Abbreviated Title: PhII Vandetanib in GIST
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Title: Phase II Trial of Vandetanib (ZD6474, Caprelsa®) in Children and Adults with Wild-Type Gastrointestinal Stromal Tumors

NCI Principal Investigator: Brigitte Widemann, M.D., POB, NCI[A-E]
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

NIH Associate Investigators:
Alice Chen, M.D., DCT, NCI[A-E]
John Glod, M.D., Ph.D., POB, CCR, NCI [A-E]
Melissa Amaya, R.N., OCD, CCR, NCI [A,B,C,E]
Trish Whitcomb, R.N., OCD, CCR, NCI [A,B,C,E]
Andrea Baldwin, MS, CRNP, POB, CCR, NCI [A-E]
Joanne Derdak, CRNP, POB, CCR, NCI [A-E]
Seth Steinberg, Ph.D., BDMS, CCR, NCI[F]
Markku Miettinen, M.D., LP, CCR, NCI [E]
Eva Dombi, POB, CCR, NCI[E-F]
Lori Wiener, Ph.D., POB, CCR, NCI [A,B,E]
Paul Meltzer, MD, Ph.D., CGB, CCR, NCI [E]
J Keith Killian, MD, Ph.D., CGB, CCR, NCI[E]
Peter Choyke, M.D., MIP, CCR, NCI [A,B,E]
Marston Linehan, M.D., UOB, CCR, NCI[E]
Ramaprasad Srinivasan, M.D., Ph.D., UOB, CCR, NCI[E]
Choh L. Yeung, B.S., POB, CCR, NCI[E]
Paul Jarosinski, PharmD., CC, NIH [A,B]

Non-NIH Associate Investigators: Claudia Derse-Anthony, R.N., Contractor, Leidos Biomedical Research, Inc.[A,B,C,E]

Referral Contact/Study Coordinator: Claudia Derse-Anthony
phone: 240-760-6102
e-mail: claudia.derse-anthony@nih.gov

For each person listed above, roles are identified with the appropriate letter:

A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
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
G. Some/all research activities performed outside NIH

Investigational Agents:

Drug Name:	Vandetanib (Caprelsa®)
IND Number:	77570
Sponsor:	Center for Cancer Research (CCR)
Manufacturer:	AstraZeneca

COMMERCIAL AGENTS: NONE

PRÉCIS

Background:

- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract, resistant to cytotoxic chemotherapy and radiation therapy. KIT and PDGFRA mutations have been identified as tumor initiating events in 85% of adult patients with GIST, but 85% of GISTs in pediatric patients lack KIT and PDGFRA mutations (wild-type) and imatinib is not as effective in eliciting objective responses.
- Recent work in the Pediatric and Wild-Type (wt) GIST Clinic at the NCI led to the identification of succinate dehydrogenase (SDH) germline mutations in 12% patients with wt-GIST (6/34). SDH protein expression evaluated using immunohistochemistry (IHC) was markedly decreased or absent in 18/18 patients with pediatric wt-GIST. Thus, the majority of wt-GIST are SDH-deficient. Vandetanib (CAPRELSA®; ZD6474; AstraZeneca) is an oral small molecule antineoplastic drug that inhibits VEGFR2, EGFR, and RET-dependent signaling. Preliminary preclinical data demonstrate marked growth inhibition of SDH-mutant/deficient renal cell carcinoma cell lines when treated with vandetanib.

Objective(s):

- Primary: To assess the clinical activity (radiographic response RECIST v1.1) of vandetanib in children and adults with wt-GIST using RECIST (v1.1).

Eligibility:

- Adults and children with measurable localized or metastatic wt-GIST confirmed in a CLIA laboratory will be eligible for trial participation. Patients must have measurable disease by RECISTv1.1 and adequate organ function.

Design:

- This phase II trial will determine whether daily oral vandetanib is active in patients with wt- GIST. Vandetanib activity will be assessed primarily by radiographic response of measurable disease using RECISTv1.1.
- Vandetanib will be administered orally once daily continuously in the absence of toxicity or disease progression, using a 28-day cycle.
- Patients will be carefully monitored for toxicity and response. A small, optimal two-stage phase II design with a target response rate of 25% will be used. Nine evaluable patients will be enrolled initially. If 1 or more of the first 9 have a response, then accrual would continue until a total of 24 patients have enrolled. If there are 3 or more responses in 24 (12.5% or more) patients, then this would be sufficiently interesting activity to warrant further study.

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1.1.1 PRIMARY OBJECTIVE:

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1.1.2 SECONDARY OBJECTIVE(S):

1.1.2.1 To assess the safety and toxicity of vandetanib in children and adults with wt- GIST at established doses.

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1.1.2.3 To evaluate the utility of FDG-PET in disease characterization and response evaluation of patients ≥ 15 years of age with wt- GIST.

1.1.2.4 To assess SDH expression using immunohistochemistry (IHC) in archival tumor tissue and to analyze the relationship of SDH expression and response.

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1.1.2.8 To describe health-related quality of life (as measured by PROMIS Patient Outcome Measures) and patient-reported symptoms (as measured by the Distress and Symptom Checklist) in patients ≥ 8 years of age at the start of therapy, at first staging (3 months) and at off treatment evaluation.

1.2 BACKGROUND AND RATIONALE:

1.2.1 GASTROINTESTINAL STROMAL TUMOR (GIST)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. KIT and PDGFRA mutations are present in 85% of these tumors. However, GISTs that affect most pediatric patients are wild-type for KIT and PDGFRA, and, not surprisingly, imatinib and sunitinib are not as effective as they are in "classic" GIST. **The exact number of pediatric GIST in the US is not known**. St. Jude Children's Research Hospital reported that GIST accounted for 2.5% of all pediatric non-rhabdomyosarcoma soft tissue sarcoma (STS). Memorial Sloan Kettering Cancer Center estimated that 1 to 2% of all GIST seen at the institution is diagnosed in pediatric patients. According to the most recent population estimates of the SEER population database, the expected incidence of pediatric GIST in the United States in patients 18 years or younger would be approximately 0.08 per million (1)

The cell of origin is thought to be the interstitial cells of Cajal (ICC)(2), which function as "pacemakers" of bowel peristalsis. The initial therapeutic approach is usually surgical resection. GISTs are resistant to cytotoxic chemotherapy and radiation therapy and can present both local

recurrence and distant metastases, including lung and bone(3). KIT (CD117) and PDGFRA mutations have been identified as tumor initiating events in 85 % of adult patients with GIST. Inhibition of these kinases with imatinib mesylate has become the mainstay of GIST therapy and prolongs survival in this patient population. Patients with classic GIST may also respond to nilotinib, sunitinib or sorafenib (3).

In contrast to GISTs in adult patients, 85 % of GISTs occurring in pediatric patients lack KIT and PDGFRA mutations (wild-type) and not surprisingly imatinib and sunitinib are not as effective in eliciting objective responses in this group of patients as they are in classic KIT-mutant GIST (4). Therefore, there is no specific targeted therapy available for patients with wt-GIST. Wild-type GISTs are slow growing tumors that can have an indolent course. However, metastatic disease can cause significant morbidity. There is currently no standard medical approach for patients with wt-GIST. Although some patients respond to imatinib or sunitinib, those responses are often short-lived and subtler than the ones observed in patients with "classic" GIST harboring KIT or PDGFRA mutations (5). Other notable differences between WT and standard adult GIST are the preponderance of gastric location in WT GIST, the marked predilection for females, and frequent multifocal presentation in WT GIST. Given the multifocal and recurrent nature of the disease, experts advocate against radical surgical approaches with the aim of achieving local control from the oncological perspective, favoring the use of surgery when indicated to control tumor-related symptoms such as gastrointestinal bleeding(1, 5).

1.2.1.1 Succinate Dehydrogenase (SDH) Germline Mutations

Since germline inactivation of SDHB, C and D have been described in Carney-Stratakis syndrome, a condition in which affected individuals are predisposed to paragangliomas and WT-GIST, we recently evaluated pediatric and adult patients seen in the Pediatric and Wild-Type GIST Clinic at the NCI. We have found succinate dehydrogenase (SDH) germline mutations in 12 % patients with wt-GIST (6/34). More recent data suggests that the rate of germline mutation in WT GIST patients may be significantly higher. SDH (as SDH-ubiquinone complex II) is a component of the Krebs cycle and the respiratory chain. It is composed of four different subunits (A, B, C and D). SDH protein expression evaluated using immunohistochemistry (IHC) was markedly decreased or absent in 18/18 patients with wt-GIST (0-5% tumor cells reactive by standard IHC scores (4). Transmission of Carney-Stratakis Syndrome is autosomal dominant with incomplete penetrance. Demonstration of loss of the non-mutated copy of the SDH gene is consistent with a tumor suppressor gene model (6, 7).

The lack of cell lines or animal models to evaluate preclinical activity is a major obstacle in the development of therapies aimed towards wt-GIST. However, SDH deficient renal cell carcinomas have also been described and cell lines are available for study and have led to important observations that may have relevance to SDH deficient GISTs.

The best surrogate model currently available is a SDH deficient cell line from a patient with renal cell carcinoma (RCC). Due to the loss of SDH, this cell line has accumulation of succinate and subsequent increase in hypoxia inducible factor 1 alpha (HIF1a)(8, 9).

Mutations in another Kreb's cycle member, fumarate hydratase (FH) lead to hereditary leiomyomatosis renal cell carcinoma (HLRCC)(10-12). Work utilizing a cell line derived from a patient with FH deficiency has shown increased concentration of fumarate, inhibition of HIF prolyl hydroxylase and subsequent stabilization and accumulation of HIF1a (13, 14). The latter promotes the transcription of genes that are relevant for growth and survival of cancer cells. Additional

pathways that are implicated in HIF1a activation include EGFR and VEGFR2, amongst others. Agents that target these receptors, such as erlotinib and bevacizumab and more recently vandetanib, show promising results in vitro. This has resulted in a phase II trial at the NCI evaluating erlotinib and bevacizumab in subjects with HLRCC(15). Moreover, an aggressive phenotype of renal cell carcinoma associated with SDH germline mutations has recently been described (16).

In general, SDHB is ubiquitously expressed in all cells, whether normal or neoplastic, and this typically manifests as granular cytoplasmic staining. A small group of SDH-deficient tumor is now recognized to exist, and these include approximately 30% of extra-adrenal paragangliomas, 7.5% gastric GISTs, and rare renal carcinomas (< 1%).

These SDH-deficient tumors, among them SDH-deficient GISTs are detected by immunohistochemical loss of SDHB in the tumor cells. These tumor cells do not show granular cytoplasmic staining, although they may show weak diffuse cytoplasmic staining. The loss is assessed comparing tumor cells with non-neoplastic elements, such as endothelial cells, smooth muscle, epithelia, and lymphoid cells, which may appear as streaks and nests of high expression around the neoplastic elements. SDH-deficient GISTs demonstrate a strong contrast between immunostaining of non-neoplastic elements and tumor cells.

Parallel examination of SDHA could be helpful for assessment of the SDHB-status. Approximately 30% of SDH-deficient GISTs lack SDHA-immunoreactivity, similar to lack of SDHB. However, in the rest of cases observation of strong retained SDHA-immunoreactivity helps in comparison with SDHB-loss.

The SDHB-loss is generally all or none phenomenon, and percentage of loss is not used as a definitional measure. In very rare cases, the SDHB-status may remain ambiguous by immunohistochemistry. It is theoretically possible that some genetic alternations allow partial retention of expression.

SDHB-loss is accompanied with mutations in the SDH-complex (A, B, C or D subunits) in approximately 50% of cases, so that SDHB-loss is by no means synonymous with SDH-mutations. The other half of SDHB-negative tumors may have other deficiencies, especially epigenetic silencing. Based on available information, it is best to consider loss of SDHB-expression the umbrella feature that identifies SDH-deficient GISTs.

The results of the SDH staining are reported as negative (loss), positive, or indeterminate (the latter to be reserved for rare cases that cannot be interpreted in a straightforward manner).

SDH deficiency causes accumulation of succinate. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-prolyl hydroxylase, as widely shown in different tumor models by several investigators (9).

As noted above, most wt-GIST are SDH deficient, and many of them harbor mutations in the various genes encoding for SDH subunits (4). Although the rarity of the tumors and the lack of preclinical models does not allow us to directly show this in SDH-deficient GIST, evidence of HIF activation in GISTs has been published (17).

Examples of SDH staining as they pertain to SDH-deficient GISTs are highlighted in **Figure 1** and **Figure 2** below:

Figure 1

Representative H&E stains (Left) and corresponding SDHB IHC (Right) in KIT mutant (Top), SDH mutant (Middle), and WT GIST (Bottom), highlighting strong SDHB immunoexpression in the KIT mutant GIST and absence of SDHB expression in the SDH mutant GIST and the WT GIST. (B) Summary of SDHB IHC scores in pediatric (n = 14) and adult (n = 12) WT GIST, KIT mutant GIST (n = 15), and NF-1–associated GIST (n = 5). **Janeway K A et al. PNAS 2011;108:314-318**

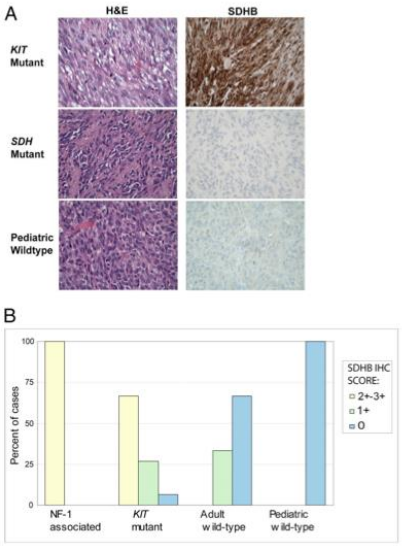
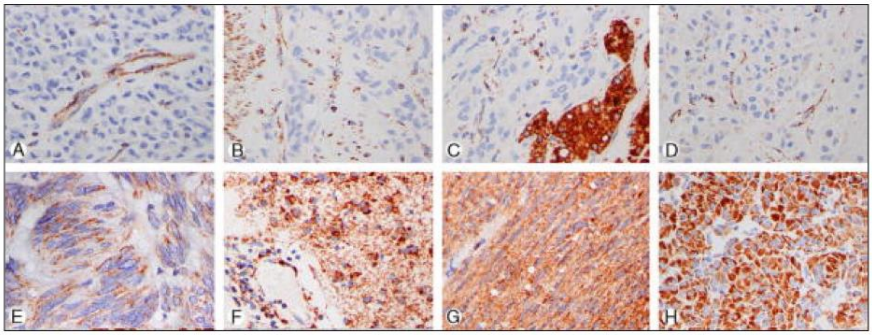


Figure 2

Examples of immunohistochemically SDHB-negative and SDHB-positive gastric GISTs. A to D, SDHB-negative cases with staining limited to blood vessels, lymphohistiocytic infiltration, smooth muscle, or hepatocytes. C, Liver metastasis with positive hepatocytes. Note a faint cytoplasmic blush in panel D. E to H, SDHB-positive spindle cell and epithelioid GISTs with granular cytoplasmic staining of various intensities in tumor cells and vessel walls. (Miettinen et al, American Journal of Surgical Pathology. 35(11): 1712-1721, November 2011).



