TITLE: A Phase II Trial of Pazopanib in Von Hippel-Lindau Syndrome

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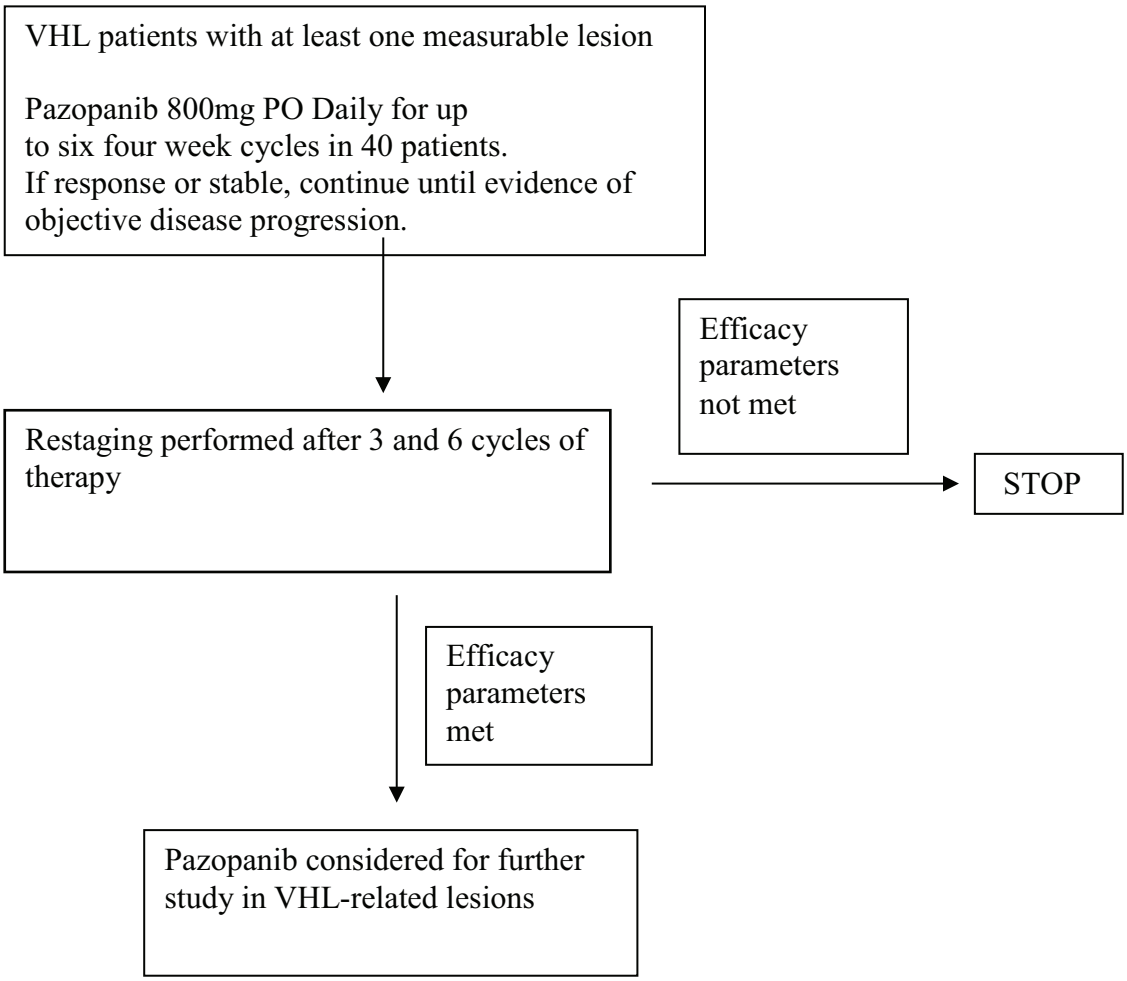


TABLE OF CONTENTS

1.0 OBJECTIVES

1.1. Primary objectives

- Evaluate safety and efficacy of treatment with pazopanib for 6 months in patients with VHL who have a measurable VHL related lesion.

- Secondary objectives
  - Evaluate rate of growth over time in target lesions before and after pazopanib treatment
  - Evaluate need for surgical intervention over time in patients who receive pazopanib and compare to rate prior to receipt of drug
  - Create an annotated tissue resource from patients with VHL for use in future research related to cancer.

1.2. Preclinical objectives

- Evaluate circulating factors in patients with VHL undergoing treatment with pazopanib
- Evaluate relationship between VHL genotype and response to pazopanib.

2.0 BACKGROUND

2.1 Von Hippel Lindau Syndrome

The VHL syndrome affects approximately 1 in 35000 live births each year worldwide. The disease results from an autosomal-dominant mutation associated with deletion of the *VHL* gene located on the short arm of chromosome 3. The VHL protein is directly responsible for downregulating hypoxia-inducible factor alpha (HIF) transcription factors responsible for several angiogenic responses to hypoxia. Thus, mutations of the *VHL* gene lead to the regulatory loss of HIF, with increased intracellular HIF during normoxia being the primary common pathway leading to the downstream manifestations of the syndrome via induction of VEGF, PDGF, erythropoietin, and a variety of other angiogenic pathways. The clinical presentation of this syndrome is characterized in late childhood and early adulthood by hemangioblastomas of the brain, spine, and retina, in addition to renal cell carcinoma, pheochromocytoma, neuroendocrine tumors of the pancreas, other benign tumors (e.g., endolymphatic sac tumors) as well as cystic lesions in various organs such as the kidneys and pancreas. Renal cell carcinomas and hemangioblastomas are directly related to HIF pathway activation, while pheochromocytomas appear to be induced via non-HIF pathways. The multi-organ morbidity of these lesions as well as their treatment is significant in these patients, who must often endure repeated, serial interventions of the CNS, eye, kidneys, pancreas, adrenal, and other organs. While little data has been published in regard to the multiplicity of interventions for all the involved organ systems, one report has shown that by age 30, most patients with VHL have had greater than 2 interventions for any involved organ. Of those with RCC, 88% required intervention at an average range of 1.4 to 3 interventions per year[1]. Renal and CNS tumors comprise the majority of those causing

the greatest impact, as does their treatment.

Genetic characterization of the various mutations has been classified as Type 1 (no pheochromocytoma) and Type 2 (presence of pheochromocytoma) which is further characterized into 2a, low risk of renal cancer, 2b, high risk of renal cancer; and 2c, pheochromocytoma only.

2.2 Pazopanib

Angiogenesis, the process of new blood vessel formation, plays an important role in the development of malignancy as well as the growth and progression of metastatic lesions. The molecular pathways involved in angiogenesis have been targeted for anti-tumor therapy. Numerous growth factors and cytokines are involved in the angiogenic process. Among these factors, vascular endothelial growth factor (VEGF) has a predominant role as a central mediator of tumor-related angiogenesis, and its expression has been shown to be an adverse prognostic factor for a number of solid tumors[2,3,4].

Pazopanib is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β) [redacted][5] and c-Kit and Pazopanib is being developed by Novartis Pharmaceuticals for the treatment of a variety of cancers. In nonclinical experiments, pazopanib has demonstrated encouraging potency and selectivity for VEGF receptors: for example, pazopanib demonstrated significant inhibition of VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells and was 3- to 400-fold selective for VEGF receptors compared to 23 other kinases tested. Pazopanib showed significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibited angiogenesis in several different models of angiogenesis (e.g., the Matrigel plug assay, the cornea micropocket, and the laser-induced choroidal neovascularization models).

Pazopanib 800 mg once daily is the recommended monotherapy dose based on clinical and preclinical results. Once daily doses of 50 mg to 2000 mg pazopanib were investigated in the "First Time in Human", Phase I Study VEG10003. Increases in the pazopanib dose above 800 mg once daily when administered in the fasted state did not result in a consistent increase in systemic exposure at steady-state. Therefore, no further benefit is expected at pazopanib doses above 800 mg once daily.

