.

12.1.8 TOXICITY

Adverse events (>0.1%) by system organ class and preferred term in vandetanib emerging safety profile

Event by system organ class	Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1839)
Cardiovascular	N (%)
ECG QT prolongation	127(6.9)
Myocardial infarction	11 (0.6)

Event by system organ class	Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1839)
Angina pectoris	10 (0.5)
Nervous System	
Headache	228 (12.4)
Dysgeusia	61 (3.3)
Cerebrovascular accident	5 (0.3)
Gastrointestinal	
Diarrhea	931 (50.6)
Nausea	480 (26.1)
Vomiting	256 (13.9)
Constipation	230 (12.5)
Abdominal pain	119 (6.5)
Stomatitis	92 (5.0)
Dry mouth	85 (4.6)
Pancreatitis	3 (0.2)
Endocrine disorders	
Hypothyroidism	23 (1.3)
Blood and lymphatic system	
Thrombocytopenia	15 (0.8)
Investigations	
Weight loss	141 (7.7)
Elevated liver function tests	34-42 (1.8 – 2.3)
Metabolic and nutritional disorders	

Event by system organ class	Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1839)
Decreased appetite	253 (13.8)
Anorexia	182 (9.9)
Hypokalemia	81 (4.4)
Hypocalcemia	67 (3.6)
Dehydration	49 (2.7)
Hypomagnesemia	23 (1.3)
Hypophosphatemia	4 (0.2)
Skin/appendages	
Rash (variety of terms)[#]	46%
Renal	
Hematuria	5%
Proteinuria	1%
Respiratory	
Interstitial lung disease (including pneumonitis)[§]	5%
Pulmonary embolism	2%
Vascular	
Arterial ischemic events[¶]	2%
Venous thromboembolism	1%
General	
Asthenia	8%
Fatigue	40%
Psychiatric disorders[£]	

Event by system organ class	Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1839)
Anxiety	12%
Depression	11%
Insomnia	11%

* The values reflect the frequency of events as a reported adverse event and do not include out-of-range laboratory values or abnormal vital signs. The events of hypophosphatemia and ecchymosis occurred in phase I studies, but did not occur in study 6474IL/0003; the frequency has therefore been set as <1%. The events of interstitial lung disease/pneumonitis, pulmonary embolism and venous thromboembolism occurred in study 6474IL/0003, but these events are heavily confounded by advanced cancer, previous radiation and chemotherapy, and disease progression.

† CIOMS Council for International Organization for Medical Sciences (subset of World Health Organization).

Acneiform rash, pruritus, macular or macupapular rash (generalized or localized), localized and generalized erythema, photosensitivity reaction, sweating. On occasion (especially when given with chemotherapy) these have progressed to more serious conditions to include exfoliative dermatitis, skin desquamation, erythroderma, toxicoderma, toxic epidermal necrolysis, erythema multiforme

§ Preliminary data from the Phase III program suggest that the incidence of interstitial lung disease may be higher in Japan (≈ 10%) than in rest of world (≈ 1%).

¶ Includes myocardial infarction/stroke/peripheral arterial ischemia

£ It is possible that these events are not direct effects of vandetanib, but rather are secondary to symptoms of cancer or to other effects of vandetanib (rash, etc).

In addition to the above toxicity profile, we have also observed cramping abdominal pain associated with drug-related diarrhea and hypothyroidism manifested as an increase in TSH requiring an increase in the dose of thyroid hormone replacement.

12.2 Enalapril

12.2.1 Chemical Information

Chemical name (IUPAC): 1-[2-(1-ethoxycarbonyl-3-phenyl-propyl) aminopropanoyl] pyrrolidine-2-carboxylic acid

Other Names: Enalapril maleate

Molecular Formula: $C_{20}H_{28}N_2O_5$

Molecular Weight: 376.45

12.2.2 Mechanism of Action

Enalapril is an anti-hypertensive agent that inhibits angiotensin converting enzyme (ACE).

12.2.3 Source

Enalapril maleate tablets are available as a generic from commercial sources. Enalapril is on the NIH Pharmacy formulary.