Unfortunately, no wt-GIST cell lines are available for preclinical studies. However, a SDH-deficient renal cell carcinoma has been generated.

UOK269 cell line was established at the Urologic Oncology Branch (CCR, NCI) and is derived from the tumor of a 36 year old woman with a metastatic kidney cancer due to a germline mutation in the gene encoding for SDH-B. The effect of vandetanib on the viability of SDHB-deficient tumor cells was assessed. With an IC50 of about 50nM in two different clones of UOK269 (labeled as "UOK269EV") and no significant cytotoxicity on two molecularly restored cell lines

(UOK269WT1 and UOK269WT2; i.e. cell lines in which SDH-B function had been restored), vandetanib might have a therapeutic value in targeting SDHB-deficient tumors.

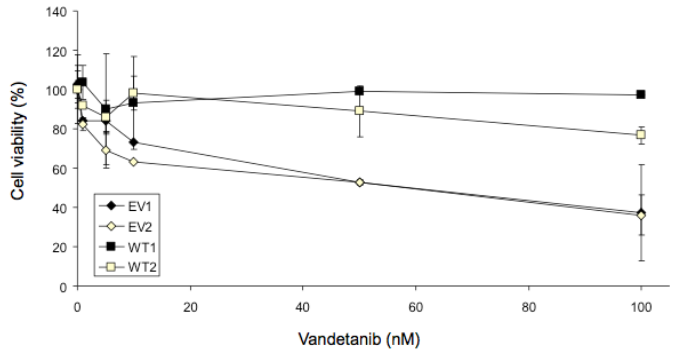


Figure 3. Vandetanib is cytotoxic to SDHB-deficient tumor cells in vitro. Viability of SDHB-deficient cells (UOK269EV1, UOK269EV2) and of molecularly restored cells (UOK269WT1, UOK269WT2) was assessed after 24hrs treatment with vandetanib.

A phase II trial of vandetanib in patients with clear cell renal cell carcinoma (RCC) at the NCI was recently terminated due to low accrual rate. (18). Clinical evaluation of vandetanib in patients with VHL-related RCC is ongoing. Combined VEGF/EGFR blockade has significant activity in metastatic papillary renal cell carcinoma (RCC) associated with hereditary leiomiomatosis renal cell carcinoma syndrome (HLRCC). HLRCC is a familial condition resulting from germline alterations in fumarate hydratase (FH) and is characterized by an aggressive form of RCC. FH-/- kidney cancer cell lines rely on aerobic glycolysis for energy production.

Eighteen patients with metastatic RCC received systemic therapy from 1998-2008; 7/18 patients received combined VEGF/EGFR blockade (bevacizumab 10 mg/Kg IV every 2 weeks plus either erlotinib [N=6] or gefitinib [N=1] PO daily). The remaining patients received a variety of agents. Patients receiving VEGF/EGFR blockade had an overall response rate of 71% (5/7), including one patient with a complete response (14%) and 4 patients with a partial response (57%). Responses were durable, with one patient remaining disease free 74 months after treatment initiation. Combined VEGF/EGFR blockade resulted in significantly improved overall survival compared to other regimens (median 51 months vs. 14 months; P=0.0012). A phase II trial combining bevacizumab plus erlotinib (NCT 01130519) is currently ongoing. (Srinivasan et al, Can J of Urol, 2012, 19:5 6510-6511)

Preliminary preclinical data demonstrate marked growth inhibition of SDH-mutant/deficient RCC cell lines when treated with vandetanib. This effect may be due to VHL-independent HIFs stabilization since accumulation of fumarate and succinate inhibit prolyl hydroxylases therefore causing increased expression of HIF downstream targets such us EGFR and VEGF(9). Thus, there might be a role for vandetanib in the treatment of GIST. Interestingly, SDH polymorphisms have been described in patients with MTC (19), a disease for which vandetanib has demonstrated activity.

1.2.2 VANDETANIB

Vandetanib (CAPRELSA®; ZD6474; AstraZeneca, Macclesfield, UK) is a small molecule receptor tyrosine kinase (RTK) inhibitor, given as a once-daily oral drug that inhibits VEGFR2- and EGFR- dependent signaling. It is also potent inhibitor of RET, which is frequently activated by mutation or rearrangement in medullary thyroid carcinoma (MTC)(20). Vandetanib has activity in MTC in adults at doses ranging from 100 to 300 mg once daily on a continuous dosing schedule and in children receiving 100 mg/m^2/dose (equivalent to 180 mg fixed dose based on a BSA of 1.8 m^2), or 150 mg/m^2/dose (equivalent to 270 mg fixed dose). At this time the active dose in children with GIST is unknown; we therefore will use the highest tolerable dose evaluated in children: 150 mg/m^2/dose for children 13 years and older, and 100 mg/m^2/dose with option for dose escalation to 150 mg/m2/dose for children less than 13 years old. In children and adults with MTC vandetanib has been well tolerated with prolonged administration with diarrhea, rash, and TSH elevation being the most frequent toxicities. Tumor shrinkage is occurring slowly over multiple treatment cycles(20, 21).

Vandetanib is currently undergoing evaluation in a phase II trial for patients with clear cell renal cell carcinoma at the NCI based on concomitant VEGFR and EGFR inhibition(18). Preliminary data from this trial demonstrate marked growth inhibition of SDH-mutant/deficient RCC when treated with vandetanib. Thus, there might be a role for vandetanib in the treatment of wt-GIST and SDH mutations.

1.2.2.1 Prior Clinical Experience in Pediatric Patients

A phase I/II trial (NCI# 07-C-0189) of vandetanib for children and adolescents with hereditary MTC is ongoing with the primary objectives to define a safe dose, the drug's toxicity profile, pharmacokinetics, and the activity of vandetanib in children (ages 5 to 18 years of age) with hereditary medullary thyroid cancer (MTC). The starting dose level was 100 mg/m$^{2/}$ dose once daily on a continuous dosing schedule with the option for a dose increase to 150 mg/m^2. A single stage design targeting a response rate of 30% using RECIST is used for the phase II component; a response rate of ≥5/21 is consistent with up to 40% response rate. 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 (22).

Thus, the previous experience in patients with SDH-mutant/deficient clear cell renal carcinoma and the recent observation that the vast majority of patients with wt-GIST lack SDH expression

supports the role of vandetanib in the treatment of wt-GIST. In addition, our ongoing study of vandetanib in MTC has demonstrated the safety of vandetanib in children and adolescents at doses proposed in this clinical trial.

1.2.3 HEALTH-RELATED QUALITY OF LIFE AND PATIENT-REPORTED SYMPTOMS

The psychosocial stresses associated with living and coping with cancer have been well described for adults, as well as in children and their family members. Most of these studies have been conducted in heterogeneous cohorts that are not disease specific. Gastrointestinal stromal tumors (GISTs) are rare in children and adults, and limited data are available on how the disease impacts the quality of life of those living with this disease. What is known about the common physical symptoms associated with these tumors raises concern pertaining to psychosocial outcomes. These include anemia and symptoms related to bleeding, mild epigastric discomfort, and for some, chronic to acute abdominal pain (23, 24). The importance of abdominal pain and discomfort in the HRQOL of children, adolescents or adults with GIST has not been examined.

Numerous articles have shown that children with chronic abdominal pain were more likely to have increased health service use, restrictions in daily living, and suffer from functional impairments in adulthood (25-27). The association of abdominal pain with mental health outcomes has been studied in adolescents, with patients living with irritable bowel disease (28), and with those living with juvenile rheumatoid arthritis (JRA). Adolescents with frequent abdominal pain have been found to be at increased risk for depressive symptoms, social isolation, and for more somatic complaints compared with healthy children, including headache, stomachache, backache, and morning fatigue, possibly as a response to stress (27, 29). Frequent abdominal pain in children and adolescents has also been associated with social and peer withdrawal, school absenteeism, and a poor quality of life for patients and their parents (30).

Psychiatric morbidities are also common in adults who suffer from frequent abdominal pain. Adult patients with chronic pain have higher rates of suicidal ideation(31). Suicidal ideation has been shown to increase with symptom severity and perceived pain interference in adults with irritable bowel syndrome (32).

While it is understood that frequent abdominal pain places individuals at increased risk for depressive symptoms, social isolation, and missing work/school, the role that pain plays in the quality of life of individuals living with GIST is not known. In order to learn about the psychosocial concerns of both children and adults living with GIST, 60 adults and 18 pediatric patients who participated in the NIH GIST clinic completed a self-administered psychosocial screening tool. Frequently reported chronic pain and significant anxiety was found in the pediatric and adult cohorts, regardless of time since diagnosis. Furthermore, those who endorsed pain were significantly more likely to be prescribed psychotropic medication (33).

Particularly in a Phase I/II trial, it is important for toxicities and their outcomes to be specified and measured so that appropriate interventions can be designed to prevent or diminish their effects. Known toxicities associated with Vandetanib include insomnia (11%) and depression (4.7%) and anxiety (4.4%) (As described in Investigator's Brochure, Vandetanib, 17 October 2012).

Therefore, using patient reported outcome measures (PROMIS) and a symptom checklist, we will extend the knowledge gained from our initial psychosocial screening study and assess psychosocial symptoms associated with GIST and Vandetanib treatment, including physical function, anxiety, depressive symptoms, fatigue, pain interference, and global health.

As parents tend to underrate their child's health related quality of life, they may be poor judges of which consequences of illness matter most to their children and may be influenced by their own response to their child's illness (34). Therefore, for the pediatric patients over the age of 8, we will include patient and parent-proxy reports of patients' quality of life and symptom experience during each clinic visit.

1.2.3.1 Study Measures

Distress and Symptom Checklist (**Appendix 15**): The Distress Thermometer (35) is a brief screening tool endorsed by the National Comprehensive Cancer Network (NCCN) to assess for distress in adult cancer patients. The Distress Thermometer (DT) is a visual-analog scale similar to those used to assess pain. The DT obtains an overall distress score based on the visual analog scale, and includes a "problem list", or checklist, where patients can identify specific physical and emotional symptoms and practical and family concerns that can cause their distress. The DT has been widely validated in adult (≥18 years old) cancer patients, and has been recognized as a good alternative to many of the longer measures commonly used to screen for distress in cancer patients (36-38).

Whereas the Distress Thermometer was originally written for adult cancer patients, early evaluation of the scale shows validity for children and adolescents with cancer (39). In an ongoing study at the NIH with 163 pediatric patients ages 7-21 undergoing treatment for cancer, NF1, HIV or a primary immune deficiency and their caregivers, an adapted DT has shown convergent validity when compared with standardized measures and with specific items on the symptom checklist. It has also shown reasonable concordance with parent and provider ratings (40). For this study, we will use the DT as a distress and symptom rating tool. It is quick to administer and a low burden to patients and their caregivers (40). In order to assess how the severity of symptoms may change over the course of treatment, the participant will rank each endorsed symptom (from the problem checklist) on a scale of 1-5, with "1" indicating a little problem and "5" indicating maximum amount of difficulty. Two versions of the tool will be available for this protocol, one for parents of children (caregiver) to complete about their child, and a second for patients ages 8 and older to complete on their own. Whereas most patient reported outcome measures utilize a 7–day recall period (including the PROMIS measures), the adapted DT utilizes a 30 day recall period which allows problems or symptoms that might have been present in the past month, but not necessarily the past week to be documented. The distress and symptom rating scales will take approximately 5 minutes to complete.

Patient-Reported Outcomes Measurement Information System (PROMIS) is a health related quality of life measurement tool that was developed by NIH to standardize patient-reported outcomes for national use by research clinicians. Two versions of PROMIS are available to researchers: computer-adaptive tests (CATs) and short forms. The short forms are brief, static instruments that have demonstrated similar reliability to the longer, dynamic CATs, which provide precise measures for studying populations with widely varied responses and longitudinal self-report data (41). Each short form includes 4 to 8 items, measures reported health outcomes in the past 7 days on a Likert type scale, and takes approximately 5 minutes to complete. PROMIS instruments, measuring a broad range of health domains, have been validated for adults (≥18) with a variety of health conditions (42).

Early evaluation of PROMIS pediatric instruments indicates validity for children ages 8 to 17 (43). Six pediatric PROMIS instruments and six parallel Parent Proxy PROMIS instruments (See

Appendix 13) are available to assess five quality of life health domains (physical function, pain interference, fatigue, emotional health, and social health) and are intended for use with both healthy and chronically ill pediatric populations. This protocol will utilize pediatric PROMIS short forms and the Parent Proxy short forms to assess symptoms that can be associated with GIST. These include physical function, anxiety, depressive symptoms, fatigue, pain interference, and peer relationships.

Assessments of Health Related Quality of Life will be administered at the start of therapy, at first staging (3 months) and at off treatment evaluation. The PROMIS Patient Outcome Measures (6) and patient-reported symptom severity (Distress and Symptom Checklist) will provide us with essential information regarding how symptoms may change over the course of treatment, and will also provide a more in-depth assessment of the known toxicities associated with Vandetanib (insomnia, anxiety and depression) in this patient population.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

Subjects must meet the following criteria to be eligible to participate:

2.1.1 INCLUSION CRITERIA

2.1.1.1 Age: ≥ 3 years of age and BSA ≥ 0.5 m^2

2.1.1.2 Diagnosis

2.1.1.2.1 Histologically or cytologically confirmed GIST by the Laboratory of Pathology, NCI.

2.1.1.2.2 Absence of Kit and PDGFRA mutation confirmed in a CLIA certified laboratory.

2.1.1.3 Participants must have measurable disease as defined in RECIST (v1.1) as the presence of at least one lesion, not previously irradiated, that can be accurately measured at baseline ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

2.1.1.4 Prior therapy:

There are no standard chemotherapy regimens known to be effective for wt-GIST. Therefore, previously untreated participants are eligible if their tumor(s) are measurable.

2.1.1.4.1 Participants must be at least 4 weeks from prior surgical procedures and surgical incisions must be healed.

2.1.1.4.2 Participants must have had their last fraction of external beam radiation therapy at least 4 weeks prior to enrollment.

2.1.1.4.3 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.

2.1.1.4.4 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.

2.1.1.4.5 Participants must have recovered from the acute toxic effects of prior therapy to a grade 1 (CTCAE v.4.0) level prior to enrollment (does not apply to alopecia).

2.1.1.5 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**)

2.1.1.6 Patients must have normal organ and marrow function as defined below:

2.1.1.6.1 *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.

