A Phase II Study of Pazopanib in the Treatment of Surgically Unresectable or Metastatic Chondrosarcoma

PROTOCOL NUMBER: AAPSMCS1002

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Amendment 1
Amendment 2
Amendment 3
Amendment 4

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For Vector Oncology protocol AAPSMCS1002, A Phase II Study of Pazopanib in the Treatment of Surgically Unresectable or Metastatic Chondrosarcoma, Amendment 4:

I agree to conduct the study as detailed in the protocol and in compliance with ICH Guidelines for Good Clinical Practice.

I acknowledge that I am responsible for overall study conduct, and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

_____
Principal Investigator printed name

_____ _____
Principal Investigator signature Date

PROTOCOL SYNOPSIS

Protocol Title:	A Phase II Study of Pazopanib in the Treatment of Surgically Unresectable or Metastatic Chondrosarcoma
Study Sites:	The study will be conducted at approximately 7 oncology centers associated with Vector Oncology.
Study Design:	This is a Phase II, multicenter, prospective, open-label, single arm study.
Study Schema:	Pazopanib 800 mg orally once daily administered continuously for a 28-day cycle. Subjects may continue study treatment until they develop disease progression or unacceptable toxicity.
Accrual Goal:	47 subjects
Accrual Rate:	Estimated to be two subjects per month across approximately 7 sites
Study Objectives:	The primary objective is to determine the treatment efficacy of single agent pazopanib in subjects with chondrosarcoma. Secondary objectives are to determine the safety profile of pazopanib in this population.
Main Eligibility Criteria:	Adults with histologically confirmed conventional chondrosarcoma of any grade that is metastatic or surgically unresectable.
Criteria for Evaluation:	CT or PET/CT scans will be repeated after every 2 cycles of treatment. Subjects may continue study treatment until they develop disease progression or unacceptable toxicity. Adverse events will be recorded and graded using the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). Other safety assessments will include clinical laboratory values, electrocardiograms (EKGs), echocardiograms (ECHOs) or multiple gated acquisition (MUGA) scans, physical examinations, and vital sign measurements.

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As of 09 september 2015 there have been 3 reports of pregnancy involving 2 female subjects who were enrolled in pazopanib clinical trials. Both subjects became pregnant after pazopanib was discontinued. 25

A 28-year-old enrolled in the ovarian cancer study veg110655 had a spontaneous abortion at 8 weeks gestation, which was 155 days after the last pazopanib dose. About2 years after her last pazopanib dose, the subject gave birth to a normal baby boy at 39 weeks gestation. 25

A 26-year-old enrolled in a gsk-supported rcc study had a positive pregnancy test 47 days after her last pazopanib dose. On 08 august 2014, the patient underwent an elective caesarian section in order for her to receive chemotherapy due to malignancy progression. An infant male was delivered uneventfully, although prematurely at27 weeks gestation. The investigator noted that no aes associated with the patient's pazopanib treatment were observed 25

In addition to the above reports, a spontaneous report of congenital anomalies in an infant whose mother received pazopanib is described in the marketing experience: 25

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the plasma concentration curve
BP	Blood pressure
BS	Bone sarcomas
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
Cl_{CR}	Calculated creatinine clearance
C_{max}	Maximum plasma concentrations
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE v4.0	Common Terminology Criteria for Adverse Events Version 4.0
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP2E1	Cytochrome P450 2E1
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic blood pressure
DVT	Deep venous thrombosis
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EC_{50}	Half maximal effective concentration
EDC	Electronic data capture
EKG	Electrocardiogram
EOT	End of Treatment
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	Follicle stimulating hormone
F/U	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase

GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRT	Hormone replacement therapy
HUS	Hemolytic uremic syndrome
ICH	International Conference on Harmonisation
iCRF	Internet case report form
ID	identification
IND	Investigational New Drug (Application)
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
LD	Longest diameter
LFT	Liver function test
LLN	Lower limit normal
LT	Long-term
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
NCI	National Cancer Institute
Novartis	Novartis Pharmaceuticals
NYHA	New York Heart Association
OS	Overall survival
P	Pulse
PD	Progressive disease
PET/CT	Positron emission tomography/Computed tomography
PFR12 weeks	Progression-free rate at 12 weeks
PFS	Progression-free survival
P-gp	Permeability glycoprotein
PK	Pharmacokinetics
PPI	Proton pump inhibitor
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	(Taken) once daily
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease

STS	Soft-tissue sarcoma
T	Body temperature
TIA	Transient ischemic attack
TSH	Thyroid stimulating hormone
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit normal
UPC	Urine protein to creatinine ratio
USA	United States of America
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WOCBP	Women of child-bearing potential

1. INTRODUCTION

1.1. Pazopanib Background

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 [Folkman, 1971; Folkman 1997; Ferrara, 1997].

Pazopanib is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β), and c-Kit [Kumar, 2007]. Pazopanib is being developed by GlaxoSmithKline (GSK) 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). Further physico-chemical characteristics of pazopanib as well as more detailed results of nonclinical studies are described in the Investigator's Brochure (IB) [Ariazi, 2014].

As of the clinical data cut-off date for the current IB, 09 September 2013, 47 GSK-sponsored studies of pazopanib (plus 1 additional study initiated by the NCI) have been conducted or are in progress in adult subjects with cancer including renal cell cancer (RCC), non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, soft tissue sarcoma (STS), cervical cancer, colorectal cancer, hepatocellular cancer (HCC), multiple myeloma (MM), and glioma. Approximately 5000 subjects have received pazopanib as monotherapy or in combination out of approximately 7000 subjects enrolled in pazopanib oncology clinical studies as of the cut-off. Data collected to date show that oral pazopanib is absorbed after administration and that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings [Ariazi, 2014].

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. In 2009, pazopanib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma (RCC) [Votrient PI, 2014]. In 2012, pazopanib was FDA-approved for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy. However, the efficacy of pazopanib for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated [Votrient PI, 2014].

Renal Cell Carcinoma

The safety and efficacy of pazopanib in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial. Patients (N = 435) with locally advanced and/or metastatic RCC who had received either no prior therapy or one prior cytokine-based systemic therapy were randomized (2:1) to receive pazopanib 800 mg once daily or placebo once daily. The primary objective of the trial was to evaluate and compare the 2 treatment arms for progression-free survival (PFS); the secondary endpoints included overall survival (OS), overall response rate (RR), and duration of response.

Of the total of 435 patients enrolled in this trial, 233 patients had no prior systemic therapy (treatment-naïve subgroup) and 202 patients received one prior IL-2 or INFα-based therapy (cytokine-pretreated subgroup). The baseline demographic and disease characteristics were balanced between the pazopanib and placebo arms. The majority of patients were male (71%) with a median age of 59 years. Eighty-six percent of patients were Caucasian, 14% were Asian, and less than 1% were other. Forty-two percent were ECOG performance status 0 and 58% were ECOG performance status 1. All patients had clear cell histology (90%) or predominantly clear cell histology (10%). Approximately 50% of all patients had 3 or more organs involved with metastatic disease. The most common metastatic sites at baseline were lung (74%), lymph nodes (56%), bone (27%), and liver (25%).

A similar proportion of patients in each arm were treatment-naïve and cytokine-pretreated. In the cytokine-pretreated subgroup, the majority (75%) had received interferon-based treatment. Similar proportions of patients in each arm had prior nephrectomy (89% and 88% for pazopanib and placebo, respectively).

The analysis of the primary endpoint PFS was based on disease assessment by independent radiological review in the entire trial population. At the protocol-specified final analysis of OS, the median OS was 22.9 months for patients randomized to pazopanib and 20.5 months for the placebo arm [HR = 0.91 (95% CI: 0.71, 1.16)]. The median OS for the placebo arm includes 79 patients (54%) who discontinued placebo treatment because of disease progression and crossed over to treatment with pazopanib. In the placebo arm, 95 (66%) patients received at least one systemic anti-cancer treatment after progression compared to 88 (30%) patients randomized to pazopanib [Votrient PI, 2014].

Soft Tissue Sarcoma

The safety and efficacy of pazopanib in patients with STS were evaluated in a Phase III, randomized, double-blind, placebo-controlled, multicenter trial. Patients (N = 369) with metastatic STS who had received prior chemotherapy, including anthracycline treatment, or were unsuited for such therapy, were randomized (2:1) to receive pazopanib 800 mg once daily or placebo. Patients with gastrointestinal stromal tumors (GIST) or adipocytic sarcoma were excluded from the trial. Randomization was stratified by the factors of WHO performance status (WHO PS) 0 or 1 at baseline and the number of lines of prior systemic therapy for advanced disease (0 or 1 versus 2+). Progression-free survival (PFS) was assessed by independent radiological review. Other efficacy endpoints included overall survival (OS), overall response rate, and duration of response.

The majority of patients were female (59%) with a median age of 55 years. Seventy-two percent of patients were Caucasian, 22% were Asian, and 6% were Other. Forty-three percent of patients had leiomyosarcoma, 10% had synovial sarcoma, and 47% had other soft tissue sarcomas. Fifty-six percent of patients had received 2 or more lines of prior systemic therapy and 44% had received 0 or 1 lines of prior systemic therapy. The median duration of treatment was 4.5 months for patients on the pazopanib arm and 1.9 months for patients on the placebo arm. At the protocol-specified final analysis of OS, the median OS was 12.6 months for patients randomized to pazopanib and 10.7 months for the placebo arm [HR = 0.87 (95% CI: 0.67, 1.12)] [Votrient PI, 2014].

1.2. Adverse Reactions

The following safety data is from the Prescribing Information for pazopanib, revised September 2015, and from the Investigator's Brochure for pazopanib, version number 14 dated January 7, 2016.

1.2.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Potentially serious adverse reactions with pazopanib included:

- Hepatotoxicity
- QT prolongation and torsades de pointes
- Cardiac dysfunction
- Hemorrhagic events
- Arterial and venous thromboembolic events
- Thrombotic microangiopathy

- Gastrointestinal perforation and fistula
- Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Hypertension
- Hypothyroidism
- Proteinuria
- Infection
- Interstitial Lung Disease (ILD)/Pneumonitis
- Increased toxicity with other cancer therapies

Renal Cell Carcinoma:

The safety of pazopanib has been evaluated in 977 patients in the monotherapy trials which included 586 patients with RCC at the time of NDA submission. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions (≥ 20%) in the 586 patients were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting.

The data described below reflect the safety profile of pazopanib in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled trial. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received pazopanib and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent of patients on pazopanib required a dose interruption. Thirty-six percent of patients on pazopanib were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥ 10% of patients who received pazopanib.

Table 2. Adverse Reactions Occurring in ≥ 10% of Patients with RCC who Received Pazopanib

	Pazopanib (N=290)			Placebo (N=145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	**%**	**%**	**%**	**%**	**%**	**%**
Diarrhea	52	3	< 1	9	< 1	0
Hypertension	40	4	0	10	< 1	0
Hair color changes	38	< 1	0	3	0	0
Nausea	26	< 1	0	9	0	0
Anorexia	22	2	0	10	< 1	0
Vomiting	21	2	< 1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0

Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with pazopanib than placebo and that occurred in < 10% (any grade) were alopecia (8% versus < 1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus < 1%), dyspepsia (5% versus < 1%), dysphonia (4% versus < 1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus < 1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

Additional adverse reactions from other clinical trials in RCC patients treated with pazopanib are listed below:

Musculoskeletal and Connective Tissue Disorders: Arthralgia, muscle spasms.

Table 3. Selected Laboratory Abnormalities Occurring in ≥ 15% of Patients with RCC who Received Pazopanib and More Commonly (≥ 5%) in Patients who Received Pazopanib Versus Placebo

	Pazopanib (N=290)			**Placebo (N=145)**		
	All Grades[a]	**Grade 3**	**Grade 4**	**All Grades[a]**	**Grade 3**	**Grade 4**
Parameters	**%**	**%**	**%**	**%**	**%**	**%**
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	< 1	6	0	0
Thrombocytopenia	32	< 1	< 1	5	0	< 1
Lymphocytopenia	31	4	< 1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	< 1	19	< 1	0
Glucose increased	41	< 1	0	33	1	0
Total bilirubin increased	36	3	< 1	10	1	< 1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	< 1	1	14	0	0
Glucose decreased	17	0	< 1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Soft Tissue Sarcoma:

The safety of pazopanib has been evaluated in 382 patients with advanced soft tissue sarcoma, with a median duration of treatment of 3.6 months (range 0 to 53). The most commonly observed adverse reactions (≥ 20%) in the 382 patients were fatigue, diarrhea,

nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, and skin hypopigmentation.