12.2.4 Formulation and preparation

Enalapril maleate is available in 2.5, 5, and 20 mg tablets. Enalaprilat (Vasotec) is also available as an IV formulation

12.2.5 Stability and Storage

Refer to the product label.

12.2.6 Administration procedures

Enalapril tablets will be administered once daily in the morning at a dose of 2.5 mg in children weighing <50 kg and a dose of 5 mg for children who weigh ≥50 kg.

12.2.7 Toxicity

In a study of 110 children between the ages of 6 and 16 years treat with enalapril at one of 3 dose levels (low dose = 0.625 mg if <50 kg or 1.25 mg if ≥50 kg; middle dose = 2.5 mg if <50 kg or 5 mg if ≥50 kg; or high dose = 20 mg if <50 kg or 40 mg if ≥50 kg), 14 adverse events that were believed to be possibly, probably, or definitely drug related were reported in 12 patients. Dizziness was the most common adverse event, occurring in 4 patients (3 in the high-dose group and 1 in the middle-dose group). Two patients complained of headaches. The following adverse experiences were recorded in 1 patient each: chest pain, increased blood pressure, hypotension, diarrhea, cough, dyspnea, pruritis, rash, and blurred vision. In the low-, middle-, and high-dose groups, 2, 4, and 6 patients reported adverse events. A total of 3 patients reported cough, but none were discontinued from the study and only one episode was considered drug related. None of the patients experienced renal failure, angioedema, or hyperkalemia. No serious laboratory abnormalities were observed. Five adverse events that were believed to be possibly, probably, or definitely related to the study drug were reported in 3 patients. The adverse events were slight increases in BUN, creatinine, and serum uric acid and decreased hemoglobin and hematocrit. In the aggregate, there were no differences in mean pre- and post-dose hemoglobin, serum sodium, potassium, creatinine, AST, or ALT.

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14 Appendix 1: Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Patients >10 years old : use Karnofsky performance criteria

Patients ≤ 10 years old: use Lansky performance criteria

15 Appendix 2: Normal Blood Pressure Range for Children

Diastolic blood pressure levels for BOYS aged 1-18 years

	1	2	3	4
Age (years)	ULN* DBP mmHg	DBP ≤10 mmHg above ULN	10<DBP ≤25 mmHg above ULN	DBP>25 mmHg above ULN
1	58	59-68	69-83	84
2	62	63-72	73-87	88
3	66	67-76	77-91	92
4	69	70-79	80-94	95
5	71	72-81	82-96	97
6	73	74-83	84-98	99
7	74	75-84	85-99	100
8	75	76-85	86-100	101
9	77	78-87	88-102	103
10	78	79-88	89-103	104
11	79	80-89	90-104	105
12	80	81-90	91-105	106
13	82	83-92	93-107	108
14	83	84-93	94-108	109
15	83	84-93	94108	109
16	84	85-94	95-109	110
17	84	85-94	95-109	110
18	84	85-94	95-109	110

* ≤95th percentile for age and 50% height percentile

Diastolic blood pressure levels for GIRLS aged 1-18 years

	1	2	3	4
Age (years)	ULN* DBP mmHg	DBP ≤10 mmHg above ULN	10<DBP ≤25 mmHg above ULN	DBP>25 mmHg above ULN
1	57	58-67	68-82	83
2	61	62-71	72-86	87
3	65	66-75	76-90	91
4	68	69-78	79-93	94
5	71	72-81	82-96	97
6	74	75-84	85-99	100
7	76	77-86	87-101	102
8	77	78-87	88-102	103
9	79	80-89	90-104	105
10	80	81-90	91-105	106
11	80	81-90	91-105	106
12	81	82-91	92-106	107
13	82	83-92	93-107	108
14	82	83-92	93-107	108
15	83	84-93	94-108	109
16	85	86-95	96-110	111
17	87	88-97	98-112	113
18	87	88-97	98-112	113

* ≤95th percentile for age and 50% height percentile

These Charts list DBP levels within the ULN (1), within 10 mmHg above the ULN (2), within 11-25 mmHg above the ULN (3), and >25 mmHg above the ULN (4).