2.1.1.6.2 *Coagulation*: PT and PTT must not be more than 1.5 x ULN within 72 hours prior to enrollment. PT and PTT should drawn by venipuncture, rather than from a central venous catheter when feasible.

2.1.1.6.3 *Hepatic Function*: Bilirubin must not be more than 1.5 x ULN (does not apply to patients with Gilbert's Disease) and the AST and ALT must not be more than 2.5 x ULN within 72 hours prior to enrollment, or greater than 5.0 X ULN if in the Investigator's judgment it is related to liver metastases. AST and ALT may be up to 5 x ULN within 72 hours prior to enrollment in participants with hepatic metastases.

2.1.1.6.4 *Renal Function*: Participants must have an age-adjusted normal serum creatinine (see Table) or a creatinine clearance of at least 50 ml/min/1.73 m^2.

Age (years)	Maximum Serum Creatinine (mg/dL)	
	Male	Female
3 to 5	.42	.42
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

2.1.1.7 Hypertension:

Participants should have normal blood pressure according to age. Participants 18 years of age and younger should have a blood pressure ≤ 95th percentile for age, height and gender, and should not be receiving medication for treatment of hypertension. Preexisting hypertension in adults should be controlled (either with pharmacological or non-pharmacological methods) at the time of enrollment (See **Appendix 2**).

2.1.1.8 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 3months after the last dose. [Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign the informed consent form [ICF]) and for 3 months after the last dose of vandetanib to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.

Male patients must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign the ICF) and for 3 months after the last dose of vandetanib to prevent pregnancy in a partner.]

Negative pregnancy test for women of childbearing potential.

2.1.1.9 Informed Consent:

Participants who are ≥ 18 years of age or Legally Authorized Representative (LAR) of participants who are younger than 18 years must sign an informed consent for the POB Screening Protocol (01-C-0157: Eligibility Screening and Tissue Procurement for the National Cancer Institute (NCI), Pediatric Oncology Branch (POB) Clinical Research Protocols) prior to participating in studies required to determine eligibility for this trial. After confirmation of eligibility, participants who are ≥ 18 years of age or LAR 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, prior to the conduct of any study procedures.

2.1.2 EXCLUSION CRITERIA

Presence of any of the following will prevent a subject from participation:

2.1.2.1 Pregnant or breastfeeding females because vandetanib may be harmful to the developing fetus or nursing infant and has been found to be embryotoxic, fetotoxic and teratogenic in rats.

2.1.2.2 Subjects who are receiving any other investigational agents or who have received an investigational agent within 28 days prior to enrollment (does not apply to participation in survival follow up), or who have previous exposure to vandetanib.

2.1.2.3 Abnormal Electrolyte Levels: Participants with a serum potassium less than 3.5 mmol/L or a serum ionized calcium or magnesium below the lower limits of normal (or above CTCAE Grade 1 upper limit). Correction of these electrolyte abnormalities with supplements is allowed. (Serum calcium above the CTCAE Grade 1 upper limit. In cases where the serum calcium is below the normal range, the calcium adjusted for

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

2.1.2.4 Presence of hypertension: Diastolic blood pressure above the 95% for age in children (**Appendix 2**) and > 160 mmHg systolic or >100 mmHg diastolic in adults on at least 2 of 3 measurements with an appropriate-size cuff who are unable to achieve blood pressure control with optimal anti-hypertensive therapy. Patients who are treated with antihypertensive medications with good response are eligible.

2.1.2.5 History of Cardiac Disorder:

2.1.2.5.1 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).

2.1.2.5.2 History of any significant cardiac event (e.g. myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease ≥ 2 within 12 weeks before starting treatment (See **Appendix 3**), or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.

2.1.2.5.3 Participants with a history of congenitally prolonged QTc, a first-degree relative with unexplained sudden death under 40 years of age, or a measured QTcB (Bazett's correction) longer than 480 msec on ECG. ECGs should be performed after correction of electrolyte abnormalities. Participants with a prolonged QTcB should have a repeat ECG twice, at least 24 hours apart, and the average of the 3 QTcBs should not exceed 480 msec. History of QT prolongation associated with other medications that required discontinuation of that medication.

2.1.2.5.4 Participants receiving a medication that has a known risk of QTc prolongation or is associated with Torsades de Pointes (**Appendix 7**) or any prohibited medications, concomitantly or within 14 days (28 days for levomethadyl) of enrollment.

2.1.2.6 Other clinically severe or uncontrolled systemic illness or any concurrent condition that in the view of the principal investigator could compromise the participant's ability to tolerate vandetanib or could compromise study procedures or endpoints, including interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease.

2.1.2.7 Unstable brain metastases or spinal cord compression that requires treatment, unless the treatment ended at least 4 weeks before starting treatment and the condition has been stable without steroid treatment for at least 10 days.

2.1.2.8 Major surgery (includes surgery that carries significant risk of blood loss, extended periods of general anesthesia, or requires at least an overnight hospital admission) within 28 days before starting treatment.

2.1.2.9 Involvement in the planning and/or conduct of the study.

2.1.2.10 Previous enrollment in the present study.

2.1.2.11 Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix and adequately treated basal cell or squamous cell carcinoma of the skin.

2.1.3 RECRUITMENT STRATEGIES

The NCI, POB has established a collaborative wt-GIST Clinic with the goals to increase the understanding of the molecular biology and natural history of wt-GIST and to develop effective therapies for these tumors. The following recruitment strategies will also be employed to elicit potential candidates for this trial:

1. Listed on www.clinical trials.gov;
2. Listed in PDQ;
3. In addition, patients from POB clinic who are eligible for participation will be offered participation in this study

Prior to distribution of any recruitment materials, such materials will be submitted to the NCI IRB for review.

2.2 SCREENING EVALUATION

The following evaluations should be performed within 7 days of enrollment unless otherwise specified.

2.2.1 CLINICAL EVALUATION

2.2.1.1 History and Physical Examination:

A complete history and physical examination, (including vital signs with blood pressure, pulse, respiratory rate and temperature), and a description of signs and symptoms is required.

- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:
    1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
    2) Average the systolic blood pressure from the 2nd and 3rd measurements.
    3) Average the diastolic blood pressure from the 2nd and 3rd measurements.
    4) The baseline BP is the average of the systolic over the average of the diastolic measurements.

2.2.1.2 Height, Weight and Body Surface Area:

For patients < 18 years old, 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:

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

2.2.1.3 Performance status determination

2.2.2 LABORATORY STUDIES

The following laboratory studies will be performed within 7 days of enrollment.

2.2.2.1 β-HCG pregnancy test on all women of child-bearing potential

2.2.2.2 Hematology: complete blood count, differential, platelet count, PT, PTT.

2.2.2.3 Chemistries: BUN, creatinine, electrolytes (sodium, potassium, chloride, CO2), calcium, magnesium, phosphorus, uric acid, total protein, and albumin LDH, and glucose.

2.2.2.4 Hepatic Panel: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, (Direct Bilirubin, if total bilirubin is elevated)

2.2.3 ELECTROCARDIOGRAM (ECG)

ECG with Calculation of QTc using Bazett's correction (QTc = $QT/RR^{0.5}$). Electrocardiograms will be evaluated by suitably qualified personnel for the presence of QTcB prolongation or other abnormalities, in particular, any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia.

2.2.4 SCANS AND X-RAYS

Scans must be performed within 4 weeks of enrollment.

2.2.4.1 CT scan of chest, abdomen and pelvis;

2.2.4.2 MRI of abdomen and pelvis.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. Prior to registration, contact the research nurse, Claudia Derse-Anthony (240-760-6102) or claudia.derse-anthony@nih.gov. A registration Eligibility Checklist from the web site (http:// http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 TREATMENT ASSIGNMENT AND RANDOMIZATION/STRATIFICATION PROCEDURES

Cohorts

Number	Name	Description
1	Adults and children (patients older than 3 years) with wild type GIST	Adults and children with measurable localized or metastatic wt-GIST.
2	Parents of children with wild type GIST enrolled on this clinical trial	Consenting parents of children with wild type GIST who are enrolled on this clinical trial

Arms

Number	Name	Description
1	Experimental therapy	Patients younger than 18 years of age at the time of enrollment receive vandetanib at a dose of 100 mg/m2/dose for cycles 1, 2 and 3; and 150 mg/m^2/dose for Cycles ≥4
2	Experimental therapy	Patients 18 years and older at the time of enrollment receive vandetanib at a fixed dose of 200 mg once daily (QD) for cycles 1, 2, and 3; and 300 mg/dose for Cycles ≥4.
3	Companion parental questionaire	Consenting parents will be asked to complete the parent version of the QOL questionnaires.

Randomization and Arm Assignments

- There is no Randomization in this study.
- Patients in cohort 1 will be directly assigned to arm 1 or 2, depending on their age at the time of enrollment.
- Patients in cohort 2 will be directly assigned to arm 3.

2.5 BASELINE EVALUATION

2.5.1 LABORATORY EVALUATIONS

Pre-treatment laboratory tests should be repeated if necessary within 7 days prior to starting therapy.

2.5.1.1 Hematology: complete blood count, differential, platelet count, PT, PTT.

2.5.1.2 Chemistries: BUN, creatinine, electrolytes (sodium, potassium, chloride, CO_2), calcium, magnesium, phosphorus, uric acid, total protein, and albumin, LDH, and glucose.

2.5.1.3 Hepatic Panel: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, (Direct Bilirubin, if total bilirubin is elevated)

2.5.1.4 Thyroid Function Tests: TSH, Free T4

2.5.1.5 Urinalysis

2.5.2 SCANS

2.5.2.1 MRI of abdomen and pelvis. In the exceptional event of extraabdominal disease, MRI will be obtained of the relevant anatomic sites at discretion of the PI.

2.5.2.2 CT (CT of chest, abdomen and pelvis) with contrast since MRI might overlook small lesions.

2.5.2.3 FDG-PET (torso)

2.5.2.4 Lower extremity scanogram (x-ray to evaluate bone, leg length and growth plates) in all participants less than 18 years old.

Patients with fused growth plates will not undergo additional evaluations. Patients with open growth plate(s) will also undergo a unilateral knee MRI to determine the growth plate volume at baseline to evaluate for bony toxicity according to **Appendix 11**. Scanogram (when clinically indicated) and growth plate knee MRIs are performed in patients with open growth plates to monitor for potential bony toxicity of VEGFR inhibitors.

2.5.3 HEALTH-RELATED QUALITY OF LIFE AND PATIENT-REPORTED SYMPTOMS

English or Spanish speaking parents and/or caregivers of enrolled minor subjects and research subjects 8 years of age and older will be undergo psychosocial evaluation. The following evaluations will be administered prior to starting the study agent.

2.5.3.1 Distress and Symptom Checklist: The Distress Thermometer will be administered to patients (8 years of age and older) and parents (on behalf of their child), and will be completed prior to initiating Vandetanib therapy (**Appendix 15**).

2.5.3.2 PROMIS Patient Outcome Measures: The PROMIS short forms will be administered to patients (8 years of age and older) and parents of minor participants who will be completing the form as an evaluation of their child's functioning, and will be completed prior to initiating Vandetanib therapy (**Appendix 12**).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 STUDY OVERVIEW

This phase II trial is designed to determine whether daily oral vandetanib is active (clinical activity as per RECIST v1.1) in patients with wt- GIST. Vandetanib activity will be primarily assessed by response of measurable disease using RECIST (v1.1), but change in tumor-related symptoms from baseline will also be monitored to assess drug effect.

Adults and children (patients older than 3 years) with measurable wt-GIST will be eligible for trial participation. Patients must have measurable disease by RECIST and adequate organ function.

Vandetanib will be administered orally once a day on a continuous dosing schedule. One treatment cycle equals 28 days.

- Patients 18 years and older at the time of enrollment on this study will start vandetanib at a fixed dose of 200 mg once daily (QD) for cycles 1, 2, and 3.

- Patients younger than 18 years of age at the time of enrollment will start vandetanib at a dose of 100 mg/m^2/dose for cycles 1, 2 and 3. (see table below).

Table 1: Vandetanib Dose Escalation Schedule	
Age at Enrollment	**Daily Dose of Vandetanib**
Patients < 18 years of age	Cycles 1-3: 100 mg/m^2/dose
	If vandetanib is well tolerated : Cycles ≥4: 150 mg/m^2/dose
Patients ≥ 18 years of age	Cycles 1-3: 200 mg/dose
	If vandetanib is well tolerated : Cycles ≥4: 300 mg/dose

A one time intra patient dose escalation to 150 mg/m^2/dose for patients < 18 years, and to 300 mg/dose for patients ≥ 18 years will be allowed after completion of 3 cycles, provided provided the intra patient dose escalation criteria below are fulfilled:

Vandetanib is well tolerated at the starting dose defined as:

- All vandetanib related toxicities during cycle 1-3 are less than grade 2, except grade 2 toxicities that are:
  - isolated laboratory abnormalities and not present at repeat blood draw, or
  - short lived and resolve within approximately 72 hours with or without supportive therapy.

There is no limit on the number of cycles that a patient may receive. The dosing nomogram provided in section **3.2** will be used to determine the vandatenib dose for pediatric patients.

Patients will be carefully monitored for toxicity during treatment with vandetanib including history, physical exam, blood pressure monitoring, and laboratory evaluations and assessment of concomitant medications. Section **3.1.2** details treatment limiting toxicities. Restaging studies (RECIST) with appropriate imaging studies and evaluation of disease-related symptoms will be performed after every 3 cycles x 4 (prior to cycles 1 (baseline), 4, 7, 10, and 13) and then after every 6 cycles. In addition the health related quality of life (PROMIS) and patient-reported symptoms (Distress and Symptom Checklist) will be administered to consenting patients 8 years of age and older at the first restaging visit (3 months) and at the time the patient is taken off-treatment (**Appendices 10** and **11**). Consenting parents will be asked to complete the parent version of these assessments. Vandetanib will be discontinued if there is evidence of tumor progression clinically or by RECIST or there is intolerable toxicity that is not alleviated by dose reduction.

Secondary endpoints on this trial include progression-free survival and evaluation of safety and toxicity of vandetanib. In addition to evaluation of response by RECIST, FDG-PET at baseline and on treatment with vandetanib will be used to evaluate response. The PET scan at baseline and restaging (prior to cycle 4) will be considered standard of care. Additional PET scans will be performed as clinically indicated. The option of one additional PET scan day 3 to day 6 after starting treatment with vandetanib will be offered to consenting patients aged 15 years or older who do not require sedation to undergo PET scans. The purpose of this research PET scan will be to evaluate the utility of FDG-PET to predict response early in the treatment of wt- GIST.

3.1.2 TREATMENT LIMITING TOXICITY

Although not a phase 1 study, toxicity will be evaluated and treatment limited by the toxicities defined below. This study will utilize the CTEP Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for toxicity and Adverse Event grading and reporting. An adverse event must be judged to be possibly, probably, or definitely related to vandetanib to be a treatment limiting toxicity. Vandetanib will be held for treatment-limiting toxicities and re-started after resolution of toxicity at reduced dose as described in section **3.3**.