The data described below reflect the safety profile of pazopanib in 240 patients who participated in a randomized, double-blind, placebo-controlled trial. The median duration of treatment was 4.5 months (range 0 to 24) for patients who received pazopanib and 1.9 months (range 0 to 24) for the placebo arm. Fifty-eight percent of patients on pazopanib required a dose interruption. Thirty-eight percent of patients on pazopanib had their dose reduced. Fourteen percent of patients who received pazopanib discontinued therapy due to adverse reactions. Table 3 presents the most common adverse reactions occurring in ≥ 10% of patients who received pazopanib.

Table 4. Adverse Reactions Occurring in ≥ 10% of Patients with STS who Received Pazopanib

	Pazopanib (N=240)			Placebo (N=123)		
Adverse Reactions	**All Grades[a] %**	**Grade 3 %**	**Grade 4 %**	**All Grades[a] %**	**Grade 3 %**	**Grade 4 %**
Fatigue	65	13	1	48	4	1
Diarrhea	59	5	0	15	1	0
Nausea	56	3	0	22	2	0
Weight decreased	48	4	0	15	0	0
Hypertension	42	7	0	6	0	0
Appetite decreased	40	6	0	19	0	0
Hair color changes	39	0	0	2	0	0
Vomiting	33	3	0	11	1	0
Tumor pain	29	8	0	21	7	2
Dysgeusia	28	0	0	3	0	0
Headache	23	1	0	8	0	0
Musculoskeletal pain	23	2	0	20	2	0
Myalgia	23	2	0	9	0	0
Gastrointestinal pain	23	3	0	9	4	0
Dyspnea	20	5	< 1	17	5	1
Exfoliative rash	18	< 1	0	9	0	0
Cough	17	< 1	0	12	< 1	0
Peripheral edema	14	2	0	9	2	0
Mucositis	12	2	0	2	0	0
Alopecia	12	0	0	1	0	0
Dizziness	11	1	0	4	0	0
Skin disorder[b]	11	2	0	1	0	0
Skin hypopigmentation	11	0	0	0	0	0
Stomatitis	11	< 1	0	3	0	0
Chest pain	10	2	0	6	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.
[b] 27 of the 28 cases of skin disorder were palmar-plantar erythrodysesthesia.

Other adverse reactions observed more commonly in patients treated with pazopanib that occurred in ≥ 5% of patients and at an incidence of more than 2% difference from placebo included insomnia (9% versus 6%), hypothyroidism (8% versus 0), dysphonia (8% versus 2%), epistaxis (8% versus 2%), left ventricular dysfunction (8% versus 4%), dyspepsia (7% versus 2%), dry skin (6% versus <1%), chills (5% versus 1%), vision blurred (5% versus 2%), and nail disorder (5% versus 0%).

Table 4 presents the most common laboratory abnormalities occurring in >10% of patients who received pazopanib and more commonly (≥ 5%) in patients who received pazopanib versus placebo.

Table 5. Selected Laboratory Abnormalities Occurring in ≥ 15% of Patients with STS who Received Pazopanib and More Commonly (≥ 5%) in Patients who Received Pazopanib versus Placebo

	Pazopanib (N=240)			Placebo (N=123)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	**%**	**%**	**%**	**%**	**%**	**%**
Hematologic						
Leukopenia	44	1	0	15	0	0
Lymphocytopenia	43	10	0	36	9	2
Thrombocytopenia	36	3	1	6	0	0
Neutropenia	33	4	0	7	0	0
Anaemia	27	5	2	23	<1	
Chemistry						
AST increased	51	5	3	22	2	0
ALT increased	46	8	2	18	2	1
Glucose increased	45	< 1	0	35	2	0
Albumin decreased	34	1	0	21	0	0
Alkaline phosphatase increased	32	3	0	23	1	0
Sodium decreased	31	4	0	20	3	0
Total bilirubin increased	29	1	0	7	2	0
Potassium increased	16	1	0	11	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity in both the RCC and STS clinical trials. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact.

Lipase Elevations: In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. Elevations in lipase as an adverse reaction were reported for 4%

(10/225) of patients and were Grade 3 for 6 patients and Grade 4 for 1 patient. In the RCC trials of pazopanib, clinical pancreatitis was observed in <1% (4/586) of patients.

Pneumothorax: Two of 290 patients treated with pazopanib and no patient on the placebo arm in the randomized RCC trial developed a pneumothorax. In the randomized trial of pazopanib for the treatment of STS, pneumothorax occurred in 3% (8/240) of patients treated with pazopanib and in no patients on the placebo arm.

Bradycardia: In the randomized trial of pazopanib for the treatment of RCC, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with pazopanib and in 11% (16/144) of patients on the placebo arm. Bradycardia was reported as an adverse reaction in 2% (7/290) of patients treated with pazopanib compared to <1% (1/145) of patients treated with placebo. In the randomized trial of pazopanib for the treatment of STS, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (45/238) of patients treated with pazopanib and in 4% (5/121) of patients on the placebo arm. Bradycardia was reported as an adverse reaction in 2% (4/240) of patients treated with pazopanib compared to <1% (1/123) of patients treated with placebo.

1.2.2. Postmarketing Data

The following adverse reactions presented in Table 5 have been identified during post-approval use of pazopanib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, clinical pharmacology studies and exploratory studies in unapproved indications.

Table 5. Post Marketing Data

System Organ Class	Frequency and MedDRA event Preferred Term
Infections and infestations	Uncommon: Infections (with or without neutropenia; see Special Warnings and Special
Blood and lymphatic system disorders	Rare: Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome; see Special

Nervous system disorders	Uncommon: Posterior reversible encephalopathy syndrome (see Special
System Organ Class	**Frequency and MedDRA event Preferred Term**
Eye disorders	Uncommon: Retinal detachment/tear
Respiratory, thoracic and mediastinal disorders	Rare: Interstitial lung disease/pneumonitis (see Special Warnings and Special Precautions for
Gastrointestinal disorders	Common: Flatulence
Hepatobiliary disorders	Common: Gamma-glutamyl transpeptidase
Musculoskeletal and connective tissue	Very common: Arthralgia

1.2.3. Warnings and Precautions for use

1.2.3.1. Hepatic Toxicity and Hepatic Impairment

Hepatic Effects: Cases of hepatic failure (including fatalities) have been reported during the use of pazopanib. In clinical trials with pazopanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed (*see Undesirable Effects*). In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Patients over 60 years of age may be at greater risk for ALT >3 X ULN. Patients who carry the *HLA-B**57:01 allele also have an increased risk of pazopanib-associated ALT elevations. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype or age. The vast majority (over 90%) of all transaminase elevations of any grade occurred in the first 18 weeks. Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE).

Monitor serum liver tests before initiation of treatment with pazopanib and at Weeks 3, 5,7 and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4.

The following guidelines are provided for patients with baseline values of total bilirubin

≤1.5 X ULN, and AST and ALT ≤2 X ULN.

- Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on pazopanib with weekly monitoring of liver function until ALT return to Grade 1 (NCI CTCAE, defined in Version 3 as <2.5 X ULN) or baseline.

- Patients with ALT of >8 X ULN should have pazopanib interrupted until they return to Grade 1 (NCI CTCAE) or baseline. If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks *(see Posology and Method of Administration)*. Following reintroduction of pazopanib, if ALT elevations >3 X ULN recur, then pazopanib should be permanently discontinued.

  If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN pazopanib should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, knownor suspected Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations (*see Interactions*) and should be undertaken with caution and close monitoring.

Beyond recommending that patients with mild hepatic impairment are treated with 800 mg pazopanib once daily and reducing the initial starting dose to 200 mg per day for patients with moderate impairment, no further dose modification guidelines based on results of serum liver tests during therapy have been established for patients with pre-existing hepatic impairment. Pazopanib is not recommended for patients with severe hepatic impairment

The safety and pharmacokinetics of pazopanib in patients with pre-existing hepatic impairment have not been fully established (*see Warnings and Precautions for Use*).

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (*see Clinical Pharmacology*).

The dose of pazopanib should be reduced to 200 mg per day in patients with moderate hepatic impairment.

There are insufficient data in patients with severe hepatic impairment (total bilirubin >3 times the upper limit of normal [X ULN] regardless of any level of ALT); therefore, pazopanib is not recommended in these patients

1.2.3.2. QT Prolongation and Torsades de Pointes

In the RCC trials of pazopanib, QT prolongation (≥ 500 msec) was identified on routine electrocardiogram monitoring in 2% (11/558) of patients. Torsades de pointes occurred in < 1% (2/977) of patients who received pazopanib in the monotherapy trials.

In the randomized RCC and STS trials, 1% (3/290) of patients and 0.2% (1/240) of patients, respectively, who received pazopanib had post-baseline values between 500 to 549 msec. Post-baseline QT data were only collected in the STS trial if ECG abnormalities were reported as an adverse reaction. None of the 268 patients who received placebo on the two trials has post-baseline QTc values ≥ 500 msec.

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.

When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

1.2.3.3. Cardiac Dysfunction

In clinical trials with pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred. In a randomised RCC trial of pazopanib compared with sunitinib, in subjects who had baseline and follow-up LVEF measurements, myocardial dysfunction was observed in 13% (47/362) of subjects in the pazopanib arm compared to 11% (42/369) of subjects in the sunitinib arm. Congestive heart failure was observed in 0.5% of subjects in each treatment arm. In the phase III STS clinical trial, congestive heart failure was reported in 3 out of 240 subjects (1%). In this trial decreases in LVEF in subjects who had post-baseline measurement were detected in 11% (16/142) in the pazopanib arm compared with 5% (2/40) in the placebo arm. Fourteen of the 16 subjects in the pazopanib arm had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk (e.g., those with prior anthracycline therapy) by increasing cardiac after-load. Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of pazopanib (interruption and re-initiation at a reduced dose based on clinical judgment). Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction.

1.2.3.4. Hemorrhagic Events

Fatal hemorrhage occurred in 0.9% (5/586) in the RCC trials; there were no reports of fatal hemorrhage in the STS trials. In the randomized RCC trial, 13% (37/290) of patients treated with pazopanib and 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic

event. The most common hemorrhagic events in the patients treated with pazopanib were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine of 37 patients treated with pazopanib who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. One percent (4/290) of patients treated with pazopanib died from hemorrhage compared with no (0/145) patients on placebo. In the overall safety population in RCC (N=586), cerebral/intracranial hemorrhage was observed in < 1% (2/586) of patients treated with pazopanib.

In the randomized STS trial, 22% (53/240) of patients treated with pazopanib compared to 8% (10/123) treated with placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were epistaxis (8%), mouth hemorrhage (3%), and anal hemorrhage (2%). Grade 4 hemorrhagic events in the STS population occurred in 1% (3/240) patients and included intracranial hemorrhage, subarachnoid hemorrhage, and peritoneal hemorrhage.

Pazopanib has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.

1.2.3.5. Arterial Thromboembolic Events

Fatal arterial thromboembolic events were observed in 0.3% (2/586) of patients in the RCC trials and in no patients in the STS trials. In the randomized RCC trial, 2% (5/290) of patients receiving pazopanib experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident, and 1% (4/290) had an event of transient ischemic attack. In the randomized STS trial, 2% (4/240) of patients receiving pazopanib experienced a myocardial infarction or ischemia, 0.4% (1/240) had a cerebrovascular accident and there were no incidents of transient ischemic attack. No arterial thrombotic events were reported in patients who received placebo in either trial. Pazopanib should be used with caution in patients who are at increased risk for these events or who have had a history of these events. Pazopanib has not been studied in patients who have had an arterial thrombotic event within the previous 6 months and should not be used in those patients.

1.2.3.6. Venous Thromboembolic Events

In RCC and STS trials of pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. In the randomized STS trial, venous thromboembolic events were reported in 5% of patients treated with pazopanib compared to 2% with placebo. In the randomized RCC trial, the rate was 1% in both arms. Fatal pulmonary embolus occurred in 1% (2/240) of STS patients receiving pazopanib and in no patients receiving placebo. There were no fatal pulmonary emboli in the RCC trial. Monitor for signs and symptoms of VTE and PE.

1.2.3.7. Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), has been reported in clinical trials of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan.