Pharmacodynamic data indicate that pazopanib, at a monotherapy dose of 800 mg once daily, results in effects consistent with inhibition of the VEGF receptors it was designed to target. Concentration-effect relationships were observed between trough plasma pazopanib concentrations and the development of hypertension in Study VEG10003 and the percent change from baseline in sVEGFR2 nadir in Study VEG102616. The trough plasma pazopanib concentrations associated with one-half the maximal effect (EC_{50}) in both concentration-effect relationships were similar (21.3 µg/mL and 15.3 µg/mL) and demonstrate that there is a consistent inhibition of VEGF receptor(s) in subjects with

cancer when plasma pazopanib concentrations are maintained above 15 µg/mL. The plasma pazopanib EC_{50} values for biologic effects observed in the clinical studies are similar to the plasma concentration of 40 µM (17.5 µg/mL) required for optimal inhibition of VEGFR-2 phosphorylation in mice [GSK Report RH2003/00005/00]. Progression Free Survival (PFS) in subjects with renal cell cancer in study VEG102616 was compared between subjects whose trough plasma pazopanib concentrations at Week 4 were above or below selected threshold values that were distributed evenly across the observed predose concentrations. Subjects with trough concentrations above the threshold values had significantly better PFS, compared to the remaining subjects, when the threshold concentrations were 12.6 µg/mL, 17.4 µg/mL, and 20.7 µg/mL. Use of thresholds higher than 21 µg/mL did not result in a significant difference in PFS between patients above and below the threshold. Using thresholds of 15 µg/mL and 20.7 µg/mL, patients with trough concentrations above the thresholds also had significantly better response rate and tumor shrinkage than the remaining patients.

Pazopanib C24 at steady-state was greater than 15 µg/mL in 93% of subjects who received 800 mg once daily in Study VEG10003. Individual subjects receiving pazopanib doses below 800 mg once daily can achieve plasma concentrations over 15 µg/mL, albeit at a lower frequency compared with what is observed at 800 mg once daily. Therefore, the pharmacokinetic and pharmacodynamic results across clinical studies demonstrate that pazopanib 800 mg once daily results in plasma concentrations that provide optimal biologic effects associated with VEGFR inhibition in the greatest proportion of subjects.

Additional support for an 800 mg once daily pazopanib dose comes in results from Study VEG105192, a 435-subject Phase III study of pazopanib (800 mg once daily) versus placebo in treatment-naïve and cytokine-pretreated subjects with renal cell carcinoma (RCC). In this study, the median progression-free survival (PFS) in the pazopanib arm was 9.2 months (95% CI, 7.4, 12.9) compared to 4.2 months (95% CI, 2.8, 4.2) in the placebo arm. This finding represented a statistically significant improvement in PFS in response to pazopanib monotherapy (HR 0.46, 95% CI 0.34 to 0.62, $p<0.0000001$). In addition, the response rate (defined as the percentage of subjects achieving either a confirmed complete or partial response according to RECIST) in the pazopanib arm was 30% versus 3% in the placebo arm, and the median duration of response in pazopanib-treated subjects was 58.7 weeks. Results from Study VEG105192 therefore clearly indicate that an 800 mg once daily dose of pazopanib is highly effective in treating subjects with advanced RCC.

Clinical data from more than 20 clinical Phase I, II, and III studies are available. As of the cutoff date, 09 September 2008, approximately 1600 subjects with cancer have received pazopanib in clinical studies conducted by Novartis Pharmaceuticals or NCI. Clinical data indicate that (a) pazopanib is absorbed after oral administration, (b) the 800 mg daily dosing regimen is an active monotherapy dose for subjects with cancer, providing optimal biologic and clinical effects associated with VEGFR inhibition, (c)

pazopanib is generally well-tolerated at the 800 mg daily dosing regimen, and (d) pazopanib has encouraging efficacy in specific tumor settings such as RCC, sarcoma, NSCLC, cervical and ovarian cancer.

The most common adverse events reported for pazopanib monotherapy to date are diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the National Cancer Institute-Common Toxicity Criteria of Adverse Events, Version 4.0 (NCI-CTCAE, v4.0). The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon.
The most common serious adverse events (SAEs), derived from all pazopanib studies that include studies where pazopanib was administered in combination with chemotherapy, are diarrhea, abdominal pain, vomiting, dyspnoea, hypertension (including one report of hypertensive crisis), pyrexia, anaemia, dehydration, fatigue, pneumonia, pleural effusion, neutropenia, pulmonary embolism, increase in ALT and nausea. Two cases of Torsades de Pointes have been reported in the pazopanib clinical program; however, whether or not there is a causal relationship to pazopanib remains unclear. A number of these events are known class effects of VEGF inhibitors. Therefore, this protocol is designed to closely monitor and provide clear management guidelines for these events based on the clinical experience with pazopanib to date.

2.3 Clinical and Preclinical Studies Assessing Response to Sunitinib in VHL, and Assessment of Endothelial Receptors in Renal Tumor and Hemangioblastoma Endothelium

A concerted effort to elucidate the functional consequences of a mutated VHL gene revealed that VHL is a key regulator of cellular hypoxia signaling. VHL controls protein levels of hypoxia-inducible factor 1 alpha (HIF1α) and HIF2α,[6] transcription factors that heterodimerize with HIF1α and result in the transcription of proangiogenic proteins in an HIFα isoform–dependent manner.[7]Agents developed to alter the downstream consequences of VHL inactivation and inappropriate angiogenesis include bevacizumab,[8] an anti-VEGF antibody, and sorafenib,[9] sunitinib,[10] and pazopanib,[11] which are small-molecule inhibitors of VEGF receptors (VEGFRs). Because all four of these agents demonstrated significant efficacy in patients with metastatic sporadic clear-cell RCC, which harbors the VHL mutation in most cases,[12] they were approved by the U.S. Food and Drug Administration for the treatment of advanced RCC.

The effect of these agents on VHL-specific lesions is not well known. We hypothesized that if the major functional consequence of VHL mutation is inappropriate angiogenesis,

then blocking VEGF signaling with a potent and specific VEGFR inhibitor will alter the growth pattern of all VHL-related lesions. To test this hypothesis, we initiated a clinical trial in which we treated individuals who have genetically proven VHL with sunitinib. Because interim findings on efficacy suggested that RCCs and HB respond differently to sunitinib, we analyzed the expression and activation of various molecular markers (endothelial VEGFR, PDGFR, Tie-2, fibroblast growth factor receptor 3 [FGFR3], and fibroblast growth factor receptor substrate 2 (FRS2), an intracellular signaling molecule specifically activated by FGFRs) in 20 archived tissue specimens each from sporadic RCCs and VHL-related HBs.

2.3.1 Clinical Outcome Data with Sunitinib

At least one follow-up imaging study was conducted on all patients. Table 1 shows the best responses of individual lesions according to RECIST.

Table 1. Best Response of von Hippel-Lindau Lesions by RECIST after Sunitinib

		Best Response N (%)		
Lesion Type	**No. of Lesions**	**Partial Response**	**Stable Disease**	**Progressive Disease**
Hemangioblastoma	21	0	19 (91)	2 (9)
Renal cell carcinoma	18	6 (33)	10 (67)	2 (10)
Renal cyst	9	0	9 (100)	0
Retinal angioma	7	0	7 (100)	0
Pancreatic NET	5	0	5 (100)	0
Pancreatic cyst	3	0	3 (100)	0

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; NET, neuroendocrine tumors.

Of the 21 evaluable individual HB lesions, there were no partial responses (PR). In comparison, 6 of 18 RCC lesions responded with a PR, (P=0.014). All five pancreatic NETs responded with SD. None of the seven retinal angiomas demonstrated any shrinkage on ophthalmoscopy; however, two patients with retinal angiomas complained of increased hyperemia and eye discomfort during sunitinib treatment. When change in

lesion size was evaluated as a percentage by organ site per individual, RCC decreased a mean of 14.4% by the end of cycle four, NETs a mean 12.7%, and HB, 5.9% (Table 2). When size change was assessed as a continuous variable, both RCCs and NETs showed significant size decrease after four cycles of sunitinib therapy.