Treatment-limiting toxicity is defined as:

- **Hematologic Toxicity (H-T)**:
  - 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 treatment -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 treatment-limiting toxicity. However, grade 3 or 4 hemolysis is a treatment -limiting toxicity if it is judged to be vandetanib-related.
  - Grade 3 or 4 leucopenia or lymphopenia will not be considered treatment -limiting toxicities.
- **Non-Hematologic Toxicity (NH-T)**: NH-T is any grade 3 or higher non-hematologic toxicity, with the exception of:
  - Grade 3 nausea or vomiting that is controlled by symptomatic treatment with anti-emetics (see **Appendix 7** 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 14 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 treatment-limiting toxicity.

- Grade 3 electrolyte abnormalities that are asymptomatic and correctable to grade 2 or less within 48 hours.

- **Hypertension (HTN)**:
  - **Pediatric Participants:**

    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**). Pediatric 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 (See **Appendix 2** and **Appendix 3**). Treatment-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.4) hypertension.

  - **Adult Participants:**

    Appendix 4 will be used for the grading of vandetanib-associated hypertension in adults, for immediate and intermediate-term management, and for the determination of vandetanib modification. Hypertension in adult patients is defined as a systolic blood pressure > 150 mmHg or a diastolic pressure > 90 mm HG despite optimal medical management, for patients ≥18 years of age, and may include hypertension-related symptoms as reported by patient (e.g., headache), or other relevant changes associated with development of hypertension (e.g., ECG abnormalities) (See **Appendix 4** and **Appendix 5**).

    Treatment-limiting hypertension is defined as:

    - A diastolic BP on at least 2 of 3 measurements that is more than 90 mm Hg or systolic BP that is more than 150 mm Hg, that does not return to within the normal range after 14 days despite maximum medical therapy.
    - Grade ≥4 (CTCAE v.4) hypertension.

- **QTc Prolongation**:

  Any clinically significant abnormal findings or QTcB prolongations will be recorded as AEs.

  Participants with QTc prolongation should have serum electrolytes (including potassium, calcium and magnesium) measured. If serum electrolytes are outside the normal range, the abnormality should be corrected before determining whether a patient has treatment - limiting QTc prolongation.

  In addition to scheduled ECG, additional ECGs should also be performed in the event of QTcB prolongation, both during and post the prolongation period.

- During the QTcB prolongation period: For a single QTcB value of >500 ms, vandetanib must be withheld. Electrocardiograms will be followed at least once per week (done at the same day each week) along with electrolytes, until QTcB falls ≤480 ms. Vandetanib treatment may be resumed at a permanently lower dose after the QTcB returns to ≤480 ms.

Treatment-limiting QTc prolongation is defined as a single QTc value ≥500 msec. Post the QTcB prolongation period: If vandetanib (at the reduced dose) is restarted after the QTcB prolongation has resolved, ECGs and electrolytes (including potassium, calcium and magnesium) must be obtained at 3, 8, and 12 weeks following the start of the lower dose. Serum potassium levels should be maintained at 4 mEq/L or higher, and serum magnesium and serum calcium should be kept within normal range to reduce the risk of QT prolongation. ECG and electrolyte monitoring can then resume every 3 weeks at the normal visit schedule for the patient.

If a patient is on 100 mg vandetanib dose and has QTcB >500 ms, vandetanib 100 mg may be given every other day.

3.1.3 Criteria for Starting Subsequent Treatment Cycles

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

3.1.3.1 Disease Status: The patient does not have radiographic or clinical evidence of progressive disease (see section **6.3**) 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 pain, nausea or vomiting, or stable for cycles that are not proceeded by restaging.

3.1.3.2 Toxicity: Patients who experienced treatment-limiting toxicity in the previous cycle should have the dose modified (see Section **3.3**).

3.1.3.3 Criteria for discontinuation of protocol treatment or off-study criteria (see Section **3.6**) have not been met.

There is no limit on the number of cycles that a patient may receive.

Criteria for intra patient dose escalation after completion of cycles 1, 2, and 3 of vandetanib are provided in Section **3.1.1**.

3.2 Drug Administration

Vandetanib (50 mg and 100 mg tablets) 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). Patients 18 years or older at the time of enrollment on this study will receive a fixed initial dose of 200 mg orally daily, which can be increased to 300 mg orally daily after 3 cycles, if tolerated (Section **3.1.1**). The dose of vandetanib in children and adolescents is determined from the patient's body surface area using the dosing nomogram below. The BSA should be recalculated at the time of restaging evaluations, and the dose should be adjusted if necessary based on the nomogram. Treatment will be administered in an outpatient setting.

Dose Level (mg/m²)						
100	BSA (m²)	0.50-0.74	0.75-1.24	1.25-1.74	≥ 1.75	
	Dose(mg)	50	100	150	200	
150	BSA (m²)	0.50-0.83	0.84-1.16	1.17-1.49	1.5-1.83	≥1.84
	Dose mg)	100	150	200	250	300

Vandetanib is supplied as 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**). Vandetanib absorption is not affected by a meal, so it need not be administered in the fasted state.

The tablet should be swallowed whole or dissolved in water (see Section **11.1.5**). If a patient misses a scheduled dose of vandetanib and less than 12 hours have passed since the scheduled dosing time, the dose should be taken immediately. If more than 12 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 30 minutes of taking vandetanib, then another dose can be administered. The dose may only be repeated once. If more than 30 minutes has passed from the time of oral dosing then no additional doses should be given.

Patients or their guardians will keep a diary (**Appendix 8**) to document the intake of each dose, concomitant medications, and any toxicity. The diary should be evaluated at each clinic visit. Self-Administered Study Drugs: Policy, procedures and forms are available on the CCR Intranet for internal monitoring for study drug compliance and accountability at the CCR Intranet site: *http://home.ccr.cancer.gov/intra/clin_ops/policies/*.

3.3 DOSE MODIFICATIONS

3.3.1 GENERAL GUIDANCE

Vandetanib should be held for any treatment-limiting toxicity (see Section **3.1.2**). For treatment limiting toxicities 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 reaches the grade defined in treatment limiting (e.g., after the second ANC <1,000/µL).

If vandetanib-related treatment-limiting toxicity resolves to grade ≤1 or baseline in ≤6 consecutive weeks of drug free period, vandetanib may be restarted at a reduced dose.

If the vandetanib-related treatment-limiting toxicity does not resolve to grade ≤1 or baseline in ≤ 6 consecutive weeks 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.

If a patient happens to miss 6 weeks of dosing for non-toxic events, if monitoring is initiated as described in Section **3.5.1**, the patient may initiate re-dosing.

Refer to Section **4** Concomitant Medications/Measures for management of specific toxicities.

Refer to Section **3.1.1** for intra patient dose escalations.

3.3.2 DOSE MODIFICATION RULES

The NCI Principal Investigator should be consulted for all dose reductions. Dose modifications will be conducted according to the following guide:

- Patients who experience a treatment-limiting toxicity (Section **3.1.2**) that is possibly, probably, or definitely related to vandetanib should have a dose reduction of their vandetanib dose after recovery from toxicity (to a CTCAE Grade 1 or baseline) (Section **3.2** Drug Administration) following the table below for the remainder of the current course and for the subsequent cycles of treatment.

Vandetanib starting dose (mg/dose) once daily	**Dose reduction (mg/dose)**	**Dose reduction (%)**
50	50 mg 5 times/week (e.g. Monday, Tuesday, Thursday, Friday, Sunday)	29%
100	100 mg 5 times/week (e.g. Monday, Tuesday, Thursday, Friday, Sunday)	29%
150	100 daily	33%
200	200 mg 5 times/week (e.g. Monday, Tuesday, Thursday, Friday, Sunday)	29%
250	200 mg 6 times/week (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday)	40%
300	200 daily	33%

- Patients who experience treatment-limiting toxicity after a dose reduction can have one additional dose reduction. All dose reductions should be approximately 30% of the administered dose. The protocol PI or lead AI should confirm the dose reduction.

- Patients who have a dose reduction for a non-life-threatening treatment-limiting toxicity (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 treatment-limiting toxicity at the higher dose level must not have exceeded grade 1 at the reduced dose level in order to re-escalate the dose.

3.3.3 Dose Modification to Promote Wound Healing

- Subjects 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. Subjects should have restaging studies performed prior to restarting the treatment.
- Subjects 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 Questionnaires

As described in Section 1.2.3, the pediatric PROMIS instruments and the Distress Rating Tool will be administered to all consenting patients who speak English or Spanish with parallel Parent Proxy instruments administered to parents of patients ages 8-17. These instruments will be administered at baseline, at the first re-staging visit (3 months) and at the time a patient is taken off treatment (See **Appendix 12**, **Appendix** 13, and **Appendix** 14). Since the measures have not been validated in other languages, participation in this portion of the study will be limited to subjects who speak either English or Spanish.

3.5 Study Calendar

*See **Appendix 9**.*

Subjects will be monitored according to study requirements, including history and physical examinations, blood pressure monitoring, performance status, urinalysis and routine laboratory tests (blood counts and chemistries), as per **Appendix 9**.

3.5.1 Monitoring During Drug Therapy

3.5.1.1 Blood Pressure

Blood pressure should be monitored and recorded prior to the first dose of vandetanib, and with physical exams during cycle 1. In addition, blood pressure should be monitored and recorded cycle 1, day 14, prior to each cycle on cycles 2, 3, 4, then every 3 cycles (prior to cycle 7, 10, 13, etc). See **Appendix 2** for management of elevated diastolic BP.

3.5.1.2 Physical Examination:

A physical examination should be performed at Day 14 during cycle 1. Then prior to cycle 2, 3 and 4; then every 3 cycles prior to cycle 7, 10, 13, etc.

3.5.1.3 Height, Weight, and BSA:

Recorded prior to the first treatment and then on each restaging cycle (cycle 4, 7, 10, 13, and then every 6 cycles, i.e. prior to cycle 19, 25, 31, etc.).

3.5.1.4 Performance Status:

Record prior to the first treatment cycle and then on each restaging cycle (cycle 4, 7, 10, 13, and then every 6 cycles, i.e. prior to cycle 19, 25, 31, etc.) (**Appendix 1**).

3.5.1.5 Laboratory

3.5.1.5.1 Hematology:

Complete blood count, differential and platelet count on Day 14 (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 cycle 2, cycle 3 and cycle 4; then every 3 cycles prior to cycle 7, 10, 13, etc.

3.5.1.5.2 Chemistries:

On Day 14: BUN, creatinine, electrolytes (including (sodium, potassium, chloride, CO2),), LDH, AST, ALT, alkaline phosphatase, bilirubin (total and direct if total is elevated), calcium, magnesium, phosphorus, glucose, and uric acid during cycle 1, and then prior to cycle 2, 3, and 4. Then every 3 cycles prior to cycle 7, 10, 13, etc.

3.5.1.5.3 Thyroid Stimulating Hormone:

Prior to cycle 2, 3 and 4; then every 3 cycles i.e. cycle 7, 10, 13, etc. If TSH is abnormal, T4 will be evaluated.

3.5.1.5.4 Urinalysis:

Prior to cycle 2, 3 and 4; then every 3 cycles i.e. cycle 7, 10, 13, etc.

3.5.1.5.5 Serum/Urine Pregnancy Test:

Prior to the first cycle in females with child bearing potential, and then prior to cycles 4, 7, 10, 13, then every 6 cycles (19, 25, 31, etc).

3.5.1.6 ECG with Calculation of QTc

Prior to cycle 1, 2, 3 and 4; then every 3 cycles i.e. cycle 7, 10, 13, etc. See Section 4 for management of QTc prolongation.

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

3.5.1.7 A unilateral knee MRI:

Will be performed in all patients with open growth plates on lower extremity scanogram (See **Appendix 11**). Repeat knee MRIs will be performed every 3 cycles x 4 (prior to cycle 4, 7, 10, 13) and then every 6 cycles (prior to cycle 19, 25, 31, etc) until growth plates are fused.

3.5.1.8 Patient Diary

Patients will document daily reactions/symptoms and concomitant meds on the patient diary until cycle 13 (See **Appendix 10**). The patient diary will be reviewed at each clinic

visit. After cycle 13, patients will be asked to document their reactions/symptoms and concomitant medications on the log (See **Appendix 10**).

3.5.2 RESPONSE EVALUATION

Restaging studies (RECISTv1.1) with appropriate imaging studies and evaluation of disease-related symptoms will be performed at NIH after every 3 cycles x 4 (prior to cycle 4, 7, 10, 13) and then every 6 cycles (prior to cycle 19, 25, 31, etc).

- MRI of the abdomen/pelvis will be performed for restaging purposes. In the exceptional case of extraabdominal disease, the anatomical sites to be evaluated by MRI will be at discretion of the PI.
- FDG-PET will be performed prior to cycle 4, and then as clinically indicated. Patients ≥ 15 years of age will be given the option to consent for an early research FDG-PET (on day 3 to day 6) after initiation of therapy during cycle 1.
- CT of the chest will be performed for restaging purposes and if clinically indicated.

3.5.3 POST TREATMENT FOLLOW UP

3.5.3.1 Off-Treatment Evaluation

Patients who have been taken off treatment for any of the criteria in Section 3.6.1, will be monitored until resolution of toxicity, as clinically indicated, and efforts will be made to return to NIH at least once for Off-Treatment evaluation (at least 60 days after the last dose of vandetanib) for:

- Physical Examination with vital signs
- Laboratory Evaluation: CBC and differential, chemistry and liver function tests
- Toxicity assessment

Patients unable to return to NIH will be contacted by a member of the research team approximately 60 days after the last dose of investigational drug for an evaluation of toxicity.

Patients or the local medical provider will be contacted at least annually to obtain current status on patients who have completed the off treatment evaluation, until one of the off study criteria (Section 3.6.2) are met.

3.6 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 60 days following the last dose of study therapy.

3.6.1 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY

Subjects will be removed from study therapy and followed until off-study criteria are met for any one of the following:

- Unacceptable toxicity (treatment limiting toxicity after two dose reductions, or treatment-limiting toxicity does not resolve to grade ≤1 or baseline in ≤ 6 weeks of a drug free period). Patients who are removed from therapy for unacceptable toxicity will continue to undergo disease evaluations as per **Appendix 9** until they develop progressive disease.