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.

2. Select appropriate chart for a female or male patient.
3. Using the "age" row determine if the DBP is within the ULN (1) or elevated (2, 3, 4).
4. See Section **3.1.4** for definition of dose limiting hypertension.
5. See Section **6.1** for management of vandetanib related hypertension.

16 Appendix 3: Pharmacokinetic Worksheet for Vandetanib

Patient Study ID #: _____ Weight (kg): _____ Height (cm): _____

BSA (m^2): _____ Dose level (mg/m^2): _____ Actual Dose (mg): _____

Date: _____ Time dose taken: _____ Cycle/Day: _____

Sample #	Cycle	Day	Hour	Target Date & Time	Actual Time Obtained
Pre	1	0	Pre dose #1		
1	1	2	24*		
2	2	1	24*		
3	2	28	Pre dose		
4	2	28	1		
5	2	28	2		
6	2	28	4		
7	2	28	6		
8	2	28	8		
9	2	28	10 to 12		
10	3	1	24*		

11	4§	1	24*		
12	5§	1	24*		

* Draw hr 24 sample prior to administering the next days dose.

§ Only in patients who have their dose escalated to 150 mg/m^2/d after cycle 2.

Blood samples of approximately 2 ml will be collected by venipuncture or from an indwelling venous central or peripheral line (after discarding appropriate waste) into a lithium heparin Vacutainer tube (green top). Following blood collection, the tubes should be inverted several times to ensure mixing with the anticoagulant. The tubes should be placed on crushed ice, and samples centrifuged for 10 minutes at approximately 1000 x g at room temperature within 30 minutes after collection. The plasma samples will be transferred using plastic pipettes into screw-capped polypropylene tubes labeled with vandetanib study number, the patient ID number, date, study day, collection time, and sample #. The plasma samples will be frozen within 1 hours after collection and will remain frozen at < -20°C until shipped.

Plasma samples can be stored frozen at -20°C or -70°C for a period of up to 6 months after which time they should be shipped to BASi (see details below). They should be packed securely to avoid breakage during transit and with enough dry ice to prevent thawing for at least 72 hours. A sample itinerary detailing sample numbers and identification should be sent with each shipment and BASi should be contacted by fax or email prior to each sample shipment. Samples should be shipped to avoid arrival at the laboratory during weekends and public holidays and should be sent to the following address.

Jason Plassard
Bioanalytical Systems Inc. (BASi)
2701 Kent Avenue
West Lafayette
IN 47906-1350
Phone: 765.497.5853
Fax: 765.497.5863
Email: japlassard@bioanalytical.com

17 Appendix 4: Medications Known to Prolong the QT Interval or Induce Torsades de Pointes

It has been recognized for a number of years that certain medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval or have a risk of inducing Torsade de Pointes (TdP) are listed below, divided into two groups based on their known or perceived risk of causing TdP.

Group 1. Drugs that are generally accepted as having a risk of causing Torsades de Pointes

Concomitant use of these drugs is not allowed during the study or within 2 weeks of enrollment (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of vandetanib:

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Amiodarone	Anti-arrhythmic (heart rhythm)	F>M, TdP Cases in Literature
Arsenic trioxide	Anti-cancer (leukemia)	TdP Cases in Literature
Astemizole	Antihistamine (Allergic rhinitis)	No longer available in U.S.
Bepridil	Anti-anginal (heart pain)	F>M
Chlorpromazine	Anti-psychotic/antiemetic (schizophrenia/nausea)	TdP Cases in Literature
Chloroquine	Anti-malaria (malaria infection)	
Cisapride	GI stimulant (stimulates GI motility)	Open Prescription Restricted F>M
Clarithromycin	Antibiotic (bacterial infection)	
Disopyramide	Anti-arrhythmic (heart rhythm)	F>M
Dofetilide	Anti-arrhythmic (heart rhythm)	
Domperidone	Anti-nausea (nausea)	
Droperidol	Sedative/hypnotic (anesthesia adjunct)	TdP Cases in Literature
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F>M
Halofantrine	Anti-malarial (malaria infection)	F>M