Forty-eight–week follow-up scans were obtained for renal lesions in five patients. In these patients, who had been finished with therapy for 6 months, RCC and NETs had regrown to close to baseline measurements but no larger (Table 2).

Table 2. Mean Change from Baseline in Size of von Hippel-Lindau Lesions after Treatment with Sunitinib.

	Mean (Standard Error)						
Tumor Type	**Baseline Size(cm)**	**Cycle 2 Size (cm)**	**Percent Change**	**Cycle 4 Size (cm)**	**Percent change**	**Week 48 Size (cm)**	**Percent change**
Renal Cell Carcinoma	2.41 (0.21)	2.04 (0.21)	–16.41 (3.9)	2.06 (0.22)	–14.42 (4.5)	2.34 (0.24)	–3.37 (5.7)
P value		0.0004		0.0035		0.6098	
Pancreas NET	1.89 (0.28)	1.81 (0.28)	–3.59 (3.7)	1.64 (0.28)	–12.69 (4.0)	1.89 (0.29)	–1.72 (5.2)
P value		0.284		0.011		0.959	
Hemangioblastoma	0.81 (0.08)	0.81 (0.08)	0.65 (3.4)	0.76 (0.08)	–5.9 (5.4)	0.76 (0.09)	–6.2 (5.4)
P value		0.850		0.280		0.320	

2.3.2 ARCHIVED TISSUE ANALYSIS

After obtaining IRB approval, we retrieved 20 sequential formalin-fixed and paraffin-embedded specimens each of VHL-related HBs and sporadic RCCs at random from The University of Texas M. D. Anderson Cancer Center tissue bank. The specimens were analyzed at ApoCell, Inc. (Houston, TX), by using a laser-scanning cytometer (CompuCyte Corporation, Cambridge, MA), which is designed to enable fluorescence-based quantitative measurements on tissues at the single-cell level. This modality, like fluorescence-activated cell sorting analysis, provides multicolor immunofluorescence-intensity information from heterogeneous tissue specimens.

To detect biomarkers of interest, we incubated formalin-fixed tissues with CD31 (M0823, DakoCytomation), phosphorylated VEGFR2 (pVEGFR2; PC460, Calbiochem), VEGFR2 (SC-19530, Santa Cruz), FGFR3 (4574, Cell Signaling), Tie2 (334208, Biolegend),

pPDGFR-beta (SC-12909-R, Santa Cruz), PDGFR (SC-339-G, Santa Cruz), and pFRS2 (3864, Cell Signaling) antibodies, followed by species-specific secondary antibodies conjugated to fluorescent dyes (Cy5/FITC/PE; Jackson ImmunoResearch Laboratories). Each slide was placed on the computer-controlled motorized stage, and the area for scanning was visually located using the epifluorescence microscope of the cytometer, excluding normal and necrotic tissue regions. Slides were scanned using a 200× objective, and relative levels of fluorescence for each antigen were plotted on a scattergram. Results for biomarkers are represented as mean fluorescence intensity. Ratios of the fluorescence intensity of the phosphorylated to the total forms of VEGFR2 and PDGFR were also calculated. To detect signal in endothelial cells, relative fluorescence levels were assessed on a background of CD31 staining. For total tumor signal of antibody of interest, signal was assessed against a background of hematoxylin and eosin staining, in regions determined to be representative of tumor tissue.

The results of LSC on the archived tissue specimens from patients with VHL (20 untreated HBs and 20 untreated sporadic clear-cell RCCs) are summarized in Table 3. VEGFR2, pVEGFR2, and phosphorylated-to-total VEGFR2 ratios were statistically significantly higher in the RCC than in the HB samples. Conversely, FGFR3 and pFRS2 levels were higher in the HBs, with a strong trend in the endothelial cells (p=0.059) and significant differences in the overall tumor sample, with levels 11.45 (0.26) seen in HB vs. 11.26 (0.089) in RCC (P=0.003).

Table 3. Endothelial Receptor Levels in Hemangioblastomas and Renal Cell Carcinomas

	log(Hemangioblastoma)			**log(RCC)**			**t-test**	**Wilcoxon' rank test**
	N	mean	SD	N	mean	SD	p-value	p-value
pVEGFR2	20	11.268	0.498	20	11.752	0.378	0.001	0.003
VEGFR.total	20	12.977	0.478	20	13.081	0.859	0.639	0.192
pPDGFR	20	10.952	0.654	20	10.805	0.839	0.539	0.82
PDGFR.total	20	13.078	0.659	20	12.842	0.851	0.333	0.947
VEGFR.ratio	20	0.206	0.122	20	0.372	0.431	0.105	0.043
PDGFR.ratio	20	0.145	0.067	20	0.157	0.077	0.608	0.602

	log(Hemangioblastoma)			**log(RCC)**			**t-test**	**Wilcoxon' rank test**
	N	mean	SD	N	mean	SD	p-value	p-value
Tie2 in CD31PositiveCells	20	12.654	0.455	20	12.63	0.817	0.909	0.883
Tie2 in TumorCells	20	11.598	0.321	20	11.614	0.303	0.866	0.947
FGFR3 in CD31PositiveCells	20	12.265	0.448	20	12.29	0.961	0.914	0.495
FGFR3 in	20	11.439	0.224	20	11.338	0.106	0.075	0.174

TumorCells								
pFRS2 in CD31PositiveCells	20	12.495	0.492	20	11.91	0.989	0.023	0.059
pFRS2 in TumorCells	20	11.452	0.258	20	11.258	0.089	0.003	0.003

2.4 Rationale for Current Study:

In our previous study we found that sunitinib, an oral small-molecule inhibitor of VEGFR, PDGFR, Flt3, and cKit, provides a consistent response in RCCs but not in CNS hemangioblastomas from patients with VHL. Endothelial VEGFR and FGFR are expressed differently in RCCs and HBs. Based on these observations, we would like to further expand our observations in VHL patients with measurable VHL lesions. We predict that pazopanib, an orally bioavailable small molecule inhibitor of VEGFR as well as other receptor tyrosine kinases, will provide at least the same benefit as sunitinib in a broad VHL patient population, but may provide superior overall quality of life. Phase III studies and MD Anderson Cancer Center clinical experience with pazopanib suggests that this agent may result in fewer toxicities when compared with sunitinib. As individuals with VHL need to balance the impact of disease progression on their overall outlook with the possible consequences of being on chronic therapy which produces continuous side effects, pazopanib may be an acceptable choice. In addition, although our initial clinical and tissue based observations suggest that sunitinib did not provide any clear shrinkage of hemangioblastomas in our clinical study, these observations require further validation. For this reason, we have chosen to proceed with a larger single arm study evaluating pazopanib in the treatment of patients with VHL, but will not exclude individuals with hemangioblastomas, nor will we make it a requirement for individuals who enroll on this study to have RCC.

2.5 Rationale for choice of secondary endpoints

It may be difficult to measure success with an antiangiogenic agent using classical measures, such as RECIST, or progression free survival, due to the relative indolent rate of growth of some VHL related lesions. For that reason, we will request, where possible and available, that individuals who enroll on the study furnish imaging studies of their target VHL lesions up to 15 years prior to study enrollment. These studies will be used to generate a growth rate curve of target lesions, onto which the imaging studies acquired during the course of the study will be added. These data will provide information on the relative growth rates of VHL lesions, as well as how this growth rate is influenced by the chronic use of antiangiogenic therapy.

In a similar manner, we will acquire information on prior interventions performed on VHL related lesions in individuals treated on this study. We will calculate the rate of intervention over time, and determine whether this rate changes over the time period the patient is being followed.

2.6 Rationale for choice of preclinical endpoints

Data on circulating cytokine and angiogenic factors suggest these factors provide important prognostic and potential predictive information in patients with RCC. Little is known about how these factors vary as a function of lesion type in VHL at baseline, and whether they predict for benefit from pazopanib therapy. We will collect circulating cells, plasma and sera from patients at baseline, after 12 weeks, 24 weeks and at time of study discontinuation.