- 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 7** is started.
- Progressive disease; clinical or radiographic evidence of progressive disease will discontinue vandetanib (see Section 6.3). If possible, tumor progression should be documented radiographically.
- Participant requests to be withdrawn from active therapy
- Positive pregnancy test
- Investigator discretion, which may include
  - 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, 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.
- Death

3.6.2 OFF-STUDY CRITERIA

Subjects will be removed from study for any of the following criteria:

- Patient or guardian withdrawal of consent. Reasons must be noted on the patient's medical record.
- Lost to follow up after three documented attempts to contact patient/family/local referring physician.
- Death

Note: Minors are to be retained on the study at least until they reach the age of majority if possible and can be consented for the future use of their specimens and data. if you are enrolling minors, you need to leave them on study until they reach age 18 and can be consented for the future use of their specimens and data. If this consent is not obtained, samples and data may not be used in this study or future research unless the reason for removal is loss to follow up (for which a waiver has been requested in section **10.6.1**) or death (as these samples would no longer fall under human subjects' protections).

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

3.6.3 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 web site (http:// 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.

4 CONCOMITANT MEDICATIONS/MEASURES

At screening, all prior anti-cancer therapy and administration of all other concomitant medication in use on the day of enrollment (signature of the ICF) will be recorded. All concomitant medications that the patient has been taking since the time of the last visit, medications the patient started between visits and all new medications will be recorded at each visit until the completion of the final analysis. If a patient discontinues vandetanib before the final analysis, all medications including any medications started within the 60 days after the last dose of vandetanib, will be recorded at the appropriate discontinuation visit and the 60-day follow-up visit.

4.1 PROHIBITED MEDICATION

Patients are not eligible to enter the study if they have taken any of the medication specified in the exclusion criteria

4.1.1 TREATMENT FOR CANCER

Prior to starting treatment (according to Section 2.1) and while the patient remains on study treatment, patients must not be given any concurrent cancer therapy, including cytotoxic agents, radiotherapy, biological response modifiers (including cytokines), hormonal therapy (used specifically for cancer treatment), or any other investigational agents.

4.1.2 CYP3A4 INDUCER

The administration of vandetanib with strong CYP3A4 inducers (those that induce ≥ 80% decrease in AUC) should be avoided (per Caprelsa package insert), including avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort. A potent CYP3A4 inhibitor has been shown to have little effects on the exposure to vandetanib and therefore, these agents can be co-administered with vandetanib when indicated.

4.1.3 MEDICATIONS KNOWN TO PROLONG QT INTERVAL AND/OR INDUCE TORSADES DE POINTES

Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see **Appendix 7**) are not allowed within the 2 weeks prior to starting treatment or during study (at least 4 weeks prior for levomethadyl). These drugs should also be avoided for at least 4 weeks following discontinuation of study treatment.

4.1.4 RESTRICTED MEDICATIONS

All medications prohibited in this study as indicated in **Appendix 7** must have been withdrawn at least 2 weeks prior to registration, and should be avoided for at least 4 weeks following discontinuation of study treatment.

Co-administration of drugs that in some reports might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes (see **Appendix 7**) should be avoided within the 2 weeks prior to registration, and during the study. However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored including regular checks of QTcB and electrolytes. The electrolytes should be maintained within the normal range using supplements if necessary.

Warfarin is allowed in therapeutic and low-doses and these patients should be monitored regularly for changes in their International Normalized Ratio, at the discretion of the Investigator.

Appropriate clinical and/or laboratory monitoring is recommended for patients receiving concomitant metformin and vandetanib, and such patients may require a lower dose of metformin. Appropriate clinical and/or laboratory monitoring is recommended for patients receiving concomitant digoxin and vandetanib, and such patients may require a lower dose of digoxin.

4.1.5 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.

4.2 HTN MANAGEMENT ALGORITHM

See **Appendix 2** and **Appendix 4** for monitoring and management of hypertension in children and adults.

4.3 MANAGEMENT OF QTC PROLONGATION

See Section 3.1.2, Treatment Limiting Toxicity.

4.4 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. Rashes should be graded as soon as possible according to the CTCAE cutaneous toxicity criteria.
- 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, immediate 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.
- It is strongly recommended that all patients use sun-protective measures while receiving vandetanib and for 3-4 weeks after discontinuing vandetanib to reduce the risk of developing skin rash or minimize the severity of skin rash.

4.5 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.

4.5.1 NAUSEA OR VOMITING

Nausea, vomiting, or both may be controlled with antiemetic therapy. The use of somatostatin or a somatostatin analogue is allowed to control diarrhea. 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 30 minutes of taking the dose.

4.5.2 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. No dose modifications will be made for Grade 1 or 2 diarrhea, however, electrolyte supplementation with regular laboratory monitoring should be used when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation. Any electrolyte imbalance must be promptly corrected since hypokalaemia and hypomagnesaemia are potential risk factors for drug-induced arrhythmia.

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.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 EVALUATION OF ARCHIVAL TUMOR TISSUE

Archival tumor tissue will be evaluated for SDH expression in consenting patients if tissue is available. Additional Immunohistochemistry (IHC) studies will be performed at the Laboratory of Pathology, CCR, NCI as they become available.

5.1.2 TUMOR TISSUE (OPTIONAL)

Patients who require surgery will be invited to participate in (prior to participation, patient must have consented to this optional analysis as contained in the informed consent document):

5.1.3 ANALYSIS OF TUMOR TISSUE

Patients who agree to allow tumor tissue for research study will have tissue evaluated for SDH expression; immunohistochemistry (IHC) performed at the Laboratory of Pathology, CCR, NCI.

5.1.4 CELL LINE ESTABLISHMENT:

Given the rare nature of tissue available from this patient population, attempts will be made to establish wt-GIST cell lines when surgery or biopsy during the trial are clinically indicated. Gene expression arrays and eventually protein lysate arrays will be created with the aim to identify potential molecular targets for new therapy development. Cell lines will also be used to perform *in vitro* testing of new agents. Informed consent will be required for this purpose, and subjects will be given the option to decline having cell lines established from their samples.

Fresh tumor samples from consenting patients who require clinically indicated surgery or biopsy will be placed immediately into tissue culture medium and transported directly to the Molecular Oncology Section of the Pediatric Oncology Branch.

Samples should be submitted to:

Choh Yeung
10 Center Drive
Bldg 10 CRC, 1W3816
Bethesda, MD 20892
Phone: (301) 496-1259

5.1.5 [^{18}F]-FDG-PET/CT SCAN (OPTIONAL)

Patients who are 15 years of age and older will be asked to participate in one additional [^{18}F]-FDG PET/CT scan (optional) on day 3 to day 6 after starting treatment with vandetanib. The purpose of this research [^{18}F]-FDG PET/CT scan will be to evaluate the utility of [^{18}F]-FDG -PET/CT to predict response early in the treatment of wt- GIST.

Patients will be required to have nothing by mouth at least 4 hours prior to the [^{18}F]-FDG PET/CT scan. They must arrive in the PET Department with IV access already in place. [^{18}F]-FDG will be administered over one minute IV in a dimly lit, quiet prep room. The patient must then remain still in a quiet room with lights dimmed and refrain from talking. Thirty minutes after the initial injection, the patient will be asked to empty their bladder. Forty- to forty-five minutes post-injection, scanning will begin. Patients will be asked to void again at 90 minutes after [^{18}F]-FDG injection and then at least every 3-4 hours for the remainder of the day.

Patients will receive radiation from one optional [^{18}F]-FDG PET/CT for research purposes on this protocol. The [^{18}F]-FDG PET/CT scan will entail the injection of 10mCi dose for all ages and body sizes. In adults, the total additional radiation dose for research purposes will be 1.14 rem, and in children 15 years of age and older, the total additional radiation dose for research purposes will be 1.4 rem.

5.2 BLOOD DRAWING LIMITS FOR RESEARCH PURPOSES

The amount of blood that may be drawn from adult patients and volunteers (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. The amount of blood to be drawn from volunteers and the frequency of collection shall be specified in the clinical research protocol, and exceptions to the 10.5 mL/kg or 550 mL limitations shall be approved by the IRB.

For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

5.3 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.

Blood and tissue collected during the course of this study will follow NIH guidelines for the research use of human samples and OHRP Issues to Consider in the Research Use of Stored Data

or Tissues. All samples (blood or tissue) are documented in LabMatrix and tracked by distinct identification labels that include a unique subject identifier and date of specimen collection with computer backup according to established standards for the Central Repository for NCI-Frederick. All cryopreserved samples are tracked for freezer location and storage criteria. All samples are stored in monitored freezers/refrigerators either in the Central Repository for NCI-Frederick or in the investigator's laboratory at specified temperatures with alarm systems in place. The system will contain data that includes, but is not limited to the unique sample identifiers, storage locations and conditions, biologic study results, clinical information, and corresponding records of all derivatives generated from samples/tissues collected on this protocol. The system will employ mechanisms for restricting users to viewing only the level of data appropriate for each individual user, will provide the capability to audit any data modification, and will be maintained and backed up according to established standards.

At the termination of this protocol, if additional studies are to be performed on any human subject samples retaining patient identifiers or codes obtained during the conduct of this trial, a Request to Conduct Research for Stored Human Samples Specimens, or Data Collected in a Terminated NCI-IRB Protocol will be submitted. Otherwise, specimens will be disposed of in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland. Any new uses of human subject samples collected during the course of this trial must be reviewed and approved by the NCI IRB. Any loss or unintentional destruction of the samples will be reported to the IRB.

6 DATA COLLECTION AND EVALUATION

6.1 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.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

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.

Questionnaire (PROMIS and Distress Thermometer) data will be entered into an SPSS (version 12.0.1), SPSS, Chicago, IL) database by a research assistant. Personal identifiers will not be used when collecting and storing data. Questionnaire data will be linked with clinical data through the use of the unique subject identification number. Files will be stored in password-protected folders and accessible only to the personnel in the POB NCI Psychosocial Support and Research Program.

6.2 DATA SHARING PLANS

6.2.1 GENOMIC DATA SHARING PLAN

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, participants must have measurable disease as defined in RECIST (v1.1) 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. Patients should be re-evaluated for response every 3 cycles x 4 (prior to cycle 4, 7, 10, 13) and then every 6 cycles. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (44) Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 DEFINITIONS

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Vandetanib.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.3.2 DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). The same criteria will be applied to measurements from MRI.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. The same criteria will be applied to measurements from MRI.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.3 METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. 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. Imaging-based evaluation is

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete

clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published (45-47). In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria, which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer(48).

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). In this study, we will explore the utility of FDG-PET in the management of patients with wt-GIST. New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.4 RESPONSE CRITERIA

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest

on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.3.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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).

6.3.4.3 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.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients 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.

6.3.5 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 progressive 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, including the baseline measurements.

6.3.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.4 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 Definitions

7.1.1 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.

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7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 SERIOUS ADVERSE EVENT

An 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.

7.1.6 DISABILITY

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

7.1.7 LIFE-THREATENING ADVERSE DRUG EXPERIENCE

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, 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.

7.1.8 PROTOCOL DEVIATION (NIH DEFINITION)

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

7.1.9 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.

7.1.10 UNANTICIPATED 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.

All treatment-limiting toxicities (see Section 3.1.2) that are possibly, probably, or definitely related to vandetanib and all serious adverse drug experiences (see Section 7.1), 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.
Pharmacology & Experimental Therapeutics Section
Pediatric Oncology Branch
National Cancer Institute
10-CRC, 1-5750, MSC 1101
10 Center Drive
Bethesda MD 20892
Phone: 240-760-6203
Pager: (301) 496-1211
FAX: (301) 480-8871
E-mail: widemanb@mail.nih.gov

7.2 NCI-IRB AND CLINICAL DIRECTOR (CD) REPORTING

7.2.1 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
- All Unanticipated Problems

- All non-compliance

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

7.2.2 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.

7.2.3 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.

7.3 IND SPONSOR REPORTING CRITERIA

During the first 30 days after the subject receives investigational agent/intervention, the 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. For serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, only report those that have an attribution of at least possibly related to the agent/intervention.

Required timing for reporting per the above guideline:

- Deaths (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- Other serious adverse events as well as deaths due to progressive disease must be reported within one business day

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

7.3.1 REPORTING PREGNANCY

7.3.1.1 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.

7.3.1.2 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.

7.4 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 study PI IND holder will notify AstraZeneca (SAE Fax line, 1-866-984-7229) 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* at the time the MedWatch is reported to the FDA.

The study PI IND holder will also notify AstraZeneca **by telephone or by FAX (302-886-1528)** 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 (at the time the MedWatch is submitted to the FDA).

A Fax cover page should accompany any 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.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented.

7.5 DATA AND SAFETY MONITORING PLAN

Vandetanib has been approved by the US Food and Drug Administration (FDA) for treatment of advanced 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.

7.5.1 PRINCIPAL INVESTIGATOR/RESEARCH TEAM

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose modification or discontinuation will be determined.

All data will be collected in a timely manner and reviewed by the principal investigator or a designated associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB using iRIS and if applicable to the FDA and drug manufacturer.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 SPONSOR MONITORING PLAN

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring

- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. 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.

8 STATISTICAL SECTION

8.1 PRIMARY ENDPOINT

The study will be conducted as a small, optimal two-stage phase II trial(49), in order to rule out an unacceptably low 5% overall response rate (ORR; p0=0.05), in favor of a slightly higher response rate of 25% (p1=0.25). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), the study will initially enroll 9 evaluable patients and if 0 of the 9 have a response, then no further patients will be accrued. If 1 or more the first 9 (11.1% or more) have a response, then accrual would continue until a total of 24 patients have enrolled. Only complete responses (CR) and partial responses (PR) will be counted towards the overall response rate. As it may take several weeks to months to determine if a patient has experienced a response, a temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 responses in 24 patients, this would be an uninterestingly low response rate, while if there were 3 or more responses in 24 (12.5% or more) patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 63%.

8.2 ANALYSIS OF SECONDARY ENDPOINTS

Safety and Tolerability

Patients will be carefully monitored for adverse events; which will be recorded in a daily patient diary and documented by the care providers. These will be graded according to CTCAE version 4.0. Information regarding type of adverse event, grade, attribution, temporal occurrence and frequency will be summarized using descriptive methods.

Progression-Free Survival (PFS) and Overall Survival

The progression free survival and overall survival for all patients enrolled on the trial will also be determined using Kaplan-Meier curves and reported along with their associated 95% two-sided confidence intervals at selected time points.

Analysis of Exploratory Pharmacodynamic Endpoints

A variety of biologic parameters will also be evaluated and the results reported as exploratory and hypothesis generating, without adjustment for multiple comparisons.

Analysis of patients' health-related quality of life (as measured by patient and parent report PROMIS measures) and patient-reported symptoms (as measured by the Distress and Symptom Checklist)

Patient's PROMIS scores (patient and parent report for minors) will be converted to t-scores and recorded at each time point. Assuming accrual of 24 patients, T-scores at baseline, first staging and study endpoint will be compared using repeated measures ANOVA to detect significant changes over time. While the sample size will not permit controlling for gender, age group, or disease status, scores will be descriptively reported stratified by these variables. Additionally, PROMIS scores that fall more than 1 standard deviation below the mean will be considered to reflect low QOL. Patient reported symptoms on the Distress and Symptom Checklist will be evaluated using frequency distributions and will be descriptively followed over the course of treatment on this protocol. These data will be reported as exploratory and hypothesis generating, without adjustment for multiple comparisons.