Haloperidol	Anti-psychotic (schizophrenia, agitation)	
Ibutilide	Anti-arrhythmic (heart rhythm)	F>M
Levomethadyl	Opiate agonist (narcotic dependence)	
Mesoridazine	Anti-psychotic (schizophrenia)	
Methadone	Opiate agonist (pain control/narcotic dependence)	F>M
Moxifloxacin	Antibiotic (bacterial infection)	
Pentamidine	Anti-infective (pneumocystis pneumonia)	F>M
Pimozide	Anti-psychotic (Tourette's tics)	F>M, TdP Cases in Literature
Probucol	Antilipemic (hypercholesterolemia)	No longer available in U.S.
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F>M
Sotalol	Anti-arrhythmic (heart rhythm)	F>M
Sparfloxacin	Antibiotic (bacterial infection)	
Terfenadine	Antihistamine (allergic rhinitis)	No longer available in U.S.
Thioridazine	Anti-psychotic (schizophrenia)	
Vandetanib (*Does not apply in this study)	Anti-cancer (thyroid cancer)	“Zactima®” is the proposed brand name

Group 2. Drugs that may be associated with Torsades de Pointes but lack substantial evidence of causing Torsades de Pointes.

These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary (no alternative is available). In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes.

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Alfuzocin	Alpha 1-blocker (Benign prostatic hyperplasia)	
Amantadine	Dopaminergic/Anti-viral/Antiinfective (Parkinson's disease)	
Atazanavir	Protease inhibitor (HIV)	
Azithromycin	Antibiotic (bacterial infection)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Dolasetron	Anti-nausea (nausea and vomiting)	
Dronedarone	Anti-arrhythmic (atrial fibrillation)	
Escitalopram	Anti-depressant (major depression, Anxiety disorders)	
Famotidine	H2-receptor antagonist (peptic ulcer, GERD)	
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron	Anti-nausea (nausea and vomiting)	
Indapamide	Diuretic (stimulates urine & salt loss)	TdP Cases in Literature, QT in animals
Isradipine	Anti-hypertensive (high blood pressure)	

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Lapatinib	Anti-cancer (breast cancer, metastatic)	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lithium	Anti-mania (bipolar disorder)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nilotinib	Anti-cancer (leukemia)	
Octreotide	Endocrine (acromegaly/carcinoid diarrhea)	
Ofloxacin	Antibiotic (bacterial infection)	
Ondansetron	Anti-emetic (nausea &vomiting)	
Oxytocin	Oxytocic (labor stimulation)	
Paliperidone	Antipsychotic, atypical (Schizophrenia)	
Perflutren lipid microspheres	Imaging contrast agent (echocardiography)	
Quetiapine	Anti-psychotic (schizophrenia)	
Ranolazine	Anti-anginal (chronic angina)	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	
Sertindole	Antipsychotic, atypical (anxiety, schizophrenia)	
Sunitinib	Anti-cancer (RCC, GIST)	
Tacrolimus	Immune suppressant	TdP Cases in Literature

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Tamoxifen	Anti-cancer (breast cancer)	
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

Updated 19 August 2011

18 Appendix 5: As of Amendment J: Care, Monitoring and Management of all Patients Remaining on Study on Long Term Vandetanib Therapy

Introduction: *As of Amendment J,* the requirements for the care, monitoring and management of all patients remaining on the trial on long term treatment with vandetanib will be consistent with the package insert Medication Guide recommendations. Evaluations may be performed by local medical doctor (LMD) or health care institution that will provide status updates to the NCI. At least annually, safety and response evaluations will be performed at NCI. LMDs will be requested to complete evaluations (as per attached letter) and notify the NCI study team of patient status. Source documents will be sent to the NIH and once the status is verified by the NCI study team, vandetanib will be ordered from the NIH CC Pharmacy (See Drug Ordering Below).