It is not known whether specific VHL mutations are associated with response to pazopanib in VHL patients. We will perform exploratory analyses of the relationship between VHL genotype and response to therapy, both globally and according to specific lesion.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

3. Genetically confirmed diagnosis of VHL or measurable disease consistent with the clinical diagnosis of VHL. (Please refer to criterion #5)

4. Measurable disease criteria:
   At least one measurable VHL related lesion, which is undergoing surveillance, and patient is not at immediate risk of needing intervention for this or other lesions. Biopsy is not required given the known likely etiology and natural history in the setting of a positive genetic test.
   a. Brain: asymptomatic hemangioblastoma, $\geq$ 0.5 cm
   b. Spine: asymptomatic hemangioblastoma, $\geq$ 0.5 cm
   c. Renal: solid mass suspicious for RCC $\geq$1 cm or cystic mass (Bosniak 3-4) $\geq$1 cm.
   d. Pancreas: solid mass $\geq$1cm and $\leq$ 3 cm suspicious for neuroendocrine tumor, or neuroendocrine tumor > 3 cm but not considered operable.
   e. Eye: asymptomatic peripapillary and/or macular hemangioblastoma, any size
   f. Adrenal: asymptomatic or controlled pheochromocytoma greater than 1cm in size

5. Patients may have received prior VHL-related systemic therapy, provided not within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib.

6. Adequate organ-system function as defined in Table 4.

Table 4. Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.0 X ULN
Renal	
Serum creatinine	≤2.0 mg/dL (133 µmol/L)
Or, if >2.0 mg/dL: Calculated creatinine clearance (Cl_{CR}) (appropriate appendix)	≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; appropriate appendix)[d]	<1

a. Subjects may not have had a transfusion within 7 days of screening assessment.
b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation or if they are on low molecular weight heparin.
c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
d. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.

7. A female is eligible to enter and participate in this study if she is of:
Non-childbearing potential including
a) any female who has had a surgical procedure rendering her incapable of becoming pregnant.
b) Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40 pg/mL (<140 pmol/L).
c) Subjects using HRT must have experienced total cessation of menses for ≥ 1 year and

be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Novartis Pharmaceuticals acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Oral contraceptive
- Injectable progestogen.
- Implants of levonorgestrel.
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD)
- Male partner sterilization
- Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

3.2 Exclusion Criteria

1. Prior malignancy. Subjects who have had another non VHL related malignancy and have been disease-free for 2 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.

2. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

   - Active peptic ulcer disease
   - Known intraluminal metastatic lesion/s with risk of bleeding
   - Inflammatory bowel disease (e.g. ulcerative colitis, Chrohn's disease), or other gastrointestinal conditions with increased risk of perforation

- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.

3. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:
   - Malabsorption syndrome
   - Major resection of the stomach or small bowel.

4. Presence of uncontrolled infection.

5. Corrected QT interval (QTc) > 480 msecs using Bazett's formula

6. History of any one or more of the following cardiovascular conditions within the past 6 months:
   - Cardiac angioplasty or stenting
   - Myocardial infarction
   - Unstable angina
   - Coronary artery bypass graft surgery
   - Symptomatic peripheral vascular disease
   - Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)

7. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥ 140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].
   Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <140/90 mmHg in order for a subject to be eligible for the study

8. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
   Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible

9. Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).

10. Evidence of active bleeding or bleeding diathesis.

11. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.

12. Unable or unwilling to discontinue use of prohibited medications list in Section 4.0 for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study (Section 5.0).

13. Treatment with any of the following anti-cancer therapies:
    1. radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR
    2. chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib

14. Any ongoing toxicity from prior investigational therapy that is >Grade 1 and/or that is progressing in severity, except alopecia.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 STUDY DRUG

4.1 Preparation and Dispensing

Pazopanib will be dispensed as capsules at the beginning of each treatment cycle. In case of dose modification, patients will be requested to return all of their previously dispensed capsules.

4.2 Concomitant Medications and Non-Drug Therapies

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by Novartis Pharmaceuticals and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

4.2.1 Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to Screening. The investigator, or designee, must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

All concomitant medications taken during the study will be recorded in the GURU database, dose information, and dates of administration.

Subjects should receive full supportive care during the study, including transfusion of blood

and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Caution should be exercised when using 5HT3 drugs in a first-line setting due to the potential for QTC prolongation.

Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

4.2.2 Permitted Medications – Use with Caution

Specific recommendations regarding anticoagulants:
Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

Specific recommendations regarding hypoglycemic therapy including insulin:
Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib[13]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

Specific recommendations regarding agents that prolong QT interval:
Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease.

The Effects of Pazopanib on Other Drugs
In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X receptor

transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to perpazopanibheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

4.2.3 The Effects of Other Drugs on Pazopanib

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with **CAUTION**.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction to 400 mg pazopanib should be considered when it must be co-administered with strong CYP3A4 inhibitors.

Strong CYP3A4 inhibitors include (but are not limited to):

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole

- Antidepressants: nefazodone CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.
- Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to):

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamezepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

Prohibited Medications

Subjects should not receive other investigational therapy while on treatment in this study. The time period that subjects should not receive any other investigational drugs prior to the first dose of study drug is 28 days. Subjects should not receive any other investigational drug within 15 days of the last dose of pazopanib and until post-treatment blood draws are completed.

5.0 TREATMENT PLAN

5.1 Pazopanib Administration

Pazopanib is a tyrosine kinase inhibitor (TKI). Pazopanib is presented as the hydrochloride salt, with the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. It has the molecular formula C21H23N7O2S•HCl and a molecular weight of 473.99.

Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

Tablets of pazopanib are for oral administration and is supplied in a 200 mg film-coated tablet. Each film-coated tablet contains pazopanib hydrochloride equivalent to 200 mg of pazopanib free base. The inactive ingredients of pazopanib are: Tablet Core: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. Coating: Hypromellose, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80, titanium dioxide and may contain iron oxide black , yellow, or red depending on tablet color. The 200 mg tablets of pazopanib are modified capsule-shaped, gray, film-coated with GS JT debossed on one side. Pazopanib should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Pazopanib is being provided by the study supporter, Novartis.

5.2 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.3 Duration of Follow Up

Patients will be followed every 3 months for 24 weeks after stopping study drug treatment or until death, whichever occurs first. Patients that have stopped study drug treatments for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow-up will consist of a phone call or medical record review.

5.4 Contingency to Continue Medication

Patients experiencing a clinical benefit will be given the option of continuing the medication until clinical or radiographic progression occurs, or intolerance to treatment develops, and will continue to be monitored.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Pazopanib dose interruptions and modifications

As a general rule, if dose reduction of pazopanib is necessary, the dose should be reduced stepwise by 200 mg at each step, and the subject should be monitored for approximately 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the pazopanib may need to be interrupted and/or the dose further decreased with continued monitoring for an additional 10-14 days at each dose level, and so on.

If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the pazopanib dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).
If a subject's treatment has been interrupted for more than 21 days, there must be a review of the subject's condition in order to resume the treatment.

Dose Interruptions/Modifications for Specific, Non-liver Related, Toxicities

Recommendations for investigational product dose interruptions/modifications in case of specific treatment-emergent AEs are provided in **Table 5**.

Table 5. **Dose Modification Algorithms for Potential Treatment-Related Adverse Events**

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Step 1. Continue pazopanib at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Consider reducing or interrupting pazopanib, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg if pazopanib was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt pazopanib Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue pazopanib and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt pazopanib. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC >3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2 Step 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow-up per protocol.
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	

AE Terms & Descriptions	Dose Modification Algorithms
Grade 1	For hemoptysis, interrupt pazopanib to discuss whether further treatment with pazopanib is appropriate. For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolved to ≤ Grade 1. Step 2. Restart pazopanib; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue pazopanib at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt pazopanib. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume pazopanib at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib dosing (eg, re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue pazopanib and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue pazopanib and continue follow-up per protocol.

AE Terms & Descriptions	Dose Modification Algorithms
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue pazopanib with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 2. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue pazopanib and follow-up per protocol
Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue pazopanib; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 1. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue pazopanib and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.	
QTc ≥ 480 < 500 msec	Continue pazopanib; monitor as clinically indicated.
QTc ≥500 msec	Discontinue pazopanib and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4)
Abbreviations: BP, blood pressure.