Pazopanib is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of pazopanib. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue pazopanib in patients developing TMA. Manage as clinically indicated.

1.2.3.8. Gastrointestinal Perforation and Fistula

In the RCC and STS trials, gastrointestinal perforation or fistula occurred in 0.9% (5/586) of patients and 1% (4/382) of patients receiving pazopanib, respectively. Fatal perforations occurred in 0.3% (2/586) of these patients in the RCC trials and in 0.3% (1/382) of these patients in the STS trials. Monitor for signs and symptoms of gastrointestinal perforation or fistula.

1.2.3.9. Posterior Reversible Encephalopathy Syndrome / Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving pazopanib and may be fatal.

PRES/RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. The diagnosis of PRES/RPLS is optimally confirmed by magnetic resonance imaging. Permanently discontinue pazopanib in patients developing PRES/RPLS.

1.2.3.10. Hypertension

In clinical trials, hypertension (systolic blood pressure $\geq$ 150 or diastolic blood pressure $\geq$ 100 mm Hg) and hypertensive crisis were observed in patients treated with pazopanib. Blood pressure should be well controlled prior to initiating pazopanib. Hypertension occurs early in the course of treatment (40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks). Blood pressure should be monitored early after starting treatment (no longer than one week) and frequently thereafter to ensure blood pressure control. Approximately 40% of patients who received pazopanib experienced hypertension. Grade 3 hypertension was reported in 4% to 7% of patients receiving pazopanib.

Increased blood pressure should be treated promptly with standard anti-hypertensive therapy and dose reduction or interruption of pazopanib as clinically warranted. Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and

persistent despite anti-hypertensive therapy and dose reduction. Approximately 1% of patients required permanent discontinuation of pazopanib because of hypertension.

1.2.3.11. Wound Healing

No formal trials on the effect of pazopanib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGF) inhibitors such as pazopanib may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgment of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

1.2.3.12. Hypothyroidism

Hypothyroidism, confirmed based on a simultaneous rise of TSH and decline of T4, was reported in 7% (19/290) of patients treated with pazopanib in the randomized RCC trial and in 5% (11/240) of patients treated with pazopanib in the randomized STS trial. No patients on the placebo arm of either trial had hypothyroidism. In RCC and STS trials of pazopanib, hypothyroidism was reported as an adverse reaction in 4% (26/586) and 5% (20/382) of patients, respectively. Proactive monitoring of thyroid function tests is recommended.

1.2.3.13. Proteinuria

In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving pazopanib and in no patients receiving placebo. In 2 patients, proteinuria led to discontinuation of treatment with pazopanib. In the randomized STS trial, proteinuria was reported as an adverse reaction in 1% (2/240) of patients, and nephrotic syndrome was reported in 1 patient treated with pazopanib compared to none in patients receiving placebo. Treatment was withdrawn in the patient with nephrotic syndrome.

Baseline and periodic urinalysis during treatment is recommended with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt pazopanib and dose reduce for 24-hour urine protein $\geq$ 3 grams; discontinue pazopanib for repeat episodes despite dose reductions.

1.2.3.14. Infection

Serious infections (with or without neutropenia), including some with fatal outcome, have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of pazopanib for serious infections.

1.2.3.15. Intersitial Lung Disease (ILD)/Pneumonitis: ILD which can be fatal, has been reported in association with pazopanib. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue pazopanib in patients developing ILD or pneumonitis.

1.2.3.16. Increased Toxicity with Other Cancer Therapy

Pazopanib is not indicated for use in combination with other agents. Clinical trials of pazopanib in combination with pemetrexed and lapatinib were terminated early due to concerns over increased toxicity and mortality. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens.

1.2.3.17. Increased Toxicity in Developing Organs

The safety and effectiveness of pazopanib in pediatric patients have not been established. Pazopanib is not indicated for use in pediatric patients. Based on its mechanism of action, pazopanib may have severe effects on organ growth and maturation during early post-natal development. Administration of pazopanib to juvenile rats less than 21 days old resulted in toxicity to the lungs, liver, heart, and kidney and in death at doses significantly lower than the clinically recommended dose or doses tolerated in older animals. Pazopanib may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age.

1.2.3.18. Pregnancy

As of 09 september 2015 there have been 3 reports of pregnancy involving 2 female subjects who were enrolled in pazopanib clinical trials. Both subjects became pregnant after pazopanib was discontinued.

A 28-year-old enrolled in the ovarian cancer study veg110655 had a spontaneous abortion at 8 weeks gestation, which was 155 days after the last pazopanib dose. About2 years after her last pazopanib dose, the subject gave birth to a normal baby boy at 39 weeks gestation.

A 26-year-old enrolled in a gsk-supported rcc study had a positive pregnancy test 47 days after her last pazopanib dose. On 08 august 2014, the patient underwent an elective caesarian section in order for her to receive chemotherapy due to malignancy progression. An infant male was delivered uneventfully, although prematurely at27 weeks gestation. The investigator noted that no aes associated with the patient's pazopanib treatment were observed.

In addition to the above reports, a spontaneous report of congenital anomalies in an infant whose mother received pazopanib is described in the marketing experience:

One report describing the use of pazopanib up to the first trimester of pregnancy, for an unapproved indication (off-label use) has been received up to 09 September 2015. A 19-year-old female began pazopanib for treatment of thyroid cancer at age 16 in August2011.

Pazopanib was discontinued in January 2014, during the first trimester of pregnancy. About 7 months after the last pazopanib dose, in August 2014, the patient delivered a baby boy at 38 weeks gestation. The baby's APGAR scores were 8 at 1 minute and 9 at 5 minutes after birth. At an unspecified period after birth, the baby was diagnosed with congenital heart disease, characterised by a subaortic septal defect, aortic coarctation, and partial anomalous pulmonary venous return. The baby underwent surgery and was described as "doing well and thriving" post-surgery. The patient resumed pazopanib following delivery until about 5 months later, in January 2015, when pazopanib was stopped for an unspecified reason.

There are no adequate and well-controlled studies of pazopanib in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking pazopanib.

1.2.3.19. Interactions

Concomitant treatment with strong inhibitors of CYP3A4 or P-gp should be avoided due to risk of increased exposure to pazopanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4 or P-gp should be considered.

1.3. Pazopanib Monotherapy Dose Rationale

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 subjects above and below the threshold. Using thresholds of 15 μg/mL and 20.7 μg/mL, subjects with trough concentrations above the thresholds also had significantly better response rate and tumor shrinkage than the remaining subjects.

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 RCC. In this study, the median progression-free survival 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.

2. STUDY RATIONALE

Bone sarcomas (BS) are uncommon mesenchymal malignancies. In 2009, the estimated number of new cases of BS in the United States will be 2,570, which will account for only 0.2% of all newly diagnosed cancers [Jemal, 2006; Fletcher, 2002].

Chondrosarcoma is the second most common malignant primary tumor of bone, with about 400 new cases per year [Yasko, 2008]. Chondrosarcomas are generally indolent, malignant tumors of bone that are characterized by the formation of cartilaginous neoplastic tissue. More than 90% are designated conventional chondrosarcomas. Approximately 90% of these are low-grade to intermediate-grade tumors (grade 1 to 2), which have indolent clinical behavior and low metastatic potential. Only 5-10% of conventional chondrosarcomas are

grade 3 lesions, which have high metastatic potential [Dorfman, 1998]. Chemotherapy is generally recognized to be ineffective in conventional chondrosarcomas [Chow, 2007].

The growth, migration, and dissemination of sarcomas depend upon angiogenesis. Neovascularization allows for growth of the primary tumor as well as a pathway for migrating tumor cells to gain access to the systemic circulation and establish distant metastases.

BS, unlike carcinomas, disseminate almost exclusively through the blood; bones lack a lymphatic system [Malawer, 2001]. Consequently, unlike most other cancers, BS almost universally metastasize to the pulmonary parenchyma as their first, and most commonly, only site of distant spread [Malawer, 2001]. Further, more than most other organs, the lungs possess a rich arterial and venous vascular supply. Additionally, elevated tumor and circulating VEGF levels are associated with the development of lung metastases [Shor, 2008]. Accordingly, inhibiting neovascularization in BS, which have a unique proclivity to metastasize solely to this receptive organ, is appealing.

Pazopanib is known to have a high degree of activity in soft-tissue sarcoma (STS). In a phase II trial of pazopanib for relapsed or refractory advanced STS, the primary end point of progression-free rate at 12 weeks (PFR12 weeks) of 40% was achieved or nearly achieved in three out of four cohorts (26% liposarcomas, 44% leiomyosarcomas, 49% synovial sarcomas, and 39% in other STS) [Sleijfer, 2009].

In a phase I study of pazopanib in subjects with advanced cancer, two subjects with chondrosarcoma achieved stable disease for 7.6 and 19.8 months [Hurwitz, 2009]. The chondrosarcoma subject who achieved stable disease for 19.8 months also had a 23% reduction in tumor [GSK data on file]. A treatment that reliably leads to stable disease in this population would represent a significant improvement over existing treatment options. This study is designed to evaluate treatment with pazopanib in subjects with surgically unresectable or metastatic chondrosarcoma.

3. OVERVIEW OF STUDY DESIGN AND EVALUATION

This is a Phase II, multicenter, prospective, open-label, single arm study. The primary endpoint of the study is disease control at week 16 defined as CR + PR + SD, where tumor response is defined by RECIST guidelines version 1.1. The secondary endpoints include progression free survival (PFS) according to RECIST guidelines version 1.1, overall survival (OS), and toxicity assessment through the reporting of adverse events.

Pazopanib 800 mg once daily will be started on Cycle 1 Day 1 and will be administered continuously for a 28-day cycle. Subjects may continue study treatment until they develop disease progression or unacceptable toxicity.

The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase of 6 months. The study will be conducted at approximately 7 oncology centers associated with Vector Oncology. Planned enrollment is approximately 47 subjects.

4. STUDY OBJECTIVES

4.1. Primary Objective

The primary objective of the study is to determine the treatment efficacy of single agent pazopanib in subjects with chondrosarcoma.

4.2. Secondary Objectives

The secondary objectives of this study are to determine the safety profile of pazopanib in this population.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

A subject must meet each of the following criteria to be considered eligible for inclusion in this study:

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. Age ≥ 18 years.
3. Histologically confirmed diagnosis of conventional chondrosarcoma of any grade.
4. Surgically unresectable or metastatic disease.
5. Any number of prior treatment regimens, including treatment naïve subjects. Prior treatment with tyrosine kinase inhibitors is permitted.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Appendix 2).
7. Measurable or evaluable (non-measurable) disease per RECIST guidelines version 1.1.
8. Adequate organ system function as defined in Table 5 determined within 14 days prior to the first dose of study treatment.

Table 6. 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]	≤ 2.5 X ULN
Renal	
Serum creatinine	≤ 1.5 mg/dL (133 µmol/L)
Or, if serum creatinine is > 1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (Appendix 3)	≥ 50 mL/min
Urine Protein to Creatinine Ratio (UPC; Appendix 4)[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.
c. Concomitant elevations in bilirubin and AST/ALT above the 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.

9. Left ventricular ejection fraction (LVEF) ≥ 50% or the institutional LLN within 28 days prior to the first dose of study treatment.

10. A female is eligible to enter and participate in this study if she is of:

Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy
- A bilateral oophorectomy (ovariectomy)
- A bilateral tubal ligation
- Is post-menopausal

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 < 40pg/mL (< 140 pmol/L).

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 7 days prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- 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 [Hatcher, 2004]
- Oral contraceptive, either combined or progestogen alone [Hatcher, 2004]
- Injectable progestogen [Hatcher, 2004]
- Implants of levonorgestrel [Hatcher, 2004]
- Estrogenic vaginal ring [Hatcher, 2004]
- Percutaneous contraceptive patches [Hatcher, 2004]
- Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year [Hatcher, 2004].
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject [Hatcher, 2004].
- 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.

5.2. Exclusion Criteria

A subject who meets any of the following criteria will be considered **not** eligible for inclusion in this study:

1. Prior treatment with pazopanib.
2. Mesenchymal, dedifferentiated, and extraskeletal myxoid chondrosarcoma subtypes.
3. Prior malignancy. Note: Subjects who have had another malignancy and have been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.