DRUG ADMINISTRATION:

Vandetanib is administered orally, once daily on a continuous dosing schedule. A cycle of vandetanib is defined as 28 consecutive days starting with the first day of treatment (day 1). The dose of vandetanib is determined from the patient's body surface area using the dosing nomogram below. The BSA should be recalculated at least annually (at least every 12 cycles, or with a major change in height or weight).

Vandetanib is supplied as either a 10 mg/ml suspension or 50 and 100 mg tablets. Vandetanib should be stored at room temperature in the original pack until use.

Vandetanib should be taken once daily at the same time of day, irrespective of meals. If liquid suspension or 50 mg tablets are not available, an every other day dosing schedule can be used to achieve the correct dose, but is not preferred. See package insert for directions regarding missed doses.

Supportive care and concomitant medications may be administered as clinically indicated and as according to the Vandetanib package insert (**Appendix 6**: Vandetanib Package Insert).

Dose Level [mg/m^2]							
100	BSA [m^2]	0.50-0.62	0.63-0.87	0.88-1.12	1.13-1.37	1.38-1.75	>1.75-200

	Dose [mg]	50	75	100	125	150	
100 (tablets only)	BSA [m^2] Dose [mg]	0.50-0.74 50		0.75-1.24 100		1.25-1.75 150	>1.75 200
150	BSA [m^2] Dose [mg]	0.50-0.83 100		084-1.16 150	1.17-1.50 200	1.51-1.83 250	>1.83 300

EVALUATIONS:

Quarterly evaluations should be performed by LMD or health care institution that has agreed to supply the information to the NCI (see attached letter)

1. Every 3 cycles (± 30 days)
- Monitor laboratory values: serum potassium, calcium, magnesium, and thyroid function tests, other evaluations as clinically indicated
- Obtain 12-lead electrocardiogram and evaluate QTc
- Evaluate for unanticipated problems (UPs); if clinical evaluations are performed by the LMD as clinically indicated, study staff will contact the patient via phone to ascertain UPs since last contact.

2. Every 6 cycles (± 30 days)
- Monitor laboratory values: serum potassium, calcium, magnesium, and thyroid function tests, Serum CTN and CEA, other evaluations as clinically indicated
- Obtain 12-lead electrocardiogram and evaluate QTc
- Evaluate for UPs; clinical evaluations are performed by the LMD as clinically indicated, study staff will contact the patient via phone to ascertain UPs since last contact.
- Pregnancy test prior to imaging tests in women of child-bearing potential
- Radiographic evaluation of disease

3. Every 12 cycles (**must be performed at NIH**) (± 30 days)

- History and Physical Exam with height and weight (BSA),
- Monitor laboratory values: serum potassium, calcium, magnesium, and thyroid function tests, Serum CTN and CEA, other evaluations as clinically indicated
- Obtain 12-lead electrocardiogram and evaluate QTc
- Evaluate for UPs
- Pregnancy test prior to imaging tests in women of child-bearing potential
- Radiographic evaluation of disease

DOSE MODIFICATIONS:

Study drug dose reductions will be allowed and are to be made based on discussions between the subject, the subject's LMD and the study investigator. Physicians (LMDs and investigators) should fully document the findings of these calls/visits in the subject's medical records. Dose modifications and delays may be made according to the package insert (See **Appendix 6**: Vandetanib Package Insert) and good clinical practice.

DATA COLLECTION AND DOCUMENTATION:
As of approval of Amendment J for all subjects remaining on trial and receiving long term therapy, only SAEs and response data will be captured in C3D. All evaluations and physician visits should be documented in the patient's medical record.

PHARMACY DISPENSING OF VANDETANIB:

Patients returning to NIH for follow up visits will be dispensed vandetanib from the Clinical Center (CC) Pharmacy. At the time of the NIH visit, patients should return any unused drug supplies, which will be discarded in CC Pharmacy as medical waste.