6.2 Dose Interruptions/Modifications for Hepatotoxicity

Note: Liver chemistry abnormalities meeting pre-defined criteria must be promptly reported as a SAE (see SAE Section 8.1.2).

Liver Chemistry Abnormalities Requiring Reporting:
ALT > 3.0 x ULN **with** concomitant elevation in bilirubin[a] (defined as total bilirubin ≥ 2.0 x ULN; with direct bilirubin > 35%) **or with** hypersensitivity symptoms (e.g., fever, rash).

ALT > 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[a] < 2.0 x ULN or direct

bilirubin ≤ 35%) and **without** hypersensitivity symptoms (e.g., fever, rash).

a. Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin > 1.5 x ULN, then the event should be promptly reported as defined.

Guidelines for investigational product dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in table **.**6. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications, and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Details on the subject's alcohol use will be captured in the eCRF. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document progression of malignancy.

Table 6. **Guidelines for Management of Treatment Emergent Hepatotoxicity**

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT > 3.0 x ULN to ≤ 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin [b] < 2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(C). ALT > 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] < 2.0 x ULN or direct bilirubin ≤ 35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria[c]:** (1) Interrupt pazopanib until toxicity resolves to ≤ Grade 1 or baseline. Report the event as a SAE **within 24 hours** of learning of its occurrence and complete the appropriate eCRF forms. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) If the subject is benefiting from the study treatment, contact Novartis Pharmaceuticals Study Physician for possible re-challenge. Re-treatment may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin < 1.5 x ULN or direct bilirubin ≤ 35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. **Recurrence – Liver Event Stopping Criteria[c]:** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. At the time of the recurrence, complete the appropriate eCRF forms.

(D). ALT > 3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥ 2.0 x ULN; with direct bilirubin > 35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria[c]:** (1) Discontinue pazopanib immediately, report the event as a SAE **within 24 hours** of learning of its occurrence, and complete the appropriate eCRF forms. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. (2) Consult a gastroenterologist / hepatologist, collect PK sample (if requested) and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging -Consider toxicological blood screen for possible contributing chemical/medical entities (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs [a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin[b] elevation **without** concurrent ALT increases (defined as ALT < 3 x ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. (2) If bilirubin is > 1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is > 35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin > 1.5 x ULN, then the event should be promptly reported as a SAE.
c. When a liver chemistry event meets the Liver Event Interruption Criteria or Liver Event Stopping Criteria, blood samples may be requested for PK analysis on a case-by-case basis.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eCRF, electronic case report form; IP, investigational product; LFT, liver function tests; PK, pharmacokinetic; SAE, serious adverse event; ULN, upper limit of normal

Laboratory Assessments: Liver Function Tests

When a separate LFT panel is tested, it should include the following: ALT, AST, alkaline phosphatase, GGT, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 x upper limit of normal (ULN). Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to assure subject safety. Guidelines for evaluation of the LFTs are described in Table 6: Guidelines for Management of Treatment Emergent Hepatotoxicity.

6.3 Diarrhea

In cancer patients, diarrhea can be debilitating and potentially life threatening, with dehydration, renal insufficiency, and electrolyte imbalances. Pazopanib as a monotherapy has been associated with an increased incidence of diarrhea, which is grade 1 or 2 in the majority with grade 3/4 diarrhea occurring in approximately 4% of subjects. The incidence and severity may increase when administered with other agents known to cause diarrhea.

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel pattern should be established so that changes in that pattern can be identified. In addition, subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

The NCI CTCAE Version 4.0 criteria for defining diarrhea are provided below.

Toxicity Grade	**Diarrhea (includes diarrhea of small bowel or colonic origin and/or ostomy diarrhea)**
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; IV fluids indicated < 24 h; moderate increase in ostomy output compared to baseline; not interfering with daily living
3	Increase of ≥7 stools/day over baseline; incontinence; IV fluids ≥ 24 h; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living
4	Life threatening consequences (e.g., hemodynamic collapse)
5	Death

Uncomplicated diarrhea is considered mild to moderate and defined as CTCAE Grade 1 to 2 with no complicating signs or symptoms.
Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with 1 or more of the following signs or symptoms; cramping, nausea/vomiting, ≥ Grade2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, and/or dehydration. If complicated diarrhea goes unrecognized or untreated, it may lead to death.
Experience thus far suggests that, when pazopanib is used as monotherapy, uncomplicated CTCAE Grade 1 or 2 diarrhea may ensue. In rare cases, subjects treated with monotherapy pazopanib may develop debilitating and potentially life-threatening diarrhea with dehydration, renal insufficiency, and electrolyte imbalances. The pathophysiologic mechanism of diarrhea with pazopanib is not known.
The following broad general management principles are recommended as means by which a subject with diarrhea may avoid more serious complications. Guidelines such as these should never replace sound clinical judgment. Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea[14]. The guidance provided here is a modification of the ASCO guidelines:
Early identification and intervention is critical for the optimal management of diarrhea.

- A subject's baseline bowel pattern should be established so that changes in that pattern can be identified.

- Subjects should be educated on the signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

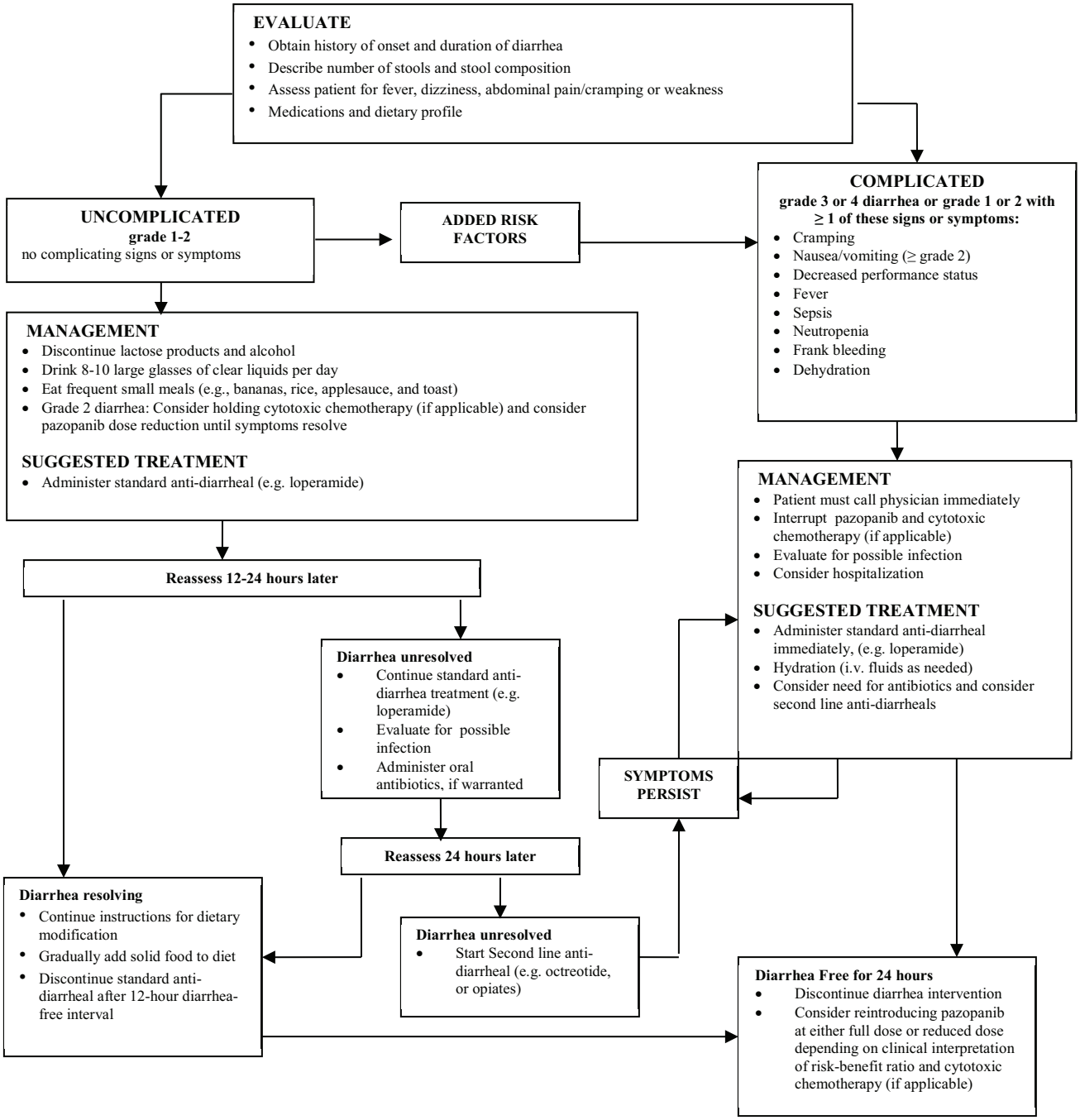
- At the initiation of diarrhea, an assessment of frequency, consistency, duration and other symptoms such as fever, cramping pain, nausea, vomiting, dizziness and thirst should be taken to identify subjects at high risk of complications.