4. History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.
5. 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, Crohn'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.
6. 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.
7. Presence of uncontrolled infection.
8. Corrected QT interval (QTc) > 480 msecs using Bazett's formula.
9. 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) [Appendix 5].
10. 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 (see Section 7.1 for details on BP control and re-assessment prior to study enrollment).

11. 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.

12. 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. Major surgery is defined by the use of general anesthesia; however, endoscopic examinations with diagnostic intent are not considered major surgery. Insertion of a vascular access device is exempt from this exclusion criterion. Subjects must have recovered from all surgery-related complications.

13. Evidence of active bleeding or bleeding diathesis.

14. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage.

    - Lesions infiltrating major pulmonary vessels (contiguous tumor and vessels) are excluded; however, the presence of a tumor that is touching, but not infiltrating (abutting) the vessels is acceptable (CT with contrast is strongly recommended to evaluate such lesions).
    - Large protruding endobronchial lesions in the main or lobar bronchi are excluded; however, endobronchial lesions in the segmented bronchi are allowed.
    - Lesions extensively infiltrating the main or lobar bronchi are excluded; however, minor infiltrations in the wall of the bronchi are allowed.

15. Hemoptysis of red blood in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug.

16. 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.

17. Unable or unwilling to discontinue use of prohibited medications (see lists in Section 6.5.1) 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 treatment.

18. Treatment with any of the following anti-cancer therapies:

    - radiation therapy, surgery (except major surgery, as described above) or tumor embolization within 14 days prior to the first dose of study drug, OR
    - 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 study drug.

19. Administration of any non-oncologic investigational drug within 30 days or five half-lives (whichever is longer) prior to receiving the first dose of study drug.

20. Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity, except alopecia.

21. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or excipients that contraindicates participation.

5.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the current Prescribing Information and Investigator's Brochure for pazopanib for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product being used in this study.

6. TREATMENT OF SUBJECTS

6.1. Subject Enrollment

Participating sites will be instructed on the procedure for enrolling subjects with Vector Oncology during site training. Subject numbers will be assigned in sequential order across all participating sites.

6.2. Study Treatment

Pazopanib 800 mg once daily will be started on Cycle 1 Day 1 and will be administered continuously for a 28-day cycle. Subjects may continue study treatment until they develop disease progression or unacceptable toxicity.

During the treatment prior of the study, a visit window of + / - 3 business days is allowed. Assessments may be performed within 3 business days before the actual visit to allow flexibility in scheduling with the exception of the BP measurements required at Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 15, and Cycle 3 Day 15, which have a window of +/- 1 business day. Other vital signs are not required at these time points, and BP can be assessed by any method (e.g., at home or by another physician) as long as the Investigator is informed of the measurement, verifies any measurement that is not normal, and takes appropriate action.

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described in this section may be administered with the intent to treat the subject's malignancy.

Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time

of day the tablets are taken should be relatively consistent. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

6.3. Pazopanib Dose Interruptions and Modifications

Guidelines for pazopanib dose interruptions/modifications in case of specific treatment-emergent AEs are provided in the following sections.

If pazopanib is interrupted for 5 days or more, Vector Oncology must be notified.

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, 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.

Pazopanib Starting Dose	800 mg once daily
Dose Reduction 1	600 mg once daily
Dose Reduction 2	400 mg once daily
Dose Reduction 3	200 mg once daily

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 is interrupted for more than 28 days, for any reason, the subject must be removed from study treatment.

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

Guidelines for pazopanib dose interruptions/modifications in case of specific treatment-emergent AEs are provided in Table 6. If an AE is considered unlikely to be related to pazopanib per Investigator's clinical judgment, then these dose modification rules will not apply.

Table 7. Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent[a] $140 \leq$ SBP < 160 mmHg, or $90 \leq$ DBP < 100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 100	Step 1. Continue pazopanib at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s) to achieve and maintain a BP level of < 140/90

AE Terms & Descriptions	Dose Modification Algorithms
mmHg).	mmHg. If BP cannot be controlled to < 140/90 mmHg within 2 weeks after 2 or more different antihypertensive medication adjustments, dose reduction of pazopanib by 200 mg should be considered.
(B). Asymptomatic SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg.	Step 1. Dose reduce by 200 mg or interrupt pazopanib as per clinical judgment. Step 2. Adjust current or initiate new antihypertensive medication(s) to achieve and maintain a BP level of < 140/90 mmHg. If BP cannot be controlled to < 140/90 mmHg within 2 weeks and pazopanib has been interrupted, it can be resumed with dose-reduced by 200 mg from pre-event dose. If BP cannot be adequately controlled with these measures, consider referring the subject to a specialist for further evaluation and management.
(C). Symptomatic hypertension or recurring SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt pazopanib. Step 2. Strongly recommend referring the subject to a specialist for further evaluation and management. Once BP is controlled to < 140/90 mmHg via adjustment of current or initiation of new antihypertensive medication(s), pazopanib can be resumed with dose-reduced by 200 mg. BP should be monitored as clinically indicated.
(D). Refractory hypertension unresponsive to above interventions including malignant hypertension, hypertensive crisis, transient or permanent neurological deficit related to uncontrolled hypertension.	Permanently 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 ≥ 3g 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 and contact Vector Oncology to discuss whether further treatment with pazopanib is appropriate. For other Grade 1 hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	For pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. For other Grade 2 hemorrhage/bleeding events, interrupt pazopanib until the AE resolves to $\leq$ Grade 1. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Permanently discontinue pazopanib and follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 1	Continue pazopanib at the current dose; monitor as clinically indicated
Grade 2 or 3	Step 1. Interrupt pazopanib. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume pazopanib dose-reduced by 200 mg 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 (e.g., 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.
AE Terms & Descriptions	**Dose Modification Algorithms**
Venous Thrombosis (DVT, PE)	
Grade 4	Permanently discontinue pazopanib and follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Permanently discontinue pazopanib and follow-up per protocol.
Palmar-Plantar Erythrodysesthesia Syndrome	

AE Terms & Descriptions	Dose Modification Algorithms
Grade 1 Minimal skin changes or dermatitis without pain (erythema, edema, hyperkeratosis)	Step 1. Continue pazopanib at present dose.
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, edema, bleed, hyperkeratosis)	Step 1. Interrupt pazopanib. Step 2. Treat as clinically appropriate. Step 3. Upon resolution to ≤ Grade 1, restart pazopanib dose-reduced by 200 mg; monitor as clinically indicated. Step 4. If recurrent, consider a further dose reduction, or discontinue.
Grade 3 Severe skin changes with pain and limiting self-care ADLs	Step 1. Permanently discontinue pazopanib.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue pazopanib at 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, permanently 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 Non-Liver Related Adverse Events	
Grade 1	Step 1. Continue pazopanib at current dose. Step 2. Manage the side effects with appropriate medical treatments/supportive care. A dose reduction of 200 mg may be considered if a subject experiences multiple Grade 1 AEs and cannot tolerate the current pazopanib dose.
Grade 2	Step 1. Manage the side effects with appropriate medical treatments/supportive care. Step 2. A dose reduction of 200 mg or interruption of pazopanib may be considered if a subject experiences a clinically significant Grade 2 AE or multiple Grade 1 and 2 AEs and cannot tolerate the current pazopanib dose. If AEs are fully resolved or recover to Grade 1, the dose can be escalated to the pre-event level or maintained at the current level.

AE Terms & Descriptions	Dose Modification Algorithms
	For subjects with dose interruption, dose can be resumed at the pre-event level or dose-reduced by 200 mg based on clinical judgment.
Grade 3	Step 1. Interrupt pazopanib. Step 2. Manage the side effects with appropriate medical treatments/supportive care. If AEs fully recover or recover to Grade 1, restart pazopanib with dose-reduced by 200 mg. Monitor as clinically indicated for AE recurrence. Dose can be interrupted or further reduced for recurrent Grade 3 AEs.
Grade 4	Permanently discontinue pazopanib and follow-up per protocol.
Prolongation of QTc Interval: If a QTc reading is $\geq$ 500 msec, the EKG should be manually read to ensure accuracy of the reading. The values below refer to manually-read EKGs.	
480 < QTc < 500 msec	Continue pazopanib; monitor as clinically indicated.
QTc ≥ 500 msec (see Section 7.3.4)	Step 1. Perform 2 additional EKGs to confirm the abnormality. Step 2. Manually evaluate each EKG tracing to obtain RR and QT intervals for QTc calculation. Step 3. Determine the average QTc from the 3 EKG tracings by manual evaluation. Step 4. If the average QTc is $\leq$ 500 msec, the subject may continue therapy. If the average QTc is > 500 msec, interrupt pazopanib and refer to Section 7.3.4 of the protocol.

a. Persistent SBP and/or DBP is defined as SBP $\geq$ 140 or DBP $\geq$ 90 for at least 24 hours per NCI CTCAE v4.0.
b. Recommendation of antihypertensive agents for treatment-emergent BP elevations: ACE inhibitors, angiotensine receptor blocking agents, beta blockers, calcium channel blockers, and diuretics have all been shown to reduce blood pressure in subjects treated with pazopanib.

Abbreviations: AE, adverse event; ADLs, activities of daily living; BP, blood pressure; DBP, diastolic blood pressure; DVT, deep venous thrombosis; EKG, electrocardiogram; GI, gastrointestinal; INR, international normalized ratio; PE, pulmonary embolism; SBP, systolic blood pressure; UPC, urine protein to creatinine ratio.

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; moderate increase in ostomy output compared to Baseline
3	Increase of ≥7 stools/day over Baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to Baseline; limiting self-care ADL
4	Life threatening consequences; urgent intervention indicated
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 ≥ Grade 2, decreased performance status, fever, sepsis, neutropenia Grade 3 or 4, 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 [Benson, 2004]. 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.

Management Guidelines

Uncomplicated diarrhea of CTCAE Grade 1 or 2:

- Hydration: have subject drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
- If Grade 2 diarrhea, consider dose reduction of investigational product.
- Dietary modifications: have subject stop all lactose-containing products and eat frequent, small meals.
- Pharmacologic intervention using loperamide:
  - Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
  - Continuation of loperamide is suggested until diarrhea-free for 12 hours.
  - If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes.
  - If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

Complicated diarrhea of CTCAE Grade 3 or 4 or Grade 1 or 2 with complicating features requires aggressive management:

- Subject must call study site physician immediately in response to any event of severe diarrhea with or without complications as listed above.
  - Hospitalization may be required for subjects most at risk for life-threatening complications.
- Interrupt investigational products until symptoms resolve; consider reintroducing at a reduced dose (discuss with Vector Oncology).
- If loperamide has not been initiated, begin loperamide usage immediately at an initial dose of 4 mg followed by 2 mg every 2 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
- If no improvement in severity after 24-hours of maximal loperamide dosing, subject must visit study site and be evaluated:

  - For dehydration, use intravenous fluids as appropriate.

- Antibiotic therapy should be considered in patients who present with signs and symptoms of bacterial diarrhea such as fever, bloody diarrhea, and presence of fecal leukocytes. Investigators should have a low threshold to start such treatment in patients with Grade 3 or Grade 4 neutropenia.
- Before initiation of antimicrobial therapy, stool cultures should be obtained. When bacterial etiology for diarrhea is suspected, study-treatment and anti-motility agents (loperamide or others) should be held.
- Intervention should be continued until diarrhea free for 24 hours.

Alternative Pharmacologic Intervention for Uncomplicated and Complicated Diarrhea

- Lomotil (diphenoxylate 2.5 mg + atropine 0.025 mg) can be used. The recommended dose is 2 tablets 4 times daily. When diarrhea is under control, a dose reduction should be attempted.

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. Octreotide can be administered at doses ranging from 100 μg twice daily to 500 μg 3 times daily, with a maximum-tolerated dose of 2000 μg 3 times daily in a 5-day regimen.

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

- cannabinoids (dronabinol).

Wound Healing

No formal studies on the effect of pazopanib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgment of adequate wound healing. Pazopanib should be discontinued in subjects with wound dehiscence.

Overdose

No maximum tolerated dose (MTD) was reached in the dose escalation study of pazopanib administered as a single agent at repeated doses of up to 2000 mg/day (Study VEG10003). Systemic exposure to pazopanib at steady-state appeared to plateau at doses greater than 800 mg once daily. Increases in the daily pazopanib dose above 800 mg in the fasted state resulted in a small or no increase in mean systemic exposure to pazopanib.