8.3 ACCRUAL TARGET AND STUDY DURATION

A total of 24 evaluable patients may need to be enrolled to meet the primary objective of this study, if 1 or more of the first 9 patients has a response. The actual accrual ceiling will be set at 27 to allow for the possibility of a small number of inevaluable patients (withdrawal prior to meeting progression or toxicity) being enrolled. It is anticipated that 1-2 patients per month may enroll on this trial for the first 6 months, and then approximately 6-8 patients per year thereafter. Thus, 2 to 3 years is anticipated as the accrual period for this study.

Please Note: Nine patients and their parents were enrolled on the study before it was closed to accrual. The parents were not included in the initial accrual ceiling of 27; but they need to be accounted for. Because the study is no longer recruiting, it is not necessary to increase the accrual ceiling; the parents will be included in the 27.

9 COLLABORATIVE AGREEMENTS

9.1 AGREEMENT TYPE

AstraZeneca has agreed to provide the drug (vandetanib) to patients participating in this clinical trial. The trial will be performed under a Clinical Trial Agreement (NCI CTA #00940-13) with AstraZeneca.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

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 or 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 greater than two years of age and adults measurable wt-GIST which is considered a low prevalence disease. 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 24 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.

10.2 PARTICIPATION OF CHILDREN

This trial is designed to determine the response rate of wt-GIST to vandetanib in children and adults. There is currently no experience with vandetanib in wt-GIST, so the tolerability of vandetanib and the toxicity are also being studied. The safety of vandetanib dosing in children has been established in NCI protocol 07-C-0189. Children and adolescents will be enrolled onto this research trial, which 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 or on the adult inpatient unit by the MOB 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 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

10.4.1 RISKS OF VANDETANIB

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. In the ongoing NCI protocol 07-C-0189 the most common toxicities in children have been diarrhea, rash, and TSH elevation. The response rate in subjects with wt-GIST is unknown, but vandetanib has show clinical activity in MTC. A complete summary of Vandetanib risks is contained in Section **11.1.6**.

10.4.2 RISK OF FDG-PET (OPTIONAL)

The additional risks of one optional FDG-PET are expected to be minimal and are related to the risks of the F-18 FDG tracer agent injection, which include rare cases of transient hypotension, hyper- or hypoglycemia and transient increases in alkaline phosphatase. Pregnant or breast-feeding women will not be allowed to participate in this study and should not be exposed to FDG^{18} contrast agent injection as the effects on a fetus or growing child are not known. This optional scan will be limited to consenting participants who do not require sedation to lie still for the duration of the scan.

10.5 RISKS/BENEFITS ANALYSIS

Current data demonstrates that GIST is resistant to cytotoxic chemotherapy and radiation therapy and while imatinib mesylate has become the mainstay of GIST therapy in adults with GIST who have KIT and PDGFRA mutations, 85 % of GISTs occurring in pediatric patients lack KIT and PDGFRA mutations, wild-type (wt) GIST, and therefore known therapies are not as effective. The emerging biology of wt-GIST has demonstrated decreased or absent SDH protein expression in this patient population, and Vandetanib may have activity in this subpopulation of patients with GIST. Therefore, this phase II 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 will only be performed if there is clinical indication for the biopsy or surgical procedure. Patients will be asked to provide consent for use of tissue for research purposes when a clinically indicated biopsy or surgical procedure is scheduled as it will potentially provide valuable data regarding the gene expression in wt-GIST and changes in response to vandetanib. In addition, establishment of pediatric wt-GIST cell lines will be invaluable in allowing future research into the diagnosis, pathophysiology and treatment avenues of this uncommon disease entity.

10.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The treatment consent for this study will explain the investigational nature and research objectives of this trial, the procedures 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 CCR will lead this discussion.

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. When guardianship status of the child is uncertain, documentation of custody status must be obtained.

In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in section **10.6.2**.

10.6.1 CONSENT FOR MINORS WHEN THEY REACH THE AGE OF MAJORITY

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We request waiver of informed consent for those individuals who have been lost to follow up during their participation in the research study.

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 last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to 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 F, have been taken off study prior to reaching the age of majority.

10.6.2 TELEPHONE RE-CONSENT

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

11.1 VANDETANIB (IND #77570)

11.1.1 DESCRIPTION

Other Names: ZD6474, vandetanib, CAPRELSA®

Chemical Structure: N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(l-methylpiperidin-4-yl)methoxy]quinazolin-4-amine

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

Molecular Weight: 475.36

11.1.2 SOURCE:

Vandetanib will be supplied by the manufacturer AstraZeneca and will be administered under an investigator held IND (BB-IND 77570).

AstraZeneca Pharmaceuticals Investigational Products will pack, label, and supply the investigational product (IP) for this study. Tablets will be packed into white high-density polythene (HDPE) bottles with child resistant, tamper evident closures. Study drug must be kept out of the reach of children. Each bottle will contain 100 tablets. Patients will be supplied with sufficient amounts of tablets at each dispensing visit plus overage.

Investigational product	Dosage form and strength	Manufacturer
Vandetanib (unblinded)	Tablet; 50 mg	AstraZeneca Pharmaceuticals
Vandetanib (unblinded)	Tablet; 100 mg	AstraZeneca Pharmaceuticals

11.1.3 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.

11.1.4 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.

11.1.5 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 for children less than 18 years old is determined from the patient's body surface area using the dosing nomogram (Section **3.2**). Treatment will be administered in an outpatient setting.

Vandetanib tablets must be taken whole or dispersed in water, without crushing. If tablets cannot be taken whole, the tablets can be dispersed in a glass containing 60 mL of non-carbonated water and stirred for approximately 10 minutes until the tablets are dispersed (will not completely dissolve). No other liquids should be used. The mixture should be swallowed immediately. To ensure the full dose is received, the patient should refill the glass with an additional half glass of water and mix with any remaining drug and drink it.

There are no food restrictions for the administration of vandetanib tablets. Vandetanib tablets should be taken in the morning at about the same time each day with a glass of water.

11.1.6 TOXICITIES

Adverse events (>0.1%) by system organ class and preferred term in vandetanib emerging safety profile (As described in Investigator's Brochure, Vandetanib, 17 October 2012)

Event by system organ class	**Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1846)**
Cardiovascular	**N (%)**
ECG QT prolongation	139(7.5)
Myocardial infarction	12 (0.7)
Angina pectoris	11 (0.6)
Cardiac Failure	7 (0.4)
Ventricular tachycardia	2 (0.1)
Torsade de pointes	1 (0.1)
Nervous System	
Headache	236 (12.8)
Dysgeusia	62 (3.4)
Cerebrovascular accident	6 (0.3)
Gastrointestinal	
Diarrhea	946 (51.2)
Nausea	489 (26.5)
Vomiting	264 (14.3)
Constipation	235 (12.7)
Abdominal pain	127 (6.9)
Abdominal pain upper	104 (5.6)
Stomatitis	94 (5.1)
Dry mouth	88 (4.8)
Pancreatitis	5 (0.3)
Endocrine disorders	
Hypothyroidism	25 (1.4)
Blood and lymphatic system	
Thrombocytopenia	16 (0.9)
Ecchymosis	2 (0.1)
Investigations	
Weight loss	149 (8.1)
Elevated liver function tests	36-45 (2.0 – 2.4)
Hemoglobin increased	6 (0.3)
Metabolic and nutritional disorders	
Decreased appetite	265 (14.4)

Event by system organ class	Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1846)
Anorexia	185 (10.0)
Hypokalemia	90 (4.9)
Hypocalcemia	75 (4.1)
Dehydration	54 (2.9)
Hypomagnesemia	25 (1.4)
Hypophosphatemia	4 (0.2)
Skin and subcutaneous tissues	
Rash	672 (36.4)
Dry skin	194 (10.5)
Pruritis	167 (9.0)
Acne	159 (8.6)
Photosensitivity reaction	98 (5.3)
Alopecia	71 (3.8)
Nail disorder	25 (1.4)
Palmar-plantar erythrodysaesthesia syndrome	20 (1.1)
Erythema multiforme	8 (0.4)
Stevens-Johnson syndrome	6 (0.3)
Renal and urinary disorders	
Proteinuria	132 (7.2)
Hematuria	29 (1.6)
Nephrolithiasis	24 (1.3)
Respiratory	
Epistaxis	81 (4.4)
Interstitial lung disease (including pneumonitis)[§]	6 (0.3)
Eye disorders	
Vision blurred	56 (3.0)
Conjunctivitis	36 (2.0)
Dry eye	34 (1.8)
Corneal opacity	16 (0.9)
Visual impairment	13 (0.7)
Vascular	
Hypertension	413 (22.4)
Hypertensive crisis	7 (0.4)
Peripheral ischemia	2 (0.1)

Event by system organ class	Percentage of patients from patients receiving vandetanib 300 mg monotherapy (N=1846)
Psychiatric disorders	
Insomnia	213 (11.5)
Depression	86 (4.7)
Anxiety	82 (4.4)

12 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

13 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

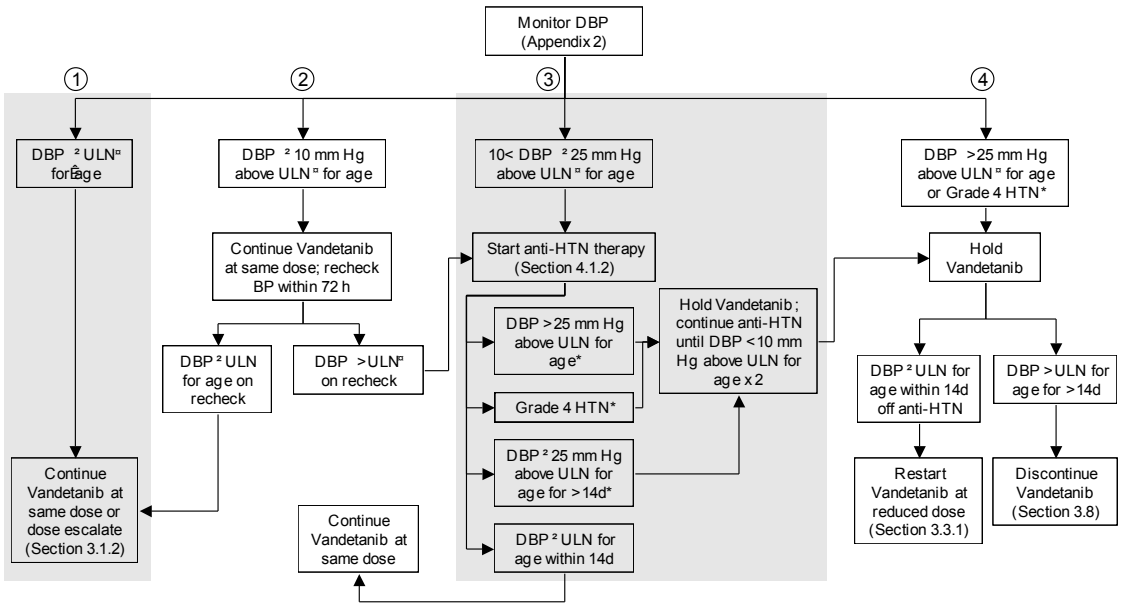
* **≤95th percentile for age and 50% height percentile**

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 **3.1.2** for definition of dose limiting hypertension.
5. See **Appendix 2** for management of vandetanib related hypertension.

14 APPENDIX 3: BLOOD PRESSURE MONITORING ALGORITHM IN CHILDREN



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, hold Vandetanib. Antihypertensive agents can be used to control hypertension as clinically indicated after Vandetanib is held.

- Refer to **Appendix 2** for age and gender normal blood pressure ranges in children and adolescents.

Directions for Algorithm:

- **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 3.1.2) 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 3.1.2), 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 3.6).
- 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.4), 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 3.6)

- **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 3.6)
- The cycle duration remains 28 consecutive days in patients who have dose interruptions.

Single Agent Anti-Hypertensive Therapy

Based on the clinical situation, the recommended agents may be substituted with alternatives at the discretion of the investigator.

- Participants with a persistently (>72 h) elevated DBP that is ≤10 mm Hg above the 95% for gender and age (ULN, **Appendix 2**) or with ≥2 of 3 DBP measurements on a single day that are 11-25 mm Hg above the ULN should be started on appropriate anti-hypertensive therapy.
- 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 14 days of optimal anti-hypertensive therapy, then the vandetanib should be held (see Section 3.3).
- If the DBP increases to >25 mm Hg above the ULN on ≥2 of 3 measurements at any time during 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 3.3).

15 APPENDIX 4: BLOOD PRESSURE COLLECTION AND MANAGEMENT IN ADULT PATIENTS

General Guidelines

Frequency of monitoring: Blood pressure (BP) should be monitored on day 14 and then prior to cycle 2, 3, and 4 and then every 3 cycles, prior to cycle 7, 10, 13, etc. Patients with significant elevation in blood pressure requiring medications will evaluate BP more frequently as clinically indicated. If blood pressure elevation occurs requiring drug therapy, the frequency of monitoring blood pressure after cycle 2 will be determined by the study doctors and the patient instructed appropriately.

Data recording: All required data should be recorded in the appropriate eCRF or on the patient's diary, as appropriate. **The following data are required at baseline and at each subsequent assessment**:

- Assessment date and time
- Pulse
- Systolic and diastolic BP

Risk factors for hypertension (assess and record data in eCRF)

- Diabetes (type 1 or type 2)
- Renal disease (specify on CRF)
- Endocrine condition associated with HTN (specify on CRF)
- Use of steroids or NSAIDs (specify all concomitant meds)
- Underlying cardiovascular condition – specify (*i.e.*, ischemic heart disease)

Baseline data collection (at registration)

All patients**:**

- Current BP
- Proteinuria, if present

Patients with preexisting hypertension (*i.e.*, those for whom "hypertension" is entered as a concomitant condition at registration, or those who are currently receiving therapy with antihypertensive medication) – also record:

- Date of HTN diagnosis (original)
- Type HTN (essential or secondary)
- CTCAE v4.0 grade of HTN (at time of study entry)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of the following:
  - Antihypertensive agents taken at study entry
  - Antihypertensive agents taken in past (e.g., discontinued for toxicity, lack of efficacy)

Follow up BP data collection (while on study)

All patients (at each clinic visit):

- Current BP
- Proteinuria, if present

Patients with treatment-emergent hypertension [defined as BP >150/90 for patients ≥18 years of age] – record at time of hypertension diagnosis and at all subsequent visits:

- BP changes from baseline (or from previous assessment) (specify grade changes)
- Hypertension-related symptoms as reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

Patients with preexisting hypertension at study entry – record at each visit:

- BP changes from previous clinic visit (specify grade changes)
- Hypertension-related symptoms reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Changes in antihypertensive medications since last assessment (*e.g.*, dose change, add/discontinue drug)

Management of Hypertension in Adults

BP measurements - systolic/diastolic	Interval	Treatment/Dose Modification
Patients **not** receiving maximal antihypertensive therapy:		
≥ 150 mmHg (systolic) **OR** ≥ 100 mmHg (diastolic)	2 BP readings at least 1 hour apart	• Add new or additional antihypertensive meds or increase dose of existing meds • Maintain dose of vandetanib
> 200 mmHg (systolic) **OR** > 110 mmHg (diastolic)	2 BP readings during a 1-week period	• Hold vandetanib • Monitor patient closely for hypotension (if on antihypertensive meds) until vandetanib is restarted. • Resume treatment when BP falls to <150/100
Patients receiving maximal antihypertensive therapy*:		
> 160 mmHg (systolic) **OR** > 105 mmHg (diastolic)	2 BP readings at least 1 hour apart	• Hold vandetanib • Maintain antihypertensive meds and monitor patient closely for hypotension until vandetanib is restarted. • Resume treatment at one lower dose level when BP falls to <150/100
* Maximal antihypertensive therapy is defined as four antihypertensive medications given for 2 weeks.		