Several treatments have demonstrated efficacy in diarrhea management:

- Loperamide, administered as an initial 4-mg dose, followed by 2-mg doses after every unformed stool with a maximum of 16mg per day. This dose and regimen are moderately effective. Continuation of loperamide is suggested until the subject is diarrhea-free for 12 hours. Dose should not exceed a maximum of 8 tablets (16 mg) per day.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. In the treatment of chemotherapy-induced diarrhea, octreotide can be administered at doses ranging from 100µg twice daily to 500µg 3 times daily, with a maximum-tolerated dose of 2000µg 3 times daily in a 5-day regimen. However, the effect of octreotide on diarrhea associated with use of pazopanib is unknown.

Other agents may be prescribed for treatment of diarrhea, such as diphenoxylate/atropine, tincture of opium, and/or psyllium, at the treating physician's preference.

Figure 1. Flow chart for management of Diarrhea



6.4 Nausea and Vomiting

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are unable to retain pazopanib.
Routine pre-medication for nausea is not necessary, but symptomatic subjects should be treated with standard anti-nausea/anti-emetic therapy as necessary.
If a subject vomits after taking study medication, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking pazopanib at the next scheduled dose on the following day. . If vomiting persists then the subject should contact their physician.

To prevent or treat nausea and vomiting standard medications are recommended. These may include: 5-HT_3 receptor antagonist (granisetron, ondansetron, dolasetron mesylate); NK-1 receptor antagonists such as aprepitant, metoclopramide, phenothiazines (prochlorperazine); corticosteroids, (dexamethasones, prednisone); and cannibinoids (dronabinol). Caution should be exercised when using 5HT3 drugs in a first-line setting due to the potential for QTC prolongation.

6.5 Prompt Reporting of Serious Adverse Events and Other Events to Novartis Pharmaceuticals

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly to Novartis Pharmaceuticals as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Table 7.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 weeks	Pregnancy Notification Form	2 weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT: >3.0 x ULN **with** concomitant elevation in bilirubin[a] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) **or with** hypersensitivity symptoms (e.g., fever, rash).	24 hours	SAE data collection tool. [b]Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. [b]Updated Liver Event CRF
ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[a] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	24 hours	SAE data collection tool. Liver Event CRF[b]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[b]

c. Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2.0 x ULN, then the event should be promptly reported as defined.
d. Liver event documents should be completed as soon as possible.

7.0 CLINICAL AND LABORATORY EVALUATIONS

7.1 Pre-treatment Evaluations

7.1.1 Within 8 weeks of signing informed consent:

- All the participants must have signed a consent form agreeing to participate in the study.
- Radiographic examination shall include CNS MRI (brain, cervical and thoracic spine, and saggital T1 post contrast view of the lumbar spine performed in same study and at same time as MRI of cervical and thoracic spine MRI) and CT scans of the chest and abdomen if evaluable lesions exist in these regions. MRI of the abdomen is allowed instead of CT. Appropriate additional studies should be obtained to fully define the extent and severity of existing or suspected VHL disease. Retinal examination will be performed for those patients with known or suspected retinal involvement.
- An electrocardiogram (ECG) will be completed to evaluate heart health.
- Those with a known pheochromocytoma should have serum or urinary evaluation for metanephrines and be under the care of an endocrinologist for management for changes in blood pressure at initiation of therapy

7.1.2 Within two weeks of study entry:

- All patients must undergo a complete history and physical examination including vital signs, ECOG performance status, height, and current weight. Concurrent non-VHL disease and medical therapy must be documented. On-study forms must be filled out completely. All prior anti-VHL treatment must be recorded in proper detail. Laboratory studies shall include CBC w/differential, platelet count, chemistry panel (albumin, alkaline phosphatase, BUN, calcium, creatinine, glucose, LDH, phosphorus, Liver Function Test (total bilirubin, SGOT[AST] and/or SGPT[ALT]), sodium, potassium, carbon dioxide, chloride, lipase, PT, PTT. Urine protein creatinine ratio. Serum pregnancy test in female patients of childbearing potential (not postmenopausal for at least one year or not surgically capable of bearing children) will also be included.

- Optional baseline blood will be collected for correlative studies (approximately 30cc).

- Any residual toxicity from prior therapies should be recorded by using the grading schema in NCI Common Toxicity Criteria v4.0.

7.2 Evaluation During Treatment

7.2.1 On-study evaluations will consist of the following study activities. A cycle is considered a 4 week period of treatment. Labs that are not drawn at the time of a visit or restaging can be obtained at a medical facility or laboratory that is not directly associated with the Investigator's institution, and forwarded to the Investigator within 96 hours (4 days).

- Liver Function Test (Serum total bilirubin, SGOT[AST], SGPT [ALT]), will be drawn every two weeks for the first eight weeks (+/- 3 days), and then at the beginning of every cycle (+/- 3 days).

- Serum chemistry and electrolytes including albumin, alkaline phosphatase, BUN, calcium, creatinine, glucose, LDH, phosphorus, total protein, sodium, potassium, carbon dioxide, chloride, lipase, are to be done at the beginning of every cycle (4 weeks +/- 3 days). Hematology including CBC with differential and platelet counts at the beginning of every cycle (4 weeks +/- 3 days).

- Interim medical history and physical examination (including vital signs and weight) every 12 weeks (+/- 7 days), at the time of restaging (physical examination will only be repeated at C1D1 if > 7 days since screening).

- ECOG performance status with each Physical Exam.

- Record concomitant medications at the time of interim medical history and physical exam (which will be done every 12 weeks +/- 7days). Monitor for adverse events.

- Repeat radiographic examination (CT, MRI, as indicated) to evaluate disease progression or response will be done at the end of cycles 3 and 6, and will coincide with interim medical history and physical examination, and every 12 weeks thereafter (if patient continues on treatment) (+/- 7days).

- Retinal examination for those with known retinal lesions at the end of cycles 3 and 6 +/- 7 days.

- Optional blood for correlative studies will be drawn while receiving study drug after 12 weeks +/- 1 week and after 24 weeks +/- 1 week to coincide with the restaging visits.

7.2.2 Early withdrawal/End of Study

Early withdrawal is defined as a patient who is unable to complete one cycle of pazopanib. The following study activities will be completed at early withdrawal or at the end of treatment:

- Physical exam. ECOG performance status. Radiographic examination and assessment of response. Retinal examination for those with known retinal lesions. Serum chemistry and electrolytes to include: albumin, alkaline phosphatase, BUN, calcium, creatinine, glucose, LDH, phosphorus, total protein, Liver Function Test (total bilirubin, SGOT[AST] and/or SGPT[ALT]), sodium, potassium, carbon dioxide, chloride, and lipase. Hematology to include: CBC with differential and platelet count.

- Record for concomitant medications. Monitor for adverse events.

- Optional blood for correlative studies will be obtained. Approximately 30cc of blood will be collected.