A pazopanib overdose is defined as the administration of more than the protocol-specified dose. Treatment of overdose of pazopanib should consist of general supportive care measures. There is no specific antidote for overdosage of pazopanib. Hemodialysis is not expected to enhance the elimination of pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

The Investigator must promptly report any overdose to Vector Oncology as an important medical event (see SAE Section 10.2.3). Decisions regarding pazopanib dose modifications or interruptions will be made by the Investigator in consultation with Vector Oncology based on the clinical evaluation of the subject.

Following an overdose, additional monitoring of the subject for AEs/SAEs and laboratory abnormalities should be considered.

Information regarding the quantity of the excess dose, as well as the duration of overdosing, should be documented in the source documents and in the iCRF.

Posterior Reversible Encephalopathy Syndrome / Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving pazopanib and may be fatal. PRES/RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. The diagnosis of PRES/RPLS is optimally confirmed

by magnetic resonance imaging. Permanently discontinue pazopanib in patients developing PRES/RPLS.

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) has been reported in clinical trials of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Permanently discontinue pazopanib in patients developing TMA. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.

6.3.2. Dose Interruptions/Modifications for Hepatotoxicity

Note: Liver chemistry abnormalities meeting pre-defined criteria must be promptly reported to Vector Oncology as an important medical event (see SAE Section 10.2.3).

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 a SAE.

Guidelines for investigational product dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 7. 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 iCRF. 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 8. 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	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel

Event	Dose Modification Algorithms
(defined as total bilirubin[b)] < 2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.

Event	Dose Modification Algorithms
(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:** (1) Interrupt pazopanib until toxicity resolves to ≤ Grade 1 or Baseline. Report the event to Vector Oncology as a SAE **within 24 hours** of learning of its occurrence and complete the iCRF. 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 potential benefit for re-initiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then re-introduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks[c]. Re-challenge 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:** 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 iCRF.
(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:** (1) Discontinue pazopanib immediately, report the event to Vector Oncology as a SAE **within 24 hours** of learning of its occurrence, and complete the appropriate iCRF. 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 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, anti-mitochondrial antibody - 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	(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.

Event	Dose Modification Algorithms
ALT < 3 X ULN).	(2) If bilirubin is > 1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue pazopanib at the same dose. 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) Please refer to Investigator's Brochure, Summary of Data and Guidance for Investigator, Warnings and Precautions, Hepatic Effects for information about rechallenge dose.

Abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; iCRF internet case report form; LFT liver function tests; SAE serious adverse event; ULN upper limit of normal

Laboratory Assessments: Full Panel Liver Function Tests for Treatment Emergent Hepatotoxicity

When full panel LFTs are conducted due to treatment emergent hepatotoxicity, this panel 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). Coagulation tests should be performed as clinically indicated. 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 7: Guidelines for Management of Treatment Emergent Hepatotoxicity.

6.4. Concomitant Medications and Non-Drug Therapies

All subjects will be asked to provide a complete list of prescription and over-the-counter medications they are taking at Screening. The Investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the 30-day post-treatment Follow-up visit.

All concomitant medications taken during the study will be recorded in the iCRF with indication, 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. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea.

6.5. Prohibited and Permitted Medications During Study Treatment

6.5.1. Prohibited Medications

Subjects should not receive other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal) while on treatment in this study. When pazopanib 800 mg was administered with lapatinib 1500 mg, the pazopanib AUC and C_{max} increased approximately 50% to 60% compared with taking pazopanib alone. Clinical trials of pazopanib in combination with pemetrexed (NSCLC) and lapatinib (cervical cancer) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose has not been established with these regimens. Pazopanib is not indicated for use in combination with other agents.

Subjects should avoid grapefruit and grapefruit juice while receiving treatment in this study. Plasma pazopanib concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations, increasing the pharmacologic effects and risk of adverse reactions. Therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study treatment. **Strong CYP3A4 inhibitors include (but are not limited to)**:

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

Medications that inhibit permeability glycoprotein (P-gp) may result in increased plasma pazopanib concentrations, increasing the pharmacologic effects and risk of adverse reactions. Therefore, concomitant administration of strong P-gp inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study treatment. **Strong P-gp inhibitors include (but are not limited to):**

- Antiarrhythmics: amiodarone, dronedarone, quinidine, verapamil
- Antibiotics: clarithromycin
- Antifungals: itraconazole, ketoconazole
- Immune modulators: cyclosporine, tacrolimus

In general, as far as pazopanib is concerned, subjects should not receive any other investigational drug within 15 days of the last dose of pazopanib and until end of treatment blood draws are completed.

6.5.2. Permitted Medications – Use with Caution

Although acetaminophen at doses of ≤ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Specific recommendations regarding the use of simvastatin and other statins:

Concomitant use of pazopanib and simvastatin (Zocor) increases the risk of ALT elevations and should be undertaken with caution and close monitoring. If a subject receiving concomitant simvastatin develops ALT elevations, follow the Guidelines for Management of Treatment Emergent Hepatotoxicity and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Specific recommendations regarding drugs that raise gastric pH:

In a drug interaction trial in patients with solid tumors, concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor (PPI), decreased the exposure of pazopanib by approximately 40% (AUC and C_{max}). Therefore, concomitant use of pazopanib with drugs that raise gastric pH should be avoided. If such drugs are needed, short-acting antacids should be considered in place of PPIs and H_2 receptor antagonists. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids.

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 [Billemont, 2008]. 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.

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 peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1.2 and 0.79 μM, respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 and OATP1B1.

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, increasing the pharmacologic effects and risk of adverse reactions. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section 6.5.1 Prohibited Medications); therefore, selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

Medications that inhibit P-gp may result in increased plasma pazopanib concentrations, increasing the pharmacologic effects and risk of adverse reactions. Co-administration of strong P-gp inhibitors is prohibited (see Section 6.5.1 Prohibited Medications); therefore, selection of an alternate concomitant medication with no or minimal potential to inhibit P-gp is recommended.

CYP3A4 inducers may reduce plasma pazopanib concentrations, decreasing the efficacy. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Pazopanib should not be given to patients who cannot avoid long-term use of strong CYP3A4 inducers. **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, carbamazepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

7. STUDY ASSESSMENTS

A Time and Events Schedule is provided in Appendix 1. During the treatment portion of the study, a visit window of +/- 3 business days is allowed. Assessments may be performed within 3 business days before the actual visit to allow flexibility in scheduling with the exception of the BP measurements required at Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day

22, Cycle 2 Day 15, and Cycle 3 Day 15, which have a window of +/- 1 business day. Other vital signs are not required at these time points, and BP can be assessed by any method (e.g., at home or by another physician) as long as the Investigator is informed of the measurement, verifies any measurement that is not normal, and takes appropriate action.

7.1. Screening Assessments

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments. 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 purposes provided these procedures are conducted as specified in the protocol. The study assessment schedules and visit windows are summarized in the Time and Events Schedule (Appendix 1).

Screening assessments must be conducted within the specified time frame prior to start of protocol therapy and will include the following:

- obtain written informed consent within 28 days prior to start of protocol therapy;
- record demographics and medical and disease history within 28 days prior to start of protocol therapy. (Disease history must include date of diagnosis, prior treatment [i.e., chemotherapy, surgery, radiotherapy], and if applicable sites of metastases. Medical history must include documentation about alcohol use and note if the subject is hepatitis B or C positive.);
- perform serum pregnancy test for WOCBP within 7 days prior to start of protocol therapy;
- perform FSH and estradiol to assess childbearing potential, if applicable (see Section 5.1, Inclusion Criterion # 10) within 14 days prior to start of protocol therapy;
- perform physical examination, vital signs [blood pressure, temperature, and pulse], weight, and ECOG performance status within 14 days prior to start of protocol therapy (If Screening physical exam is performed within 7 days prior to start of protocol therapy, the Cycle 1 Day 1 physical exam is not required.);

Note: At the Screening visit, blood pressure should be measured three times at approximately 2-minute intervals. All three blood pressure values should be recorded on the iCRF. These three values should be averaged to obtain mean diastolic blood pressure and mean systolic blood pressure. The mean diastolic and the mean systolic blood pressures are to be used to determine if the subject's blood pressure is within the well-controlled range; or if the subject needs medical attention.

At all later visits, a single blood pressure is measured. If both the systolic and the diastolic blood pressure is within the well- controlled range (defined as blood pressure below 140/90 mmHg) this value is recorded on the iCRF. If either the systolic or the diastolic pressure is outside the well-controlled range, three blood pressures are measured as described for the Screening visit and the mean blood

pressure values are entered on the iCRF and used to determine if the subject needs medical attention.

- perform CT chest, abdomen, and pelvis or PET/CT scan within 28 days prior to start of protocol therapy;
- perform CNS imaging studies (CT or MRI) if clinically indicated or if subject has a history of CNS metastases within 28 days prior to start of protocol therapy;
- document target and non-target lesions to be followed by RECIST guidelines during study within 28 days prior to start of protocol therapy;
- perform complete blood count (CBC) with differential within 14 days prior to start of protocol therapy;
- perform comprehensive metabolic panel (CMP) including magnesium and phosphorus within 14 days prior to start of protocol therapy;
- calculate creatinine clearance (if serum creatinine is > 1.5 mg/dL) using Cockcroft and Gault method within 14 days prior to start of protocol therapy (see Appendix 3);
- calculate UPC ratio and if applicable obtain 24-hour urine protein within 14 days prior to start of protocol therapy (see Appendix 4);
- perform PT/INR and PTT within 14 days prior to start of protocol therapy;
- perform TSH and Lipase within 14 days prior to start of protocol therapy;
- perform 12-lead EKG with documented QTc measurement using Bazett's formula within 28 days prior to start of protocol therapy. If the QTc interval is > 480 msecs using Bazett's formula, then 2 additional EKGs must be obtained over a brief period of time (e.g., within 15-20 minutes) to confirm the abnormality. The average QTc interval will be determined from the 3 EKG tracings by manual evaluation and will be used to determine if the subject will be excluded from the study. If the average QTc interval is > 480 msec, then the subject is not eligible to participate in the study (see Section 7.3.4).;
- perform ECHO or MUGA with documented LVEF measurement within 28 days prior to start of protocol therapy (see Section 7.3.5);
- record concomitant medications within 14 days prior to start of protocol therapy ensuring adequate washout of prohibited medications, if necessary (see Section 6.5.1).

7.2. Efficacy Assessments

Tumor response will be assessed using RECIST guidelines version 1.1. Subjects will be staged for response after every 2 cycles of treatment at the end of Cycles 2, 4, 6, 8, etc. (approximately every 8 weeks). Imaging should be conducted at the end of the indicated cycles or prior to treatment on Day 1 of the next cycle (3, 5, 7, 9, etc.) taking into account time required for receipt and review of scan results.

Repeat imaging should include all affected areas by CT or PET/CT and any other appropriate imaging studies. Contrast should be used for all scans unless contraindicated. Confirmation of PR or CR is required by repeat measurements that should be performed 4 weeks after the criteria for response are first met. EOT tumor assessments should be made within 30 days of study treatment discontinuation. Subjects may continue study treatment in the absence of disease progression or unacceptable toxicity.

7.2.1. Tumor Measurement

The procedures for solid tumor measurement are as follows:

- Measurable disease: the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions**: lesions that can be accurately measured in at least one dimension (the longest diameter), and with a minimum size of 10 mm by CT scan, or 10 mm by caliper measurement during clinical exam, or 20 mm by chest X-ray.
    - A malignant lymph node may be considered pathologically enlarged and measurable if it is ≥ 15 mm in short axis by CT scan.
    - A lytic or mixed blastic-lytic bone lesion, with identifiable soft tissue component which is evaluable by CT or MRI, may be considered as measurable lesion if the soft tissue component meets the criteria for measurable lesions.
    - Cystic metastases may be considered as measurable lesions if they meet the criteria for measurable lesions, however, non-cystic lesions, if present, are preferred as target lesions.
    - Tumor lesions in an area previously subjected to loco-regional treatment, may be considered measurable if there has been demonstrated progression.
- **Non-measurable lesions**: all other lesions, including simple cysts, small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and other truly non-measurable lesions. These include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not measurable by reproducible imaging techniques; blastic bone lesions.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All Baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during Follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint. The measurability of lesion by CT scan is based on the assumption that CT slice thickness is ≤ 5 mm.