Patients who are evaluated by their LMD / health care institution will be contacted by phone by the study team and evaluated for UPs and drug accountability (doses left). Once the study team determines the patient is eligible to continue therapy (information received from LMD), a CRIS order will be submitted for a 6 cycle supply of study drug to be shipped to the patient via priority mail, when feasible. Subjects should be directed not to finish the study drug from the previous visit. Instead, when the new drug supply arrives, the patient should be directed to hold all unused drug and bottles and to bring them to the study site at the next scheduled visit. Non-compliance by the patient in returning study drug back to the site can result in the patient being terminated from the study.

Public Health Service

National Institutes of Health

Memorandum

[**Recipient Name**]
[**Title**]
[**Company Name**]
[**Street Address**]
[**City, ST ZIP Code**]

Dear Health Care Provider/ insert MD name,

Your patient __<name>____ is enrolled on a research protocol at the National Institutes of Health Pediatric Oncology Branch ("A phase I/II Trial of Vandetanib (ZD6474, ZACTIMA) in Children and Adolescents with Hereditary Medullary Thyroid Carcinoma"). Your patient has been receiving vandetanib as part of this study for over two years. As part of our research, we ask for your participation in monitoring and evaluating _<name>____ every three cycles (each cycle is 28 days), and as clinically needed.

Vandetanib is approved by the FDA for treatment of medullary thyroid carcinoma in adults, but has **not** been approved in children. We have an agreement with AstraZeneca, the drug manufacturer, to supply vandetanib on this study for your patient. As part of our agreement, the following evaluations must be performed and the results sent to the NIH:

1. Every 3 cycles, please perform the following tests:

- Monitor laboratory values: serum potassium, calcium, magnesium, and thyroid function tests; correct electrolyte abnormalities as needed. Other evaluations performed as clinically indicated.
- Obtain 12-lead electrocardiogram and evaluate QTc
- Evaluate for serious adverse events (SAEs)
- Fax or e-mail the test results and any follow up to:

  Claudia Derse-Anthony, R.N.
  10 Center Drive, Room 1C244
  Bethesda, MD 20982
  Office Phone: (240) 760-6102

Email: derseanthonycp@mail.nih.gov

2. Every 6 cycles

- Monitor laboratory values: serum potassium, calcium, magnesium, and thyroid function tests, Serum CTN and CEA; correct electrolyte abnormalities as needed. Other evaluations performed as clinically indicated.
- Obtain 12-lead electrocardiogram and evaluate QTc
- Evaluate for serious adverse events (SAEs)
- Radiographic evaluation of disease (if indicated, perform pregnancy evaluation prior to scans)
- Fax or e-mail the test results and any follow up to:

  Claudia Derse-Anthony, R.N.
  10 Center Drive, Room 1C244
  Bethesda, MD 20982
  Office Phone: (240) 760-6102

Email: derseanthonycp@mail.nih.govIf your patient experiences any toxicities related to the vandetanib that meet the criteria in the attached package insert for dose modification, please contact Dr. Brigitte Widemann at 240-760-6203 or widemanb@mail.nih.gov to discuss any dose modifications to the vandetanib daily dose.

We will have your patient return annually to the NIH for evaluation. After we receive your evaluation results, we will contact your patient and if the patient does not have unacceptable toxicity or progression of disease, we will have a 6- cycle supply of vandetanib shipped directly to your patient.