7.3 Contingency to continue study for responders

After the initial 24 week treatment period, patients who demonstrate clear response/ and or benefit to therapy will be evaluated on a case-by-case basis and may be continued. The follow up schedule and required procedures for the additional cycles will be the same as done previous cycles.

7.4 Contingency for Surgical Intervention

Patients who progress either clinically or radiographically and require an immediate surgical intervention will proceed with the appropriate procedures. No washout period is mandated in light of the fact that bleeding and wound healing has not been documented to be a side effect of pazopanib. If there is clinically relevant neutropenia or thrombocytopenia, or other abnormal laboratory parameters that in the opinion of the surgeon or study physician will have a negative impact on surgical outcome, patients will need these values corrected prior to surgery. If patients have given consent for tissue banking, redundant excised tissue will be harvested at the time of surgery by the surgical pathologist.

If there is evidence of continued benefit in other organ(s) i.e. shrinkage or stabilization which can be attributed to study drug, patient will remain on study and drug will be restarted 2 weeks post-surgery or at a later date if patient requires further postoperative recovery, until a lack of further benefit is demonstrated in those organ(s) on restaging scans.

7.5 Study Calendar

Baseline evaluations are to be conducted within 2 weeks prior to study entry. Scans must be done within 8 weeks of signing the informed consent. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Cycle 1 physical examination will only have to be repeated in > 7days from screening.

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Additional Cycles	
	Baseline	Wk 1-4	Wk 5-8	Wk 9-12	Wk 13-16	Wk 17-20	Wk 21-24		Early Withdrawal/Post-Treatment Evaluation[d]
Pazopanib		X	X	X	X	X	X	X	
Informed Consent	X								
History and Physical[l]	X[j]	X			X			X[m]	X
Concomitant Medications	X	X			X		X	X	X
Performance Status	X	X			X			X[m]	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X
Serum Chemistry[b]	X[k]	X	X	X	X	X	X	X	X

UPRC	X								
EKG	X								
Liver Function Tests[i]	X	X	X	X	X	X	X	X	X
B-HCG	X[c]								
Optional Blood for Correlative Studies[g]	X			X			X	X	X[f]
Radiographic and Retinal Examination[e,h]	X				X		X	X	X
Adverse Event Monitoring	X	←----------					----------→	X	X

a: Pazopanib Dose as assigned; route/schedule.
b: Albumin, alkaline phosphatase, BUN, calcium, creatinine, glucose, LDH, phosphorus, total protein, sodium, potassium, carbon dioxide, chloride, lipase. Note: Add PT and PTT testing at screening only.
c: Serum pregnancy test (women of childbearing potential).
d: Off-study evaluation may take place within 5-7 months after the last dose of study drug.
e. If high-quality baseline measurement is available from an outside institution, this will be considered acceptable. For individuals who do not have retinal lesions, no further retinal evaluations will be necessary for study purposes. If retinal lesions are present, retinal exams must take place every 12 weeks (+/- 7 days)
f. A single sample (approximately 10 cc) at treatment discontinuation (only if related to disease progression).
g. Optional blood also drawn at time of dose reduction or modification
h. Follow-up radiographic scans will take place at the end of cycles 3 and 6, and every 12 weeks thereafter (+/- 7 days).
i. Liver function tests (LFTs) are defined as total bilirubin, SGPT (ALT) and SGOT (AST). For the first eight weeks of study, LFTs will be drawn EVERY TWO WEEKS and every four weeks thereafter.
j. Concurrent non-VHL disease and medical therapy must be documented. All prior anti-VHL treatment must be recorded in proper detail. Any residual toxicity from prior therapies should be recorded by using the grading schema in NCI Common Toxicity Criteria v4.0.
k. Those with known pheochromocytoma will have serum and urinary evaluation.
l. Day 1 of each Cycle. Height (baseline only), weight, and vital signs will be taken during physical exam.
m. Physician exams, interim history, vital signs and performance status will be done every 12 weeks (±7 days)

8.0 ADVERSE EVENTS AND REPORTING REQUIREMENTS

8.1 Reporting Requirements

8.1.1 Adverse Drug Reaction Reporting

Toxicity will be scored using CTC Version 4.0 for toxicity and adverse event reporting. A copy of the CTC Version 4.0 can be downloaded from the CTEP homepage (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Adverse events will for this protocol will be documented and entered into the case report form according the Recommended Adverse event Recording Guidelines for Phase II protocol.

Table 8.

Recommended Adverse Event Recording Guidelines					
Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

8.1.2 Serious Adverse Event Reporting (SAE)

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in

an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board (IRB) Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices".

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported in accordance with the IRB policy. This may include the development of a secondary malignancy.**

8.1.3 Reporting to FDA

SAE's will be reported per regulatory (local and federal) guidelines.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies.

Reporting to Novartis
The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug) and report only SAEs arising in subjects exposed to the Novartis Study Drug(s). Complete the SAE Report in English. Send the completed and signed form by fax, within 24 hours of first becoming aware of the event, to Novartis. . You must report safety data to Novartis by fax to:

- **US CPO DS&E Fax #: (877) 778-9739**
    - **Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox:**

  - **clinicalsafetyop.phuseh@novartis.com**
- **Please include Novartis SAE report coversheet for any SAE report (Attached)**
  - **Novartis Study Code (CPZP034XUS34T) must be on the SAE coversheet**

Pregnancies
Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

8.2 Clinical Laboratory Adverse Events

The results of all laboratory tests required by the protocol will be recorded in the patient's medical record. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the diagnosis that explains them is made.

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a SAE, and/or
5. Test result is considered to be an adverse event by the investigator.

*Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet Condition 2 above for reporting as an adverse event.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for Condition 4.

8.3 Management of Persistent and Refractory Toxicity

Utilizing the NCI CTCAE (version 4.0), events which are moderate and interfere with function that are not consistent with a patient's medical history, and are refractory to medical treatment, should be investigated carefully to ensure that no other etiology is present. Study drug will be held for any toxicity events deemed definitely, probably, or possibly drug-related (such as diarrhea, hypertension, vomiting, diarrhea, and dizziness) and that are greater than grade 2. Drug will be held until severity is reduced to Grade 1

or less and then resumed daily dosing with a dose reduction as outlined in Section 6.0.

8.4 Management of All Other Toxicities

Other toxicities may occur. Supportive care should be prescribed as needed. They may also be prescribed prophylactically to prevent toxicity from developing or recurring. The examples include anti-emetics for nausea/vomiting, analgesics for pain, antipyretics for fever and antidiarrheals for diarrhea

Abnormal laboratory values will be only be captured as adverse events if they are Grade 3 or higher.

8.5 Investigator Communication with Supporting Companies:

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening, and related to study intervention), Principal Investigator will report to Novartis Pharmaceuticals by facsimile any Serious Adverse Event ("SAE," as defined below) that occurs from after the first dose of pazopanib through 30 days after discontinuation of pazopanib, using the M.D. Anderson Serious Adverse Event Form. Events should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Novartis Pharmaceuticals within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of pazopanib and considered by the investigator to be related or possibly related to pazopanib must be reported to Novartis Pharmaceuticals if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

9.0 CORRELATIVE/SPECIAL STUDIES

9.1 Correlate responders/nonresponders with genetic mutation analysis in order to define genetic signatures of responses at the organ level.

9.2 Baseline, week 12 and week 24 blood will be drawn and processed for cytokine-angiogenesis factor analysis. A 50 panel Luminex bead based assay will be employed to evaluate baseline and therapy-induced changes in the profile. This profile will also be compared to internally generated data on patients with sporadic RCC to further explore the disease and therapy specificity of the profile.

9.3 Baseline, week 12 and week 24 blood will be drawn to evaluate baseline circulating endothelial cells and their changes as a function of therapy. These exploratory data will be employed to generate hypotheses on the interaction between host, tumor and therapy.