7.2.2. Baseline Documentation of Target and Non-target Lesions

- When more than one measurable lesion is present at Baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) 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 longer diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the Baseline sum diameters. The Baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
- All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required and these lesions should be followed as 'present' 'absent', or in rare cases 'unequivocal progression'. Multiple non-target lesions involving the same organ may be recorded as a single item.

7.2.3. Response Criteria

Response and progression will be evaluated in this study using RECIST guidelines version 1.1 [Eisenhauer, 2009].

7.2.3.1. Evaluation of Target Lesions

The criteria for evaluating target lesions are summarized in Table 8.

Table 9. Response Criteria for Target Lesions

Response Category	Criteria
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of the target lesions taking as reference the Baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of the target lesions taking as reference the smallest sum on study, and an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on the study.

7.2.3.2. Evaluation of Non-target Lesions

The criteria for evaluating non-target lesions are summarized in Table 9.

Table 10. Response Criteria for Non-target Lesions

Response Category	Criteria
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological (< 10 mm short axis).
Non-complete Response (non-CR)/Non-progression (non-PD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal appearance of one or more new malignant lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by a review panel or study chair/primary Investigator.

Note: If tumor markers are initially above the ULN, they must normalize for a subject to be considered in complete clinical response.

7.2.3.3. 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). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 10 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at Baseline. When subjects have non-measurable (therefore non-target) disease only, Table 11 should be used.

Table 11. Evaluation Criteria for Best Overall Response: Subjects with Target Disease, with or without Non-target Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD or not at all evaluated	No	PR
SD	Non-PD or not at all evaluated	No	SD
Not at all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; Non-CR = non-complete response; Non-PD = non-progression; PR = partial response; SD = stable disease; PD = progressive disease

Table 12. Evaluation Criteria for Best Overall Response: Subjects with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not at all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; Non-CR = non-complete response; Non-PD = non-progression; PR = partial response; SD = stable disease; PD = progressive disease

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

- When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes.
- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

7.2.3.4. Confirmation

- In non-randomized trials where response is the primary endpoint, confirmation of PR or CR must be confirmed by repeat measurements that should be performed no less than 4 weeks after the criteria for response are first met.
- In randomized trials or studies where the primary endpoints are stable disease or progression, confirmation of response is not required. Elimination of the requirement for

response confirmation may increase the importance of central review to protect against bias, particularly in studies which are not blinded.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

7.3. Safety Assessments

The definitions for an AE and SAE and the procedures for collecting and reporting these events are provided in Section 10. Toxicities will be graded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (see http://ctep.cancer.gov/reporting/ctc.html).

7.3.1. Laboratory Tests During Treatment

Laboratory tests will be performed as indicated in the Time and Events Schedule (Appendix 1).

Participating sites will use their local laboratory to perform all clinical laboratory assessments. Laboratory tests will be performed during Screening, at specified visits during study treatment, and at the end of treatment visit, all as specified in the Time and Events Schedule. Laboratory assessments may be performed within 3 business days before the actual visit to allow flexibility in scheduling. These assessments may be performed more frequently if clinically indicated.

Hematology and Chemistry

A complete blood count (CBC) with differential, a comprehensive metabolic panel (CMP), phosphorus, and magnesium will be assessed on Day 1 of each cycle (approximately every 4 weeks).

A separate liver function test (LFT) panel will be assessed on Day 15 of Cycle 1 and Cycle 2. This panel must include ALT, AST, and bilirubin.

Full Panel Liver Function Tests for Treatment Emergent Hepatotoxicity

When full panel LFTs are conducted due to treatment emergent hepatotoxicity, this panel 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). Coagulation tests should be performed as clinically indicated. Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to ensure subject safety. Guidelines for interpretation of LFT values are described in Section 6.3.2.

Evaluation of Protein

Proteinuria will be evaluated using the urine protein to creatinine ratio (UPC) as described in Appendix 4. UPC will be assessed on Day 1 of each cycle (approximately every 4 weeks).

If UPC $\geq$ 3, then the dose modification table guidelines should be followed (see Section 6.3.1, Table 7).

Thyroid Stimulating Hormone

Thyroid function tests to assess thyroid stimulating hormone (TSH) will be assessed after the first 2 cycles of treatment and then after every 4 cycles of treatment on Day 1 of Cycles 3, 7, 11, 15, etc. (approximately every 16 weeks).

Lipase

Lipase will be assessed after the first 2 cycles of treatment and then after every 4 cycles of treatment on Day 1 of Cycles 3, 7, 11, 15, etc. (approximately every 16 weeks).

7.3.2. Physical Examinations

Physical examinations will be performed on Day 1 of each cycle (approximately every 4 weeks). If Screening physical exam is performed within 7 days prior to start of protocol therapy, the Cycle 1 Day 1 physical exam is not required.

Physical examinations will be performed per standard clinical practice and should, at least, include head, eyes, ears, nose, throat, neck, chest, heart, abdomen, skin, and nodes (cervical, axillary, inguinal) with other areas examined as clinically indicated.

7.3.3. Vital Signs, Weight, and Performance Status

Vital signs, weight, and ECOG performance status will be assessed on Day 1 of each cycle (approximately every 4 weeks). Vital sign measurements will include pulse, temperature, and blood pressure. For ECOG performance status, refer to Appendix 2.

As hypertension is a common drug-related AE observed from other pazopanib studies, blood pressure monitoring is mandatory. Blood pressure must be monitored weekly during Cycle 1 and every 2 weeks during Cycles 2 and 3. Note that only a BP measurement is required at Cycle 1 Day 8 (+/- 1 business day), Cycle 1 Day 15 (+/- 1 business day), Cycle 1 Day 22 (+/- 1 business day), Cycle 2 Day 15 (+/- 1 business day), and Cycle 3 Day 15 (+/- 1 business day). Other vital signs are not required at these time points, and BP can be assessed by any method (e.g., at home or by another physician) as long as the Investigator is informed of the measurement, verifies any measurement that is not normal, and takes appropriate action.

After Cycle 3, if BP is controlled (defined as blood pressure below 140/90 mmHg), then BP may be monitored once monthly. After Cycle 3, if BP is uncontrolled (defined as blood

pressure ≥ 140/90 mmHg), then continue with every 2 week monitoring or more frequently if clinically indicated.

The following instructions must be followed for cuff measurement of blood pressure:

Sitting blood pressure should be measured after the subject has been sitting quietly for at least 10 minutes. The same cuff method should be used to measure blood pressure throughout the study. All measurements will be made on the same arm using the same cuff size and the same equipment. Diastolic blood pressure will be measured at the disappearance of Korotkoff sounds - phase V. If possible, measurements will be taken by the same staff member at each visit.

At the Screening visit, blood pressure should be measured three times at approximately 2-minute intervals. All three blood pressure values should be recorded on the iCRF. These three values should be averaged to obtain mean diastolic blood pressure and mean systolic blood pressure. The mean diastolic and the mean systolic blood pressures are to be used to determine if the subject's blood pressure is within the well-controlled range; or if the subject needs medical attention.

At all later visits, a single blood pressure is measured. If both the systolic and the diastolic blood pressure is within the well-controlled range (defined as blood pressure below 140/90 mmHg) this value is recorded on the iCRF. If either the systolic or the diastolic pressure is outside the well-controlled range, three blood pressures are measured as described for the Screening visit and the mean blood pressure values are entered on the iCRF and used to determine if the subject needs medical attention. Refer to Section 6.3.1, Table 7 for the algorithm of dose modification of study medication in the event that hypertension occurs.

7.3.4. 12-lead Electrocardiogram

In clinical studies of pazopanib, events of QT prolongation have occurred. A 12-lead EKG will be obtained on all subjects at the end of Cycle 1, and then after every 4 cycles of treatment at the end of Cycles 5, 9, 13, 17, etc. (approximately every 16 weeks). EKGs may be performed before the start of treatment on Day 1 of the next cycle as long as results are available prior to treatment.

QTc must be measured using the Bazett's formula and the result documented. Additional EKGs should be done at the Investigator's discretion to ensure the subject's safety, and in case the subject experiences a non-study drug treatment modification with a potentially QT prolonging medication.

Prior to each EKG test, the subject should be at rest for approximately 10 minutes. The subject should be in the semi-recumbent or supine position; the same position must be used for all subsequent EKG tests.

All EKGs must include QTc measurements either manually or machine calculated using Bazett's formula, and recorded in the iCRF. The Bazett's formula is:

$$QTcB\ (msec) = QT\ interval\ (msec) / \sqrt{(RR\ interval)}$$

Screening/Baseline

If the QTc interval is > 480 msecs using Bazett's formula, then 2 additional EKGs must be obtained over a brief period of time (e.g., within 15-20 minutes) to confirm the abnormality. The average QTc interval will be determined from the 3 EKG tracings by manual evaluation and will be used to determine if the subject will be excluded from the study. If the average QTc interval is > 480 msec, then the subject is not eligible to participate in the study.

During Treatment

If a QTc ≥ 500 msec is noted on a scheduled or unscheduled EKG, then 2 additional EKGs must be obtained over a brief period of time (e.g., within 15-20 minutes) to confirm the abnormality. Each EKG tracing must be evaluated manually to obtain RR and QT intervals for QTc calculation. The average QTc will be determined from the 3 EKG tracings by manual evaluation and will be used to determine appropriate next steps. If the average QTc is ≤ 500 msec, the subject may continue therapy.

If the average QTc is > 500 msec, the following steps must be taken:

- Study treatment must be interrupted immediately.
- Electrolytes, particularly potassium and magnesium, must be checked and corrected if abnormal.
- Concomitant medications with a potential for QTc interval prolongation must be discontinued if clinically appropriate.
- The subject must be treated appropriately for QTc prolongation and monitored until resolution is documented by a repeat EKG with QTc interval returning to ≤ 480 msec.
- Communicate findings to Vector Oncology.

NOTE: If the QTc prolongation > 500 msec is clearly and causally associated with an underlying situation that is clearly reversible (e.g., a subject with severe diarrhea and hypokalemia with QTc prolongation that resolves once the diarrhea improves and potassium is corrected), then the subject may restart study drug once the underlying situation has been corrected (e.g., electrolytes supplemented), the QTc interval prolongation has resolved, and a discussion with Vector Oncology has taken place.

If the QTc prolongation > 500 msec is not clearly and causally associated with an underlying situation that is clearly reversible, then the subject must have study drug permanently discontinued and be removed from the treatment portion of the study.

7.3.5. ECHO or MUGA

An ECHO or MUGA is required at the end of Cycle 3 for all subjects.

After Cycle 3, if BP is controlled (defined as blood pressure below 140/90 mmHg) and left ventricular ejection fraction (LVEF) is within institutional normal range, then repeat ECHO or MUGA per treating Investigator's discretion as clinically indicated.

After Cycle 3, if BP is uncontrolled (defined as blood pressure $\geq$ 140/90 mmHg) or LVEF is abnormal, an ECHO or MUGA must be repeated after every 3 cycles of treatment.

The ECHO or MUGA may be done before the start of treatment on Day 1 of the next cycle as long as results are available prior to treatment.

To enable comparison, the same assessment method must be used throughout the study.

8. REMOVAL OF SUBJECTS FROM TREATMENT OR THE STUDY

Subjects who do not start study treatment, but who sign the informed consent and undergo at least some of the Screening procedures will be considered Screening failures. Screening information on any subject who signs the informed consent must be entered into the EDC.

8.1. Criteria for Removal from Treatment

The criteria for stopping therapy are as follows:

- Interruption in pazopanib administration for more than 28 days for any reason.
- Permanent discontinuation of pazopanib for any reason.
- Substantial noncompliance with the requirements of the study.
- Progression of the underlying cancer.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy is not in the best interest of the subject.
- Excessive toxicity despite dose reduction.
- Request by the subject or a legal representative/relative to stop the treatment.
- At the specific request of the Sponsor (Vector Oncology).
- Pregnancy

  - All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The Investigator must immediately notify Vector Oncology in the event of a confirmed pregnancy in a subject participating in the study.
- The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The subject is lost to Follow-up.
- Development of an intercurrent illness or situation which would, in the judgment of the Investigator, affect assessments of clinical status and study endpoints to a significant degree.

8.2. Criteria for Removal from Study

Subjects will be removed from study treatment when any of the criteria listed in Section 8.1 applies. The subject should be entered into the Follow-up portion of the study unless the subject withdraws consent for Follow-up. The Investigator should ensure that all subjects are followed every three months after discontinuing study treatment.

