

Clinical Development

GW786034

Protocol VEG116731 / NCT01956669

**A Phase II Study of Pazopanib (GW786034, NSC# 737754) in
Children, Adolescents and Young Adults with Refractory Solid
Tumors**

Authors	
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Amendment 5 (23-May-2017)

Amendment rationale

As of 04-May-2017, enrollment is ongoing with 35 patients randomized, and 4 patients currently receiving study treatment. The purpose of this protocol amendment is to:

- To add duration of response among the secondary study objectives to better characterize the clinical benefit in patients responding to treatment. This information may contribute to define the benefit/risk profile in this patient population.
- To provide clarification in the description of the secondary objective on the assessment of genotype/phenotype relationships of VEGF or other members of the VEGF signaling pathway.
- To add the option of closing recruitment of further patients in a given study cohort if no objective responses are observed in patients treated in two out of the three cohorts of primary interest during stage 1 of the study.
- To update the allowed timeframe for prior use of monoclonal antibodies under eligibility criteria.
- To update the contraception/pregnancy language to align with the most recent Investigator Brochure version 15 (IBv.15) referring to specific requirements in male and female patients while receiving study treatment as well as during follow up period.
- To remove the exclusion criterion on concomitant treatment with anti-inflammatory and anti-platelet agents. Based on clinical data in adult patients a drug-to-drug interaction when pazopanib is co-administered with anti-inflammatory agents is not expected.
- To modify the criteria for starting subsequent treatment cycles. This modification will clarify the criteria for starting subsequent cycles when no radiological tumor assessments are performed and align the conditions to resume/interrupt study treatment with toxicity management guidelines.
- The sentence on “medications that increase gastric pH” is now updated to Proton Pump Inhibitors (PPI). This change is reflected in the protocol section on “Prohibited medications.”
- To add anti-inflammatory and anti-platelet agents in the protocol section “Permitted medication to be used with caution”. The use of these agents as a concomitant treatment should be monitored since pazopanib may result in an increase of blood pressure and bleeding episodes.
- To clarify that re-initiation of study treatment following hepatotoxicity requires approval from the Study Chair.
- To clarify that PK sampling is not required beyond Cycle 11 since it is unlikely that data beyond cycle 11 will provide any modification in the clinical pharmacology assessment of the study drug.
- To define the Per Protocol population and specify which analysis will be conducted in the different protocol defined datasets (Per Protocol Population and mITT population).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 1.2: Added duration of response as secondary objective and clarified genotyping assessments.
- Section: 3.1.4: Clarified end of study criteria and addition of the option of closing recruitment of further patients in a given study cohort according to the efficacy results observed in two out of the three cohorts of primary interest at the end of stage 1.
- Section: 3.2.7: Update on the allowed timeframe for prior use of monoclonal antibodies.
- Section: 3.3.1: Updated timeframe for contraceptive requirements in females, and addition of contraceptive instructions for males with partners who can become pregnant.
- Section 3.3.2: Removed exclusion criterion regarding patients currently receiving anti-inflammatory and anti-platelet agents.
- Section: 4.2: Clarification of criteria for starting subsequent cycles when no radiological tumor assessments are performed and alignment with safety management guidelines.
- Section: 4.5: Clarification of use of concomitant medications that increase gastric pH and addition of anti-inflammatory and anti-platelet agents in the protocol section of permitted medications to be used with caution.
- Section: 4.8: Change in the Prohibited Medications section, the reference of “medications that increase gastric pH” to “Proton Pump Inhibitors” (PPI).
- Section: 5.4.3: Clarification regarding approval from Study Chair to re-initiate treatment following hepatotoxicity.
- Section 7.2.4: Updated timeframe for female use of adequate contraception to align with Investigator Brochure version 15.
- Section 7.3.2: Clarified that PK sampling schedule is not required beyond cycle 11.
- Section 9.3: Introduced the definition of Per Protocol (PP) population
- Section 9.4: Clarified data sets to be used for efficacy assessment, objective response analysis and all other efficacy analyses.
- Section 9.8.2: Addition of Duration of Response (DoR) as secondary objective.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 4 (02-MAY-2016):

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound **GW786034**, the purpose of this protocol Amendment **4** is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of **02-MAY-16**:

18 patients have received study treatment in **1** country;

16 patients have discontinued study treatment.

The changes described in this amended protocol require Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) approval prior to implementation.