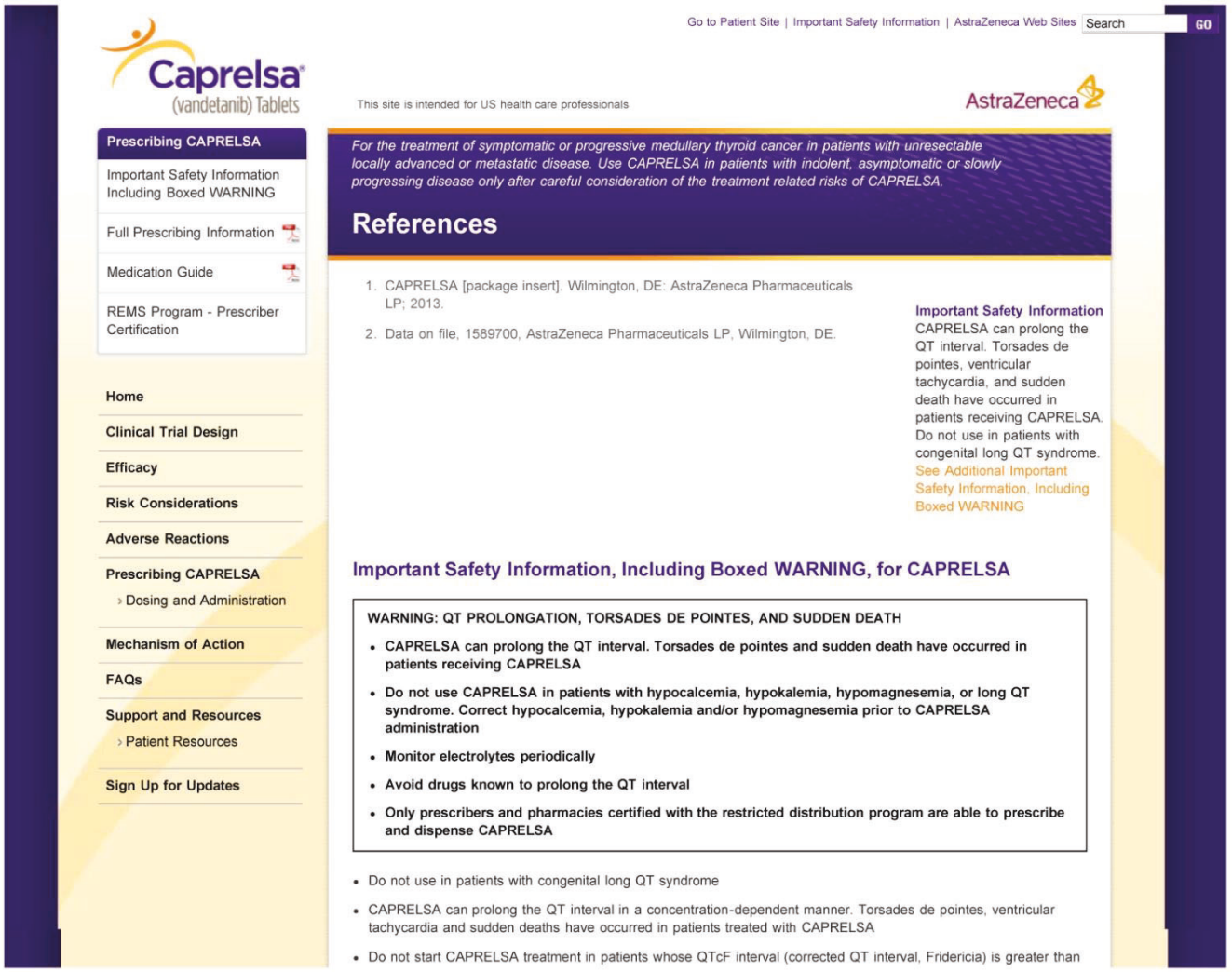
We thank you for your participation. If you have any questions at all, please do not hesitate to contact Dr. Brigitte Widemann at 240-760-6203 or widemanb@mail.nih.gov.

Best regards,

Brigitte Widemann, M.D.
Head, Pharmacology and Experimental Therapeutics Section, POB, CCR, NCI, NIH
10 Center Drive, MSC 1104
Bldg. 10 CRC, Rm. 1-3750
Bethesda, MD 20814-1104

19 Appendix 6: Vandetanib Package Insert

References | CAPRELSA® (vandetanib) Tablets



http://www.caprelsa.com/hcp/references.aspx[10/8/13 1:35:36 PM]

450 ms or who have a history of Torsades de pointes, bradyarrhythmias, or uncompensated heart failure. CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction

- Stop CAPRELSA in patients who develop a QTcF greater than 500 ms until QTcF returns to less than 450 ms. Dosing of CAPRELSA can then be resumed at a reduced dose
- Because of the risk of QT prolongation, obtain an ECG and serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) at baseline, 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter. Following any dose reduction or interruptions greater than 2 weeks, conduct QT assessments as described above
- Severe skin reactions (including Stevens-Johnson syndrome), some leading to death, have occurred in patients treated with CAPRELSA. Consider permanent discontinuation of CAPRELSA for severe skin reactions
- Photosensitivity reactions can occur during CAPRELSA treatment and up to 4 months after treatment discontinuation
- Interstitial lung disease (ILD) or pneumonitis, including fatalities, has occurred in patients treated with CAPRELSA. Interrupt CAPRELSA for acute or worsening pulmonary symptoms and discontinue CAPRELSA if ILD is confirmed
- Ischemic cerebrovascular events, including fatalities, occurred in patients treated with CAPRELSA. The safety of resumption of CAPRELSA therapy after resolution of an ischemic cerebrovascular event has not been studied. Discontinue CAPRELSA in patients who experience a severe ischemic cerebrovascular event
- Serious hemorrhagic events, including fatalities, occurred in patients treated with CAPRELSA. Do not administer CAPRELSA to patients with a recent history of hemoptysis of 1/2 teaspoon of red blood. Discontinue CAPRELSA in patients with severe hemorrhage
- Heart failure, including fatalities, occurred in patients treated with CAPRELSA. Monitor for signs and symptoms of heart failure. Consider discontinuation of CAPRELSA in patients with heart failure. Heart failure may not be reversible upon stopping CAPRELSA
- Diarrhea of Grade 3 or greater severity occurred in patients receiving CAPRELSA. If diarrhea occurs, carefully monitor serum electrolytes and ECGs to enable early detection of QT prolongation resulting from dehydration. Interrupt CAPRELSA for severe diarrhea and upon improvement resume CAPRELSA at a reduced dose
- Increased dosing of thyroid replacement therapy was required in 49% of CAPRELSA-treated patients. Obtain TSH at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter. If signs or symptoms of hypothyroidism occur, examine thyroid hormone levels and adjust thyroid replacement therapy accordingly
- Hypertension, including hypertensive crisis, has occurred in patients treated with CAPRELSA. Monitor all patients for hypertension. Dose reduction or interruption for hypertension may be necessary. If hypertension cannot be controlled, do not resume CAPRELSA
- Reversible posterior leukoencephalopathy syndrome (RPLS) has occurred in patients treated with CAPRELSA. Consider this syndrome in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. In clinical studies, three of four patients who developed RPLS while taking CAPRELSA also had hypertension. Discontinue CAPRELSA treatment in patients with RPLS
- Avoid administration of CAPRELSA with anti-arrhythmic drugs and other drugs that may prolong the QT interval
- Vandetanib exposure is increased in patients with impaired renal function. Reduce the starting dose to 200 mg in patients with moderate to severe renal impairment and monitor the QT interval closely. There is no information available for patients with end-stage renal disease requiring dialysis
- CAPRELSA is not recommended for patients with moderate and severe hepatic impairment, as safety and efficacy have not been established
- CAPRELSA can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should

avoid pregnancy and be advised that they must use effective contraception during CAPRELSA treatment and for at least 4 months following the last dose of CAPRELSA

- The most commonly reported adverse drug reactions (>20%) seen with CAPRELSA and with a between arm difference of 5% are diarrhea/colitis (57%), rash (53%), acneiform dermatitis (35%), hypertension (33%), nausea (33%), headache (26%), upper respiratory tract infections (23%), decreased appetite (21%), and abdominal pain (21%)
- **CAPRELSA REMS Program**: Because of the risks of QT prolongation, Torsades de pointes, and sudden death, CAPRELSA is available only through the CAPRELSA REMS Program. Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense CAPRELSA. To learn about the specific REMS requirements and to enroll in the CAPRELSA REMS Program, call **1-800-236-9933 or visit** www.caprelsarems.com

INDICATIONS AND USAGE

CAPRELSA is a kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Use CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment related risks of CAPRELSA.

Please see full Prescribing Information for CAPRELSA, including Boxed WARNING.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.