The reason for study removal and the date the subject was removed must be documented in the subject's source documents and in the iCRF.

8.3. Procedures for End of Treatment and Follow-up

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from treatment or declines further participation, all End of Treatment evaluations should be performed if the subject is willing and able to be assessed (see Appendix 1 for the Time and Events Schedule). The End of Treatment evaluations must be performed within 30 days of the subject discontinuing study treatment. A description of the reason(s) for discontinuation from the study treatment must be recorded in the subject's source documents and in the iCRF.

Relevant visit data should be entered in the iCRF and any unused study medication will be accounted for and returned for all subjects participating in the study, even for a brief period of time.

In general, as far as pazopanib is concerned, subjects should not receive any other investigational drug within 15 days of the last dose of pazopanib and until end of treatment blood draws are completed.

If any subject should die during the trial or within 30 days of stopping study treatment, the Investigator will inform Vector Oncology as soon as possible. The cause of death should be recorded in detail on the SAE Report Form.

After the end of treatment (whatever the reason for discontinuation), the subject will be followed for at least 30 days, during which time all procedures for the reporting of SAEs will be followed. The 30-day safety Follow-up may be completed via a phone call, and it must be documented in the subject's source documents.

All subjects who discontinue treatment secondary to an AE should be followed until resolution, stabilization or return to a Baseline condition. Subjects who discontinue treatment without documented tumor progression should be evaluated for extent of disease at the time of treatment discontinuation.

Subjects will be in long-term Follow-up for 6 months. These Follow-ups may be completed via a phone call, and they must be documented in the subject's source documents. Subjects who discontinue treatment due to disease progression will have Follow-ups conducted every 3 months for survival for six months. Subjects who discontinue treatment due to reasons other than disease progression will have Follow-ups conducted every 3 months to assess disease status. During Follow-up, repeat imaging should be performed per the treating Investigator's discretion, and assessment of the subject's disease status should be based upon the most current information available at the time the Follow-up is due. Once the subject has experienced disease progression, (s)he will be followed every 3 months for survival for six months..

The Investigator should ensure that all subjects are followed for disease status (as applicable) and survival status every 3 months for six months with the first Follow-up due 3 months from the date the 30-day safety Follow-up was completed.

9. INVESTIGATIONAL PRODUCT

9.1. Description of Investigational Product

Pazopanib monohydrochloride salt is supplied as aqueous film-coated tablets containing 200 mg or 400 mg of the free base of clinical supply. The 200-mg and the 400 mg tablets are oval-shaped and white in color. Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib and a list of excipients.

Votrient commercial available supply with auxiliary label will be also provided to the Central Pharmacy by Novartis. All bottles are made of high-density polyethylene and have a child-resistant closure. The study drug should be administrated and stored according to the instructions specified on the drug labels (refer to label, P I, and IB for detailed information).

9.1.1. Dosage and Administration

Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in area under the plasma drug concentration curve (AUC) and maximum observed plasma drug concentration (C_{max}).

Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively consistent.

If a dose is missed, the subject should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking pazopanib, the subject should not take a replacement dose on that day because it is not possible to determine how much pazopanib has actually been absorbed. The subject should resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists, the subject should be instructed to notify the Investigator.

Refer to Section 6.5 Prohibited and Permitted Medications During Study Treatment.

9.1.2. Dispensing

It is the responsibility of the Investigator to ensure that pazopanib is only dispensed to study subjects. Pazopanib must be dispensed only from official study sites by authorized personnel according to local regulations.

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of 200 mg tablets to the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of tablets for each dosage must be recorded on the drug accountability pages of record for the site.

The subject will complete a pazopanib diary throughout study participation and must be instructed to return all empty bottles and all unused pazopanib in the provided packaging at each subsequent visit.

9.2. Drug Ordering and Accountability

9.2.1. Initial Orders and Resupply Requests

Pazopanib will be provided to the Central Pharmacy by Novartis. Participating sites should request pazopanib from the Central Pharmacy by completing the Investigational Product

Request Form and faxing it to the fax number provided on the form. Pazopanib will not be automatically resupplied.

9.2.2. Accountability

It is the responsibility of the Investigator to ensure that a current record of pazopanib disposition is maintained at each study site where pazopanib are inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label identification (ID) number or batch number and use date or expiry date.
- Dates and initials of person responsible for pazopanib inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Central Pharmacy, if applicable.
- Amount destroyed at study site, if applicable.

Pazopanib dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site. Label ID numbers or batch numbers for pazopanib must be recorded in the drug accountability records.

Periodic drug accountability visits will be conducted by a Vector Oncology representative.

9.2.3. Destruction

It is the Investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

10. ADVERSE EVENTS

Toxicities will be recorded as AEs in the subject's source documents and on the Adverse Event iCRF and must be graded using the CTCAE v4.0.

10.1. Definitions

Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a

causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of pazopanib whether or not considered related to pazopanib.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., EKGs, radiological scans, vital signs measurements), including those that worsen from Baseline, and are felt to be clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication.

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Serious Adverse Event

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to

investigational product. This includes, but may not be limited to, any event that (at any dose):

- Is fatal.
- Is life threatening (places the subject at immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization. (Note that complications that occur during hospitalization are AEs unless the complication prolongs hospitalization or fulfills any other serious criteria.)
- Is a persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

- All liver chemistry abnormalities meeting pre-defined criteria must be reported as SAEs.
- A hospitalization meeting the regulatory requirement for the "serious" criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility.
- Any event that does not exactly meet this definition yet, in the Investigator's opinion represents a significant hazard can be assigned the "other significant hazard" regulatory reporting serious criteria.
- Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias. **For reporting purposes, also consider the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.**
- An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the Investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

10.2. Reporting Procedures for Adverse Events

10.2.1. All Adverse Events

All AEs occurring after the start of study treatment observed by the Investigator or reported by the subject (whether or not attributed to pazopanib), will be reported on the iCRF.

Medically significant AEs considered related to the investigational product by the Investigator or the Sponsor will be followed until resolved or considered stable. The

Investigator must assign the following attributes: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The Investigator may be asked to provide follow-up information.

If any subject should die during the trial or within 30 days of stopping study treatment, the Investigator will inform Vector Oncology as soon as possible. The cause of death should be recorded in detail on the SAE Report Form.

Vector Oncology will notify the central IRB of IND Safety reports received from Novartis, if applicable. The site will be responsible for reporting SAEs occurring at the site to the applicable IRB per the IRB's reporting guidelines. Sites that are required to utilize a local IRB will be responsible for their own local IRB submissions.

It will be left to the Investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily discontinue treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-treatment visit and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable and returns for a safety Follow-up visit. If the subject was permanently removed from the study or investigational product due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the End of Treatment iCRF.

10.2.2. Relationship to Study Drug

The following categories and definitions of causal relationship to study drug should be considered:

- Certain: There is a known causal relationship between the study drug and the AE/SAE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible. (>95% certainty of relatedness).
- Probable: There is reasonable causal relationship between the study drug and the AE/SAE. The event responds to dechallenge. Rechallenge is not required. (65%-95% probability of relatedness).
- Possible: There is reasonable causal relationship between the study drug and the AE/ SAE. Dechallenge information is lacking or unclear. (35%-65% probability of relatedness).
- Not likely: There is temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE/SAE. (5-35% probability of relatedness).
- Not related: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is known causal relationship between the AE/SAE and another drug, concurrent disease, or other circumstance. (<5% chance of relatedness).

10.2.3. Serious Adverse Events

Site responsibility:

Serious adverse events, overdoses, pregnancies, and liver chemistry abnormalities meeting pre-defined criteria must be reported **immediately*** to Vector Oncology via the SAE Report Form:

Vector Oncology
6555 Quince Road, Suite 400
Memphis, TN 38119 USA
Fax: 901-259-8292
E-mail address: Safety@vectoroncology.com

United Kingdom only: *Reporting "immediately" is clarified in European Commission guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29, which states "Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event".

Site Responsibility:	**Initial Reports**	**Follow-up Information on a Previous Report**
Type of Event	**Documents to Vector Oncology**	**Documents to Vector Oncology**
All SAEs, including overdose of study drug	SAE Report Form	SAE Report Form
Pregnancy	SAE Report Form	SAE Report 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).	SAE Report Form	SAE Report Form
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)	SAE Report Form	SAE Report Form

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 a SAE.

The site will complete the initial and follow-up SAE reports. It is the Investigator's responsibility to make sure follow-up information and supporting documentation are provided in a timely manner.

All SAEs must be collected beginning at the start of study treatment until 30 days after discontinuation of treatment. In addition, the Investigator should notify Vector Oncology of any SAE that may occur after this time period which they believe to be certainly, probably, or possibly related study treatment. Vector Oncology will then notify Novartis of the event.

SAE terminology and severity grading will be based on the CTCAE v4.0 guidelines.

An overdose is defined as the accidental or intentional ingestion of more than the protocol-specified dose. For reporting purposes, an overdose, regardless of adverse outcome, is an important medical event.

Any pregnancy that occurs during study participation must be reported to Vector Oncology. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly reported to Vector Oncology. In addition, the Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Vector Oncology for reporting to Novartis.

Sponsor (Vector Oncology) responsibility:

Vector Oncology Responsibility:	**Initial Reports**		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents to Novartis**	**Time Frame**	**Documents to Novartis**
All SAEs, including overdose of study drug	24 hours	SAE Report Form	As obtained	SAE Report Form
Pregnancy	2 weeks	SAE Report Form	2 weeks	SAE Report 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 Report Form	As obtained	SAE Report Form
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 Report Form	As obtained	SAE Report Form

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 a SAE.

Vector Oncology will:

- Expeditiously handle and report all AEs classified as "serious" to Novartis in compliance with regulatory requirements.
- Immediately report all SAEs to Novartis within 24 hours of becoming aware of the event. If only limited information is initially available, required follow-up reports will be sent. SAE reports will be kept on file at Vector Oncology.

  All SAEs should be faxed to Novartis along with Novartis SAE fax cover sheet at:

  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**

- Any pregnancy that occurs during study participation must be reported to Novartis. To ensure subject safety, each pregnancy must be reported to Novartis within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of the mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly reported to Novartis. In addition, the Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.
- For studies conducted under an Investigator Investigational New Drug (Application) (IND), any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the Investigator's or institution's initial receipt of the information. Novartis will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

- **United Kingdom only**: Reporting of SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be in accordance not only with the USA FDA requirements but also with the European Directive 2001/20/EC and Statutory Instrument 2004 No. 1031. SUSAR reporting will be handled by the Sponsor or its designee.
- Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by Novartis. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.
- AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of study drug, or those experiencing AEs that are present at the end of their participation in study treatment; such subjects should receive post-treatment follow-up as appropriate.

11. STATISTICAL METHODOLOGY

11.1. Introduction

Descriptive statistics will be generated for all study variables. These will include means, standard deviations, medians, minimum and maximum values for continuous variables; and frequency and percentage for categorical variables; and survival function graphs for description of time to event endpoints. Other details regarding analyses are presented below, under Statistical Analysis.

11.2. Analysis Populations

There is no randomization in this study. Intent to treat is defined as occurring at first administration of Pazopanib on C1D1 to eligible subjects, regardless of subsequent subject discontinuation. The intent to treat population includes all subjects who receive the first administration of Pazopanib on C1D1.

The population of subjects who are nonevaluable for disease control includes subjects in the intent to treat population who discontinue or are lost to follow-up prior to the first evaluation of disease control.

11.3. Endpoints

11.3.1. Primary

The primary endpoint is disease control at week 16. defined as CR + PR + SD, where tumor response is defined by RECIST guidelines version 1.1.

The analysis sample for primary endpoint of the study is the intent to treat population. Subjects who are not evaluable for disease control rate will be considered treatment failures for this endpoint.

11.3.2. Secondary

The secondary endpoints of this study are as follows:

- Progression free survival (PFS) according to RECIST guidelines version 1.1.
- Overall survival (OS).
- Toxicity assessment through the reporting of adverse events graded using the CTCAE v4.0.

The analysis sample for secondary endpoints of the study is the intent to treat population.

11.4. Sample Size

The primary endpoint for this study is disease control at week 16 defined as CR + PR + SD, where tumor response is defined by RECIST guidelines version 1.1. For sample size estimation, we assume a null hypothesis rate of 30%, and an alternative hypothesis rate of 50%. A sample of 47 subjects will provide power of 80% to detect this effect, with alpha = .05, two tailed.