Notes:

- While patients are receiving treatment with vandetanib, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.
- Decisions to hold or decrease the vandetanib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

*Classes of antihypertensive drugs include ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, diuretics, angiotensin II receptor antagonists.

16 APPENDIX 5: ADULT ANTIHYPERTENSIVE MEDICATION LIST

Dihydropyridine calcium-channel blockers (DHP CCB)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlopidine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate + inhibitor
Selective β blockers (BB)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	No
Acebutolol	100 mg po bid	200-300 mg po bid	400 mg po bid	Yes (CYP450 unknown)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Captopril	12.5 mg po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP450 unknown)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	No
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP450 unknown)
Rarely used:				
Perindopril	4 mg po qd	none	8 mg po qd	Yes but not CYP450
Quinapril	10 mg po qd	20 mg po qd	40 mg po qd	No
Angiotensin II Receptor Blockers (ARBs)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Losartan	25 mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4 mg po qd	8-16 mg po qd	32 mg po qd	CYP 2C9 substrate
Irbesartan	75 mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	Yes but not CYP450
Valsartan	80 mg po qd	none	160 mg po qd	Yes but not CYP450
α and β blocker				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate + inhibitor

17 APPENDIX 6: NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

Class	**Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

18 APPENDIX 7: MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL OR INDUCE TORSADES DE POINTES

It has been recognized for a number of years that certain prescription 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 and/or have a risk of inducing Torsades de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Group 1: Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

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

Table 1 Group 1 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Amiodarone	Anti-arrhythmic/abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Anti-cancer/Leukemia	
Astemizole	Antihistamine/Allergic rhinitis	No Longer available in U.S.
Azithromycin	Antibiotic/bacterial infection	
Bepridil	Anti-anginal/heart pain	Females>Males
Chloroquine	Anti-malarial/malaria infection	
Chlorpromazine	Anti-psychotic/Anti-emetic/schizophrenia/ nausea	
Cisapride	GI stimulant/heartburn	No longer available in U.S.
Citalopram	Anti-depressant/depression	
Clarithromycin	Antibiotic/bacterial infection	
Disopyramide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Dofetilide	Anti-arrhythmic/abnormal heart rhythm	Females > Males
Domperidone	Anti-nausea/nausea	Not available in U.S.
Droperidol	Sedative;Anti-nausea/anesthesia adjunct, nausea	
Erythromycin	Antibiotic;GI stimulant/bacterial infection; increase GI motility	Females>Males
Flecainide	Anti-arrhythmic/abnormal heart rhythm	
Halofantrine	Anti-malarial/malaria infection	Females>Males
Haloperidol	Anti-psychotic/schizophrenia, agitation	TdP risk with I.V. or excess dosage

Table 1 Group 1 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Ibutilide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Levomethadyl	Opiate agonist/pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Anti-psychotic/schizophrenia	
Methadone	Opiate agonist/pain control, narcotic dependence	Females>Males
Moxifloxacin	Antibiotic/bacterial infection	
Pentamidine	Anti-infective/pneumocystis pneumonia	Females>Males
Pimozide	Anti-psychotic/Tourette's tics	Females>Males
Probucol	Antilipemic/Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic/abnormal heart rhythm	
Quinidine	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sotalol	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sparfloxacin	Antibiotic/bacterial infection	No longer available in U.S.
Terfenadine	Antihistamine/Allergic rhinitis	No longer available in U.S.
Thioridazine	Anti-psychotic/schizophrenia	
Vandetanib (*Does not apply to this study)	Anti-cancer/Thyroid cancer	

[a] Source: www.QTdrugs.org. Last revised: 17 May 2012

Group 2: Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes.

Concomitant use of these drugs is not allowed within 2 weeks of randomization or during the study. These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes.

Table 2 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Alfuzosin	Alpha1-blocker/Benign prostatic hyperplasia	
Amantadine	Dopaminergic/Anti-viral/Anti-infective/ Parkinson's Disease	
Artenimol + piperaquine	Anti-malarial/	Not available in U.S.
Atazanavir	Protease inhibitor/HIV	
Chloral hydrate	Sedative/sedation/ insomnia	
Clozapine	Anti-psychotic/schizophrenia	
Dolasetron	Anti-nausea/nausea, vomiting	
Dronedarone	Anti-arrhythmic/Atrial Fibrillation	
Eribulin	Anti-cancer/metastatic breast neoplasias	
Escitalopram	Anti-depressant/Major depression/Anxiety disorders	
Famotidine	H2-receptor antagonist/Peptic ulcer/ GERD	
Felbamate	Anti-convulsant/seizure	
Fingolimod	Immunosuppressant/Multiple Sclerosis	
Foscarnet	Anti-viral/HIV infection	
Fosphenytoin	Anti-convulsant/seizure	
Gatifloxacin	Antibiotic/bacterial infection	Oral/I.V. forms no longer available in U.S. and Canada, only ophthalmic
Gemifloxacin	Antibiotic/bacterial infection	
Granisetron	Anti-nausea/nausea and vomiting	
Iloperidone	Antipsychotic, atypical/Schizophrenia	
Indapamide	Diuretic/stimulate urine & salt loss	
Isradipine	Anti-hypertensive/high blood pressure	
Lapatinib	Anti-cancer/breast cancer, metastatic	

Table 2 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Levofloxacin	Antibiotic/bacterial infection	
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 and 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	*Not available in U.S.
Sertindole	Antipsychotic, atypical/Anxiety, Schizophrenia	Not available in U.S.
Sunitinib	Anti-cancer/RCC, GIST	
Tacrolimus	Immunosuppressant/Immune suppression	
Tamoxifen	Anti-cancer/breast cancer	
Telithromycin	Antibiotic/bacterial infection	
Tizanidine	Muscle relaxant/	
Vardenafil	phosphodiesterase inhibitor/vasodilator	
Venlafaxine	Anti-depressant/depression	
Voriconazole	Anti-fungal/anti-fungal	
Ziprasidone	Anti-psychotic/schizophrenia	

[a] Source: www.QTdrugs.org. Last revised: 17 May 2012

19 APPENDIX 8: PATIENT DIARY FOR VANDETANIB (PART 1)

mail to:**Patient ID number**: _ **Daily Dose (mg)**: _____ **Cycle Number:_____ Cycle Start Date:_____Cycle Start Day: _____**

WEEK #____ Date							
Day							
Dose #							
Time vandetanib dose taken†							
Indicate reason for missed doses							

SIDE EFFECTS**

Vomiting[1]							
Diarrhea[2]							
Nausea[3]							
Rash							
OTHER SIDE EFFECTS	Should you need additional space, continue with table on back.						

OTHER MEDICATIONS (Name) **(Not your regular daily medications)**	**Dose**	**Frequency**	**Start Date**	**Stop Date**	**Reason for Use of Medication**

† Vandetanib can be taken with a meal or in between meals. If you vomit within 30 minutes of taking of vandetanib, you may re-take the dose. If more than 30 minutes has passed from the time of taking vandetanib then do *not* retake the dose.

[1] For vomiting indicate number of episodes per day.

[2] For diarrhea, indicate the number of episodes per day and the consistency (F for formed, W for watery, L for loose or partially formed).

[3] Rate nausea **mild** if you are able to eat and drink a reasonable amount, **moderate** if you can eat and drink but the amount is substantially decreased, or **severe** if you are unable to eat and drink.

Contact your study center team or local physician right away if you experience skin rash, rapid or irregular heartbeat, dizziness, light-headedness, chest discomfort, shortness of breath, loss of consciousness, or pregnancy (you or your partner)

Your skin may be more sensitive to the sun, avoid exposure and use sunblock ≥ 45+

Completed form should be returned immediately at the end of each cycle to Ms. Claudia Derse-Anthony (FAX 301-480-8871, PHONE: 240-760-6102, e-mail: claudia.derse-anthony@nih.gov)

Patient/Parent Signature: _____ Date: _____ Reviewed By:_____RN/MD Date:_____

Appendix 8: Patient Log for Symptoms/Reactions and Concomitant medications (Part 2)

Cycle(s): _____

Patient ID#: _____ Vandetanib dose (mg):_____ Frequency: _____

Symptom/Reaction	Start Date	End Date	Did you take something for it? List below.

Medication	Reason for Use	Dose	Start Date	Stop Date

Please take your study medication about the same time every day. If you miss a dose and more than 6 hours has passed from your usual dosing time, DO NOT take the dose. Record any missed doses on your diary.

Contact your study center team or local physician right away if you experience skin rash, rapid or irregular heartbeat, dizziness, light-headedness, chest discomfort, shortness of breath, loss of consciousness, or pregnancy (you or your partner).

Your skin may be more sensitive to the sun, avoid exposure and use sunblock $\geq$ 45 SPF.

Patient/Parent signature: _____ Date:_____

Reviewed by:_____ RN/MD Date:_____

20 APPENDIX 9: REQUIRED STUDY EVALUATIONS

Clinical and laboratory tests to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 7 days at the start of therapy. Laboratory tests need not be repeated if therapy starts with in 7 days of obtaining labs for eligibility. For further details see section 2.2.

STUDIES TO BE OBTAINED[1]	Screening	Baseline	During Cycle 1	Prior To Subsequent Cycles	End of Therapy[8]
PT/PTT	X				
Lower leg scanogram[2]		X			
History, physical exam, viral signs (HR, BP, Temp)	X		Day 14	Prior to cycles 2, 3, 4, and then after every 3 cycles prior to cycle 7, 10, 13, etc)	X
CBC, differential, platelets					
Chemistries: [Acute Care Panel (sodium, potassium, chloride, CO_2, creatinine, glucose, BUN), Mineral Panel (calcium, magnesium, phosphorus, albumin) Hepatic Panel (alk phos, ALT/AST, Total bilirubin, (if T Bili is elevated, draw Direct bilirubin) total protein, uric acid, LDH.					
Urinalysis		X	-	Prior to cycles 2, 3, 4, and then after every 3 cycles prior to cycle 7, 10, 13, etc)	X
Thyroid function (TSH; T4 if TSH abnormal)		X			
EKG	X				
Height, weight, BSA, Performance Status	X			Prior to cycle 4, 7, 10, 13, and then after every 6 cycles (prior to cycle 19, 25, 31, etc)	X
β-HCG pregnancy test: (if applicable)[3]					
Disease evaluation: CT chest/abdomen/pelvis, MRI abdomen/pelvis					
Unilateral knee MRI[5]					
FDG-PET scan[6]	X		Day 3 to 6[6]	Prior to cycle 4	
QOL: PROMIS and Distress Thermometer		X		Prior to cycle 4	X
Patient diary: reactions/symptoms and concomitant meds[7]	-	X	Daily	Daily until prior to cycle 13	-
Study calendar[7]	-		-	From cycle 13 on	X
NIH Advance Directives Form[9]		X			

[1]With exception of the optional FDG-PET scan, study evaluations for cycles 1 though 4 may be performed within +/- 3 days of the scheduled date.

Study evaluations for cycles ≥5 may be obtained within +/- 7days of the scheduled date.

[2]Lower extremity scanogram in all participants less than 18 years old. Patients with fused growth plates will not undergo additional evaluations. Patients with open growth plate(s) will also undergo follow up scanogram only if clinically indicated.

[3]Required in females of childbearing potential.

[5]A unilateral knee MRI in all patients with open growth plates on lower extremity scanogram (see **Appendix 11**). Repeat knee MRIs at time points indicated until growth plates are fused.

[6]Optional FDG-PET for patients ≥ 15 years old on day 3 to day 6 after starting vandetanib on cycle 1 to evaluate for early response.

[7]From cycle 13 on vandetanib intake will be monitored during patient interviews at the NIH, and patients will document adverse events and any concomitant medications on Reactions/Symptoms and Concomitant Medications Logs (see **Appendix 10**).

[8]Patients who experience adverse events at the end of therapy will continue to be monitored until at least 60 days after the last dose of vandetanib and until resolution of toxicity.

[9]As indicated in section **10.3**, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

21 APPENDIX 10: PATIENT LOG FOR REACTIONS/SYMPTOMS

Protocol # ___-__-_____*

Patient ID#: _____

Vandetanib dose (mg):_____ Frequency: _____ Cycle(s):_____

Start Date **End Date** **Took Medication (Y/N)** **Symptom/Reaction**

Complete reverse side.

Please take your study medication about the same time every day. If you miss a dose and more than 6 hours has passed from your usual dosing time, DO NOT take the dose. Record any missed doses on your diary.
Contact your study center team or local physician right away if you experience skin rash, rapid or irregular heartbeat, dizziness, light-headedness, chest discomfort, shortness of breath, loss of consciousness, or pregnancy (you or your partner).

Your skin may be more sensitive to the sun, avoid exposure and use sunblock $\geq$ 45 SPF.

Patient/Parent signature: _____ Date:_____

Reviewed by:_____ RN/MD Date:_____

Patient Log for Concomitant Medication

Patient ID#: _____ Vandetanib dose (mg):_____ Frequency: _once daily__

Medication	Reason for Use	Dose	Start Date	Stop Date

Patient/Parent signature: _____ Date:_____

Reviewed by:_____RN/MD Date:_____

22 APPENDIX 11: PROTOCOL FOR MRI STUDY OF KNEE

PATIENT ID NUMBER: _____

Note: Unilateral knee MRI. Right knee preferred over left unless prohibited by contractures, lesions, pain, or hypertrophy. This is done to examine the femoral and tibial growth plates. Only the series outlined below are required for the knee MRI for evaluation of femoral and tibial growth plates and must be performed within protocol specifications as indicated below. Two sequential scans of the knee will be performed per patient. The patient must step off the scanner and placed back on the scanner in between the two scans.