10.0 DATA AND PROTOCOL MANAGEMENT

10.1 Data Entry: All data will be entered to the Department of Genitourinary Medical Oncology Oracle database (GURU). GURU is a password protected database with an audit trail. Data can be collated with a unique GURU identification in order to de-link information. The minimum required fields will be entered to the MDACC required data collection systems (CORe/PDMS). Data will be derived from the patient chart and the Principal Investigator will be the final arbiter of any conflicting entries. The Principal Investigator will be the final arbiter of response, toxicity, or progression should a difference of opinion exist.

Patient Confidentiality: In order to maintain patient privacy, all database generated case report forms, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (21CFR312.63, 21CFR312.68).

10.2 Study Drug Management
Returned or expired study drug will be destroyed on site per MDACC Investigational Pharmacy policies.

11.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained no sooner than 6 weeks following trial completion to document cases of objective response.

11.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, with rationale for modification as noted below in Section 11.1.5. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

11.1.1 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 with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). For CNS lesions (hemangioblastomas), measurable lesions are defined as measuring at least 5mm in diameter. This change has been made in recognition of the fact that CNS lesions that equal or exceed 10mm (1cm) may already be symptomatic and require surgical intervention. In order to capture patients in a disease state where therapeutic intervention may be of benefit, lesions measuring 5mm are considered measurable.

11.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI) are all non-measurable.

11.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD (per target organ as per Section 11.1.5) will be used as reference by which to characterize the objective tumor response.

11.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.5 Rationale for Modification to RECIST Criteria

Patients with VHL have a germline genetic mutation, which displays differential organ phenotypes. Due to the same mechanisms, it is reasonable to assume that responses to targeted therapy may be different in various organ-sites as a result of epigenetic, environmental, and circulatory differences. Using strict RECIST criteria (such as using the sum of all lesions) will lead to potentially significant loss of

important information. For the purposes of this study, imaging-based measurements will follow RECIST criteria except for the following conditions:

- Target organ systems will be uncoupled and evaluated separately. Summation of lesion size will be performed separately for the kidney, pancreas, CNS (brain+spine), and retina, and changes from baseline compared using these measurements.

- The number of lesions measured from each site will be modified (specified in Section 11.2, Guidelines for Evaluation of Measurable Disease), as there may be innumerable lesions present, some probably too small to give reproducible and accurate measurements.

11.2 Guidelines 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 not more than 6 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 when both methods have been used to assess the antitumor effect of a treatment.

- CT scans: spiral, multiphasic, contrast-enhanced computed tomography of abdomen and pelvis with thin-cuts (5 mm) of adrenals, kidneys, and pancreas. Multi-channel helical CT scan only will be used, as this will provide the most reproducible and reliable size measurements, particularly for lesions in the range of 1 cm.

- CT Interpretation: all CT studies will be evaluated by a radiologist according to standard practice. Up to 5 of the largest renal lesions and 3 of the largest pancreatic lesions will be measured in the single longest dimension per RECIST guidelines.

- MRI Scans: dynamic contrast-enhanced and diffusion-weighted magnetic resonance imaging of brain and spinal column. Up to 5 of the largest CNS lesions will be measured in the single longest dimension per RECIST guidelines. MRI of the abdomen will follow same rules as for CNS lesions.

- Retinal examination: fluorescein angiography with photographs, color testing, visual field testing and echography as needed. Please refer to Appendix C, Recommendations for Retinal examination and Follow-up, for complete details on

ophthalmologic evaluation.

11.3 Response Criteria

11.3.1 Evaluation of target lesions (this will be an organ-specific evaluation, please see Section 11.1.5 *Rationale For Modified RECIST Criteria*)

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the study chair should prevail.Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

11.3.3 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.

Target Organ Lesions	Non-Target Organ Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

X For the purposes of this study, response rate (RR) is based on CR+PR+SD.

X Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.4 Confirmatory Measurement/Duration of Response

11.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no sooner than 6 weeks after the criteria for response are first met.

11.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

11.4.3 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.

12.0 STATISTICAL CONSIDERATIONS

This is a single arm phase II trial to evaluate safety and efficacy of treatment with pazopanib for 24 weeks in patients with VHL who have measurable VHL related lesions.

12.1 Design and sample size/power

In this study, we will treat up to 40 patients with VHL who have measurable VHL related lesions. Patients will receive Pazopanib 800mg PO daily for up to 24 weeks. Patients may choose to continue the regimen beyond 24 weeks until evidence of objective disease progression. Efficacy will be determined by the RECIST overall response rate (CR+PR) at 24 weeks. Early termination due to progressive disease or toxicity will be considered as a failure. Patients not completing 1 month of therapy due to a reason other than drug toxicity or progressive disease will be considered inevaluable. We will monitor for any lesion progression (PD) and drug discontinuation due to toxicity (DD) during the whole period of the treatment simutaneously. If there is a high probability that the PD rate exceeds 20% or the DD rate exceeds 10%, the trial will be stopped early and the drug will not be considered of interest for further study. Formally, the study will be terminated if Pr(PD Rate > 0.20 | Data) > 0.90 or Pr(DD Rate > 0.10 | Data) > 0.90. The assumed prior distributions for PD rate and DD rate are Beta (0.2, 0.8) and Beta (0.1, 0.9), respectively, with one patient's worth of information. The study will be monitored in cohorts of 10 patients. Consideration to stop the trial will be given according to the stopping boundaries in Table 1. The operating characteristics for these stopping rules are summarized in Table 2, based on 10,000 simulations. Specifically, if the PD rate is 20% and DD rate is 0.10, then there is a 27% chance to stop the trial early and the average expected number of patients

treated will be 33. On the other hand, if (PD rate, DD rate) are (0.10, 0.05), or (0.10, 0.30), then the early stopping probabilities will be 3% and 94% and the average numbers of patients treated are expected at 39 and 16, respectively. If the trial continues to the end with 40 patients treated, we will be able to estimate the response rate at 24 weeks with standard error not larger than 0.08, i.e., the half length of the 95% confidence interval will not exceed 15%.

Table 1. Stopping boundaries for PD and DD monitoring.

Total Number of Patients Treated	**Stop if number of Progressions >=**	**Stop if number of Drug Discontinuation (due to Toxicity) >=**
10	4	3
20	7	5
30	10	6

12.2 Analysis Plans

If the trial is stopped early, this drug will not be considered of interest for future study VHL patients. If all 40 patients are accrued, we will estimate the response rate, early progression rate, toxicity rate and their corresponding 95% posterior credible intervals.

Biomarker endpoints and genetic mutations will be measured at baseline and/or over time. Summary statistics, including frequency tabulation, means, standard deviations, median, and range, will be used to describe subject characteristics and marker data. The chi-squared (χ^2) test or Fisher's exact test will be used to test the association between two categorical variables, such as response and prognostic factors and discrete markers. The association among various continuous and discrete markers and response may be assessed first by the exploratory data analysis graphically and tested using Wilcoxon rank sum test. Correlation among continuous biomarkers will be examined by Pearson or Spearman rank correlation coefficients. Both univariate and multivariate logistic regressions may be performed to model the baseline prognostic factors such as age, gender, race, smoking history, performance status, markers, etc, on response, when appropriate. We will also use the generalized estimating equations to model correlated discrete variables. Repeated measures analysis including mixed effects model will be performed to analyze continuous biomarkers change over time. Time to progression (TTP) will be estimated using the Kaplan-Meier method. Log-rank test will be performed to test the difference in survival between prognostic groups. Regression analyses of survival data based on the Cox proportional hazards model will be

conducted on TTP. The proportional hazards assumption will be evaluated graphically and analytically, and regression diagnostics (e.g., martingale and Shoenfeld residuals) will be examined to ensure that the models are appropriate.

Table 2. Operating characteristics for the stopping rules for excessive PD rate or DD rate

True PD Rate	True DD Rate	Probability of Early Termination	Average Expected # of Patients
0.10	0.05	0.03	39.2
0.30	0.05	0.57	25.8
0.20	0.10	0.27	33.1
0.30	0.10	0.61	24.6
0.30	0.15	0.71	22.1
0.10	0.20	0.64	25.7
0.20	0.20	0.70	23.4
0.30	0.20	0.84	18.9
0.10	0.30	0.94	16.3

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