There will be no randomization in this study.

Investigator-specific bias will be minimized through the use of multiple centers.

11.5. Statistical Analysis

11.5.1. Baseline Demographic and Clinical Characteristics

Descriptive statistics will be used to characterize Baseline demographic and clinical characteristics of study subjects. As above, these will include means, standard deviations, medians, minimum and maximum values for continuous variables; and frequency and percentage for categorical variables. The disposition of subjects at end of treatment will be

reported, including the number discontinuing for toxicity, for disease progression, and for other reasons.

11.5.2. Efficacy Analysis, Primary Endpoint

Disease control at week 16 will be reported. An Exact test of a single proportion will be used to test the hypothesis that the week 16 disease control rate in the sample does not differ from the null hypothesis rate of 30%. Change from Baseline in sum of largest diameters of target lesions as of week 16 will be computed, with summary statistics reported. A waterfall plot will be generated to descriptively characterize this statistic.

11.5.3. Efficacy Analysis, Secondary Endpoints

The Kaplan Meier product limit estimator will be used to estimate PFS and OS in the sample. The time origin for analysis of PFS and OS will be C1D1. The Kaplan Meier survival function will be generated and displayed to descriptively characterize PFS and OS.

Cox regression analysis may be employed to examine subject Baseline demographic or clinical characteristics as predictors of PFS and OS in the sample.

11.5.4. Toxicity Analysis

Treatment emergent adverse events will be reported by preferred term, by system organ class, by serious vs. nonserious status. Events will be graded per CTCAE version 4.0. The frequency and percentage of subjects experiencing events within preferred term, within system organ class, and for the entire sample, will be reported.

11.5.5. Other Planned Analyses

Number of cycles treated will be reported. Descriptive statistics related to dose of study drug will be reported. The frequency and percentage of subjects who had dose reductions and dose delays will be reported, overall, and by treatment cycle.

11.5.6. Exploratory Analyses

Exploratory analysis will examine disease control and time to event endpoints by tumor grade. Depending on the distribution of tumor grade, Chi-square test or Fisher's Exact test may be used to compare disease control rate across tumor grade. Log rank tests will be used to compare time to event endpoints across tumor grades. Logistic regression may be used to examine disease control by tumor grade, controlling for other subject characteristics.

Other exploratory analyses may be conducted as indicated by preliminary findings from this study.

12. STUDY ADMINISTRATION

12.1. Ethics Review

Before study initiation, each Principal Investigator must have written and dated approval/favorable opinion from the Institutional Review Board (IRB) for the final protocol, informed consent, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to Vector Oncology.

Vector Oncology will provide the central IRB with reports, updates, and other information (e.g., Safety Updates, Amendments, Administrative Letters) according to regulatory requirements and institution procedures. Sites that are required to utilize a local IRB will be responsible for their own local IRB submissions. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected ADRs will be provided to the IRB according to local regulations and guidelines. Vector Oncology will provide the central IRB with reports of any serious ADRs from any other study conducted with the investigational product.

12.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, applicable regulatory requirements.

12.3. Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in the final approved protocol.

All revisions will be submitted to Novartis by Vector Oncology. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

See also 21Code of Federal Regulations (CFR) for definitions of amendment and requirements.

12.4. Informed Consent

Preparation of the consent form is the responsibility of Vector Oncology and will include all elements required by 21 CFR Part 50.25 and the local IRB, if applicable. If modifications

are made to the consent form according to local requirements, the new version must be approved by Vector Oncology.

The Investigator must ensure that the subject or his/her legally acceptable representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit, and other critical issues regarding clinical trials of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent(s) must be obtained before conducting any procedure specifically for the study. The Investigator(s) must store the original, signed written Informed Consent Form(s). A copy of the signed written Informed Consent Form(s) must be given to the subject.

12.5. Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation (e.g., iCRF) on each individual treated with the study drug or entered in the investigation. The Investigator is required to retain, in a confidential manner, the data pertinent to the study.

12.6. Subject Data Protection

In accordance with HIPAA, the written Informed Consent Form must include a subject authorization to release medical information to Vector Oncology and/or allow Vector Oncology, a regulatory authority, or IRB access to subject's medical information that includes all hospital records relevant to the study, including a subject's medical history.

12.7. Records Retention

The Investigator must retain study drug disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g., iCRF) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Documentation of such transfer will be provided to Novartis by Vector Oncology.

12.8. Data Management

Vector Oncology will manage all data management activities for the trial at the company's Memphis, TN facility. All sites will enter their data directly into the EDC. Training on the EDC will be conducted as part of site initiation procedures. EDC access will be password protected, and usage at each research site will be monitored by Vector Oncology.

Investigators are responsible for the integrity of the data (accuracy, completeness, legibility, and timeliness) reported to Vector Oncology. Data should be entered in the EDC within 14 days of a subject's visit.

Clinical Data Management per the study specific plan will be performed by the Vector Oncology Data Management team in accordance with Good Clinical Data Management Practices (GCDMP) with the objective of removing errors and inconsistencies in the data which would otherwise impact the analysis and reporting objectives, or the credibility of the Clinical Study Report.

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Appendix 1 Time and Events Schedule

Assessments (see Section 7 of the protocol)		Screening / Baseline	Treatment Period																				EOT Visit	30 day F/U[10]	LT F/U[11]
(Cycle length = 28 days)	Cycle		1				2			3			4			5			6, etc.[9]						
(Visit window during treatment = ± 3 business days, except BP only ± 1 business day[3])	Day		1	8	15	22	1	15	22	1	15	22	1	15	22	1	15	22	1	15	22				
Informed Consent*		X																							
Demographics*		X																							
Medical and disease history*[1]		X																							
Physical exam**[2]		X	X[2]				X			X			X			X			X			X			
Vital signs (BP[3], T, P) and weight**		X	X				X			X			X			X			X			X			
BP only[3]				X	X	X		X			X			X[3]			X[3]			X[3]					
ECOG**		X	X				X			X			X			X			X			X			
CBC with differential**		X	X				X			X			X			X			X			X			
PT/INR and PTT**		X																							
CMP including magnesium and phosphorus**		X	X				X			X			X			X			X			X			
LFT panel[4]					X			X																	
Calculate creatinine clearance (if serum creatinine > 1.5 mg/dL)**		X																							
UPC ratio (24-hour urine protein, if applicable)**		X	X				X			X			X			X			X			X			
TSH** and Lipase**[5]		X								X[4]													X		
Serum pregnancy test for WOCBP***		X																							
FSH and estradiol (if applicable)**		X																							
ECHO or MUGA with documented LVEF measurement*[6]		X										X									X[5]				
12-lead EKG with documented QTc measurement using Bazett's formula*[7]		X				X												X[6]					X		
CT CAP or PET/CT*[8]		X							X						X						X[7]		X[7]		
CNS imaging studies (CT or MRI) if clinically indicated or if hx of CNS mets*		X																							
Pazopanib administration and compliance (subject diary)			X				X			X			X			X			X						
Assess concomitant medications**		X	X				X			X			X			X			X			X	X	
Assess adverse events			X				X			X			X			X			X			X	X	
Disease status and survival status																							X	X	X

* within 28 days prior to starting treatment ** within 14 days prior to starting treatment *** within 7 days prior to starting treatment

1. Disease history must include date of diagnosis, prior treatment, and if applicable sites of metastases. Medical history must include alcohol use and if the subject is hepatitis B or C positive.
2. If Screening physical exam is performed within 7 days of starting treatment, the Cycle 1 Day 1 physical exam is not required.
3. At the Screening visit, BP should be measured three times at approximately 2-minute intervals. The three values will be averaged to determine if the subject's BP is within the well-controlled range (defined as BP < 140/90). Blood pressure must be monitored weekly during Cycle 1 and every 2 weeks during Cycles 2 and 3. BP only at Cycle 1 Day 8 (+/- 1 business day), Cycle 1 Day 15 (+/- 1 business day), Cycle 1 Day 22 (+/- 1 business day), Cycle 2 Day 15 (+/- 1 business day), and Cycle 3 Day 15 (+/- 1 business day); other vital signs are not required at these time points. BP measurement at these time points may be done at home or by another physician (see Section 7.3.3), but subject must report results to research staff. After Cycle 3, if BP is controlled (defined as BP < 140/90), then BP may be monitored once monthly. If BP is uncontrolled (defined as BP ≥ 140/90), continue with every 2 week monitoring or more frequently if clinically indicated.
4. LFT panel must include ALT, AST, and bilirubin.
5. TSH and Lipase will be assessed after the first 2 cycles of treatment and then after every 4 cycles of treatment on Day 1 of Cycles 3, 7, 11, 15, etc. (approximately every 16 weeks).

6. An ECHO or MUGA is required at Screening and at the end of Cycle 3. After Cycle 3, if BP is controlled (defined as BP < 140/90) and LVEF is within normal range, then repeat ECHO/MUGA per treating Investigator's discretion as clinically indicated. After Cycle 3, if BP is uncontrolled (defined as BP $\geq$ 140/90) or LVEF is abnormal, an ECHO or MUGA must be repeated after every 3 cycles of treatment. The ECHO or MUGA may be done before the start of treatment on Day 1 of the next cycle as long as results are available prior to treatment. The same test should be performed at all time points during the study (see Section 7.3.5).
7. A 12-lead EKG will be obtained at the end of Cycle 1 and then after every 4 cycles of treatment at the end of Cycles 5, 9, 13, 17, etc. (approximately every 16 weeks). EKGs may be done before the start of treatment on Day 1 of the next cycle as long as results are available prior to treatment. QTc must be measured using the Bazett's formula and the result documented. If QTc $\geq$ 500 msec is noted on scheduled or unscheduled EKG, then 2 additional EKGs should be obtained to confirm the abnormality (see Section 7.3.4).
8. Perform CT chest, abdomen, and pelvis or PET/CT on all subjects at Screening. Repeat imaging would include a CT or other appropriate imaging studies of all affected areas after every 2 cycles. Imaging should be conducted at the end of the indicated cycle or prior to treatment on Day 1 of the next cycle taking into account time required for receipt and review of scan results. Contrast should be used for all scans unless contraindicated. Tumor response will be assessed per RECIST version 1.1 guidelines. Tumor assessment should be repeated 4 weeks after initial response for confirmation. EOT tumor assessments should be made within 30 days of study treatment discontinuation.
9. Subjects may continue treatment in the absence of disease progression or unacceptable toxicity.
10. The 30-day safety Follow-up may be conducted via a phone call, and it must be documented in the subject's source documents.
11. Long-term Follow-ups will be conducted every 3 months from 30-day Follow-up for disease status (in subjects discontinuing treatment for reasons other than progression) and survival status for 6 months.. The long-term Follow-ups may be conducted via a phone call, and they must be documented in the subject's source documents.

Appendix 2 ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Reference: As published in Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol. 1982;5:649-655.*

Appendix 3 Determination of Creatinine Clearance (Cl_{CR})

Estimation of creatinine clearance using Cockcroft and Gault method:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \text{ X } [\text{weight (kg)}]}{(72) \text{ X } [\text{Serum creatinine (mg/dL)}]}$

Cl_{CR} for females (mL/min) = $\frac{(0.85) \text{ X } [140 - \text{age (years)}] \text{ X } [\text{weight (kg)}]}{(72) \text{ X } [\text{Serum creatinine (mg/dL)}]}$

For SI units:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \text{ X } [\text{weight(kg)}] \text{ X } (1.23)}{[\text{serum creatinine } (\mu\text{mol/L})]}$

Cl_{CR} for females (mL/min) = $\frac{[140 - \text{age(years)}] \text{ X } [\text{weight(kg)}] \text{ X } (1.05)}{[\text{serum creatinine } (\mu\text{mol/L})]}$

Appendix 4 Urine Protein Creatinine Ratio (UPC)

Clinical Meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate. Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day. Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day. Normal protein excretion is <100 mg to 150 mg/24 hours and is similar for men and women.

Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio ≈ equivalent to grams of protein excreted in urine over 24 hrs.

Example: Subject has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio= (90 mg/dL) / (30 mg/dL) = 3

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

Units for UPC ration

Note: To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or µmol/L). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in µmol/L, conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: µmol/L	Multiply by 88.4
SI Units: µmol/L	Conventional Units: mg/dL	Divide 88.4

References:

Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.

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Appendix 5 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA Classification of Cardiac Disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Reference: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.