T1 Weighted Sagittal	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	72		
TR	500-600		
TE	min full		
Slice Thickness	3		
Bandwidth	20 kHz		
GAP	1.5mm		
FOV	18		
FREQ	512		
Phase	256		
NEX	1		
PHFVO	Full		
Saturation	no FS		
OPTIONS	Fast		

23 APPENDIX 12: PEDIATRIC PROMIS INSTRUMENTS (6) AND PARALLEL PARENT PROXY PROMIS INSTRUMENTS (6) AND ADULT PATIENT PROMIS INSTRUMENTS (6)

Pediatric PROMIS Instruments (6)

PROMIS™ Pediatric Item Bank v.1.0 - Physical Function - Mobility - Short Form 8a

Pediatric Physical Function - Mobility - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…..	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
I could do sports and exercise that other kids my age could do.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could get up from the floor.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could keep up when I played with other kids.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could move my legs.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could stand up by myself.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could stand up on my tiptoes.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could walk up stairs without holding on to anything.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I have been physically able to do the activities I enjoy most.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

PROMIS™ Pediatric Item Bank v.1.0 - Anxiety - Short Form 8a

Pediatric Anxiety - Short Form

Please respond to each item by marking one box per row.

In the past 7 days.....	Never	Almost Never	Sometimes	Often	Almost Always
I felt nervous.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt scared.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt worried.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt like something awful might happen.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I thought about scary things.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was afraid that I would make mistakes.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I worried about what could happen to me.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I worried when I went to bed at night.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS™ Pediatric Item Bank v.1.0 - Depressive Symptoms - Short Form 8a

Pediatric Depressive Symptoms - Short Form

Please respond to each item by marking one box per row.

In the past 7 days.....	Never	Almost Never	Sometimes	Often	Almost Always
I could not stop feeling sad.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt alone.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt everything in my life went wrong.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt like I couldn't do anything right.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt lonely.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt sad.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt unhappy.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I thought that my life was bad.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS™ Pediatric Item Bank v.1.0 - Fatigue - Short Form 10a

Pediatric Fatigue - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…….

	Never	Almost Never	Sometimes	Often	Almost Always
Being tired made it hard for me to play or go out with my friends as much as I'd like.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt weak.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I got tired easily.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Being tired made it hard for me to keep up with my schoolwork.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble finishing things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble starting things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was so tired it was hard for me to pay attention.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to do sports or exercise.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to do things outside.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to enjoy the things I like to do.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS™ Pediatric Item Bank v.1.0 - Pain Interference - Short Form 8a

Pediatric Pain Interference - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…..	Never	Almost Never	Sometimes	Often	Almost Always
I had trouble sleeping when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt angry when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble doing schoolwork when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard for me to pay attention when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard for me to run when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard for me to walk one block when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard to have fun when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard to stay standing when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS™ Pediatric Item Bank v.1.0 - Peer Relationships - Short Form 8a

Pediatric Peer Relationships - Short Form

Please respond to each item by marking one box per row.

In the past 7 days....	Never	Almost Never	Sometimes	Often	Almost Always
I felt accepted by other kids my age.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was able to count on my friends.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was able to talk about everything with my friends.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was good at making friends.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
My friends and I helped each other out.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Other kids wanted to be my friend.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Other kids wanted to be with me.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Other kids wanted to talk to me.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

24 APPENDIX 13: PARALLEL PARENT PROXY PROMIS INSTRUMENTS (6)

PROMIS Parent Proxy Item Bank v1.0 – Physical Function Mobility 8

Physical Function Mobility – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
Pf1mobil3	My child could do sports and exercise that other kids his/her age could do.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil9	My child could get up from the floor	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf4mobil4	My child could keep up when he/she played with other kids	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil8	My child could move his/her legs	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil3	My child could stand up without help.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf2mobil7	My child could stand up on his/her tiptoes	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf2mobil4	My child could walk up stairs without holding on to anything.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf1mobil1	My child has been physically able to do the activities he/she enjoys most.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

PROMIS Parent Proxy Item Bank v1.0 – Anxiety 8

Anxiety – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf1anxiety8	My child felt nervous	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety2	My child felt scared.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety9	My child felt worried.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety1	My child felt like something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety6	My child thought about scary things.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1anxiety7	My child was afraid that he/she would make mistakes	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1anxiety3	My child worried about what could happen to him/her.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety4	My child worried when he/she went to bed at night	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Depressive Symptoms 6

Depressive Symptoms – Short Form 6

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pt2depr7	My child could not stop feeling sad	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt1depr7	My child felt everything in his/her life went wrong.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt1depr5	My child felt like he/she couldn't do anything right	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt2depr10	My child felt lonely.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt2depr3	My child felt sad.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt2depr5	My child thought that his/her life was bad	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Fatigue 10

Fatigue – Short Form 10

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf4fatigue12	Being tired made it hard for my child to play or go out with friends as much as he/she would like.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4fatigue8	My child felt weak.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4fatigue3	My child got tired easily.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2fatigue8	Being tired made it hard for my child to keep up with schoolwork.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2fatigue4	My child had trouble finishing things because he/she was too tired	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue7	My child had trouble starting things because he/she was too tired	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue12	My child was so tired it was hard for him/her to pay attention.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue8	My child was too tired to do sports or exercise.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue4	My child was too tired to do things outside	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4fatigue4	My child was too tired to enjoy the things he/she likes to do	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Pain Interference 8

Pain Interference – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf2pain5	My child had trouble sleeping when he/she had pain.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3pain7	My child felt angry when he/she had pain .	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2pain2	My child had trouble doing schoolwork when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3pain2	It was hard for my child to pay attention when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2pain4	It was hard for my child to run when he/she had pain.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1pain4	It was hard for my child to walk one block when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3pain4	It was hard for my child to have fun when he/she had pain.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4pain6	It was hard for my child to stay standing when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Peer Relationships 7

Peer Relationships – Short Form 7

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pt3socabil9	My child felt accepted by other kids his/her age	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt4socabil12	My child was able to count on his/her friends.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt3socabil4	My child was good at making friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt2socrole4	My child and his/her friends helped each other out.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt1socabil2	Other kids wanted to be my child's friend.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt3socrole4	Other kids wanted to be with my child	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pt2socabil9	Other kids wanted to talk to my child	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

25 APPENDIX 14: ADULT PATIENT PROMIS INSTRUMENTS (6)

PROMIS Item Bank v1.0 –Physical Function - Short Form 10a

Physical Function – Short Form 10a

Please respond to each item by marking one box per row.

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA01	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36	Does your health now limit you in walking more than a mile?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA05	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA03	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16	Are you able to dress yourself, including tying shoelaces and doing buttons?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45	Are you able to get on and off the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Emotional Distress - Anxiety – Short Form 7a

Please respond to each item by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX30	I felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Item Bank v. 1.0 – Emotional Distress – Depression - Short Form 8b

Emotional Distress - Depression – Short Form 8b

Please respond to each item by marking one box per row.

In the past 7 days....

		Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05	I felt that I had nothing to look forward to……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP17	I felt sad……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	I felt like a failure……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Item Bank v. 1.0 - Fatigue -Short Form 7a

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Item Bank v1.0 – Pain Interference - Short Form 6b

Pain Interference – Short Form 6b

Please respond to each item by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ3	How much did pain interfere with your enjoyment of life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ8	How much did pain interfere with your ability to concentrate?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ10	How much did pain interfere with your enjoyment of recreational activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ14	How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
PAININ26	How often did pain keep you from socializing with others?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS v.1.0/1.1 - Global

Global Health Scale

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS v.1.0/1.1 - Global

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

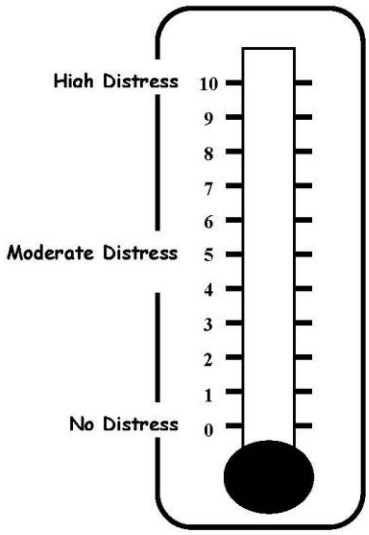
26 APPENDIX 15: THE DISTRESS AND SYMPTOM CHECKLIST: THE DISTRESS THERMOMETER

DISTRESS RATING TOOL
Patient Version

NAME: _____ DOB:_____ DATE: _____

INSTRUCTIONS: We know that all people can get sad and stressed out from time to time. Sometimes people can get overwhelmed and distressed by managing all the aspects of their own life along with their illness. When we say distress, we are referring to a range of feelings that can include sadness, being anxious, fearful, worried, or upset. These feelings may affect how you feel physically and emotionally.

On the thermometer below, circle the number that best describes how much distress **YOU** have been feeling **IN THE PAST MONTH** with a "0" indicating no distress at all and a "10" indicating the most distress you could possibly feel. Then, after indicating the level of distress on the thermometer, please check the causes of YOUR distress.



For each symptom checked, place a circle around the number that most closely measures what you are experiencing today on a scale from 1 to 5. For example, number 1 would indicate just a little problem in regard to that particular symptom and number 5 would indicate a maximum amount of difficulty

Emotional
Have you been:

- ❑ Worried/Anxious
- ❑ Sad/Depressed
- ❑ Lonely/Feeling Alone
- ❑ Guilt/self-doubt
- ❑ Bored
- ❑ Irritable
- ❑ Afraid to be alone
- ❑ Hopeless
- ❑ Difficulty making decisions
- ❑ Worthless
- ❑ Unhappy with how your body looks (If so, what part_____)
- ❑ Having trouble concentrating
- ❑ Having racing thoughts
- ❑ Scared (of _____)
- ❑ Angry
- ❑ Other Problems: _____

Physical
Have you been having problems with:

- ❑ Pain
- ❑ Getting around
- ❑ Fatigue/lack of energy
- ❑ Sleeping (too much/too little)
- ❑ My weight(too high/too low)
- ❑ Appetite poor
- ❑ Headaches
- ❑ Heart palpitations
- ❑ Stomach pain/cramps
- ❑ Feeling sick to my stomach, had to vomit
- ❑ Nauseated
- ❑ Loose stools (bowel movements) or diarrhea
- ❑ Hard stools or constipation
- ❑ Not able to exercise
- ❑ Other Problems:

Practical
Have you been stressed about:

- ❑ Not understanding what is happening to my body
- ❑ School work, work
- ❑ Taking a lot of medications
- ❑ All my medical needs
- ❑ Wanting to stay away from the doctor/hospital
- ❑ What you will do in the future for a job/career
- ❑ Not having good friends
- ❑ Other Problems:

Spiritual
Have you been stressed about:

- ❑ Spiritual Questions
- ❑ Difficulties Praying
- ❑ Feeling Distanced from God
- ❑ Loss of Faith
- ❑ Other Problems:

Family/Social
Have you been stressed about:

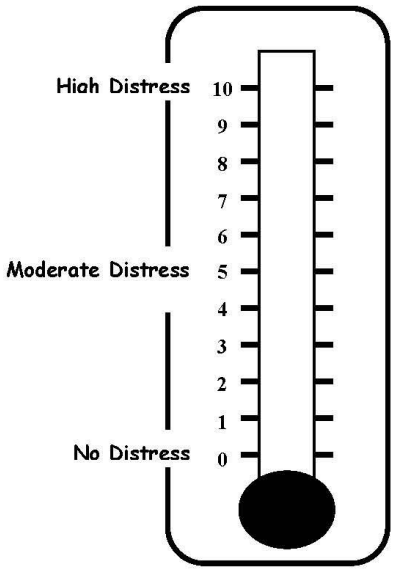
- ❑ Getting along with family
- ❑ Not having support
- ❑ Getting along with friends
- ❑ Lack of communication w/friends
- ❑ My parent(s) stress
- ❑ My sibling(s) stress
- ❑ Parent(s) or other family members being overprotective
- ❑ Other issues not on list

DISTRESS RATING TOOL
Caregiver Endocrine

NAME: _____ Mom ___ Dad____ DATE: _____

INSTRUCTIONS: We know that caregivers who have children with a medical illness can get sad and stressed out from time to time. Sometimes people can get overwhelmed and distressed by managing all the aspects of their own life along with their illness. When we say distress, we are referring to a range of feelings that can include sadness, being anxious, fearful, worried, or upset. These feelings may affect how you feel physically and emotionally.

On the thermometer below, circle the number that best describes how much distress **YOU** have been feeling **IN THE PAST MONTH** with a "0" indicating no distress at all and a "10" indicating the most distress you could possibly feel. Then, after indicating the level of distress on the thermometer, please check the causes of YOUR CHILD'S distress.



In each section, please circle the symptoms that you feel are bothering your child the most.

Emotional
Has your child been:

- ❑ Worried/Anxious
- ❑ Sad/Depressed
- ❑ Lonely/Feeling Alone
- ❑ Guilt/self-doubt
- ❑ Bored
- ❑ Irritable
- ❑ Afraid to be alone
- ❑ Hopeless
- ❑ Difficulty making decisions
- ❑ Worthless
- ❑ Unhappy with how his/her body looks (What part____)
- ❑ Having trouble concentrating
- ❑ Having racing thoughts
- ❑ Scared (of _____)
- ❑ Angry
- ❑ Other Problems: _____

Physical
Has your child had problems with:

- ❑ Pain
- ❑ Getting around
- ❑ Fatigue/lack of energy
- ❑ Falling asleep
- ❑ Sleeping (too much/too little)
- ❑ Weight(too high/too low)
- ❑ Poor appetite
- ❑ Headaches
- ❑ Heart palpitations
- ❑ Stomach pain/cramps
- ❑ Feeling sick to his/her stomach, had to vomit
- ❑ Nauseated
- ❑ Loose stools (bowel movements) or diarrhea
- ❑ Hard stools or constipation
- ❑ Not able/willing to exercise
- ❑ Other Problems:

Practical
Has your child been stressed about:

- ❑ Not understanding what is happening to his/her body
- ❑ School work, work
- ❑ Taking a lot of medications
- ❑ Medical needs
- ❑ Doctor/hospital visits
- ❑ Future plans - job/career
- ❑ Not having good friends
- ❑ Other Problems:

_____
_____

Spiritual
Has your child been stressed about:

- ❑ Spiritual Questions
- ❑ Difficulties Praying
- ❑ Feeling Distanced from God
- ❑ Loss of Faith
- ❑ Other Problems:

_____
_____

Family/Social
Has your child been stressed about:

- ❑ Getting along with family
- ❑ Not having support
- ❑ Getting along with friends
- ❑ Lack of communication w/friends/family
- ❑ Parent's stress
- ❑ Sibling(s) stress
- ❑ Parent(s) being overprotective
- ❑ Other issues not on list

_____
_____

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