A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

Amendments 1 to 3

Amendment rationale and summary of changes for previous amendments 1 to 3 are included below in Revision Chronology section and in the appendices 9, 10 and 11 to capture the tracked changes.

Revision Chronology:		
Document Number	Effective Date	Rationale
2012N131371_00	2013-May-24	Original
2012N131371_01	2013-Jun-10	Amendment No. 01 corrected the IND number throughout the protocol (title, Sponsor/Medical Monitor Information page, Sections 4.9, 4.10 and 6.1
2012N141521_02	2014-May-01	<p>Amendment No. 02</p> <p>Sponsor's medical monitor contact information updated.</p> <p>The starting dose for suspension will be 225 mg/m²/dose; the first 6 subjects enrolled who require suspension formulation will have extended PK and evaluation for DLT. Clarification around continuation of therapy following toxicity incorporated.</p> <p>The minimum BSA for patients receiving tablets will be 0.84 mg/m² based on available tablet strengths (200mg, 400 mg).</p>  <p>Monitoring of pregnancy incorporated.</p> <p>Protocol specific SAEs associated with a different investigation drug were removed.</p> <p>General administrative changes including updating TOC, formatting and Appendix and Section references changed throughout the protocol.</p>
2012N141521_03	2016-Feb-15	Amendment No. 03

		<p>Assessment of overall survival added as secondary objective.</p> <p>Evaluability of patients on powder suspension formulation for safety monitoring clarified.</p> <p>End of study definition clarified.</p> <p>To allow patients rescreening</p> <p>Clarification around the enrollment into the different cohorts.</p> <p>Clarification around inclusion criteria (relapsed/refractory disease, bone marrow evaluations, thyroid function).</p> <p>Exclusion criteria regarding hemoptysis changed to exclude patients with history of clinically significant bleeding (within 6 weeks prior to study enrollment).</p> <p>Clarification around dose reductions, treatment interruptions, and missed doses.</p> <p>Blood-product support added as supportive care.</p> <p>Therapy delivery map and visit schedule clarified.</p> <p>Clarifications around hematological dose- limiting toxicities and management of toxicities incorporated.</p> <p>Pharmacokinetic [REDACTED] [REDACTED]</p> <p>Criteria for discontinuation of protocol therapy clarified.</p> <p>Statistical considerations clarified and section on Evaluability for toxicity deleted.</p> <p>Update on contraception/pregnancy language.</p>
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		General administrative changes, change language from subject to patient, change study treatment/study drug to protocol therapy, change GSK medical monitor to medical monitor, typos corrected.
2012N141521_04	2016-May-02	Amendment 04: References to GSK or its staff were deleted or replaced with that of Novartis/Novartis and its authorized agents. Administrative changes were made to align with Novartis processes and procedures.

SPONSOR INFORMATION PAGE

Clinical Study Identifier: VEG116731

Sponsor Contact Information

Novartis Pharmaceuticals Corporation

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Serious Adverse Events (SAE) Contact Information:

For study conduct questions not related to study subject safety, the first line of contact should be with the designated local country company contact. In the event that the designated company contact is not available please contact the Medical Lead. Please refer to the Study Procedures Manual (SPM) for further details.

Sponsor Medical lead Contact Information

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Switzerland ██████████ Email: ██████████ If you have any questions regarding the protocol, please contact your local Novartis office.

Regulatory Agency Identifying Number(s):

IND No: 065747

Sponsor Signatory:

Signature:

Date:

[REDACTED], MD
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
Novartis Pharmaceuticals
Corporation

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number VEG116731:

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. 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.

Investigator Name:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha FetoProtein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society for Clinical Oncology
AST	Aspartate Aminotransferase
ATP	Adenosine tri-phosphate
AUC	Area Under the Curve
BM	Bone Marrow
BSA	Body Surface Area
c-fms or CSF-1	Colony Stimulating Factor 1
CD31	Cluster of Differentiation 31
CEC	Circulating Endothelial Cell
CI	Confidence Interval
COG	Children's Oncology Group
CPK	Creatinine Phosphokinase
CR	Complete Response
CT	Computed Tomography
Ctrough	Steady-State Trough Concentration
CTCAE	Common Terminology Criteria for Adverse Events
CVL	Central Venous Line
DCE-MRI	Dynamic Contrast Enhanced MRI
DLT	Dose Limiting Toxicity
ECG/EKG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
FGF, FGFR	Fibroblast Growth Factor (Receptor)
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B Surface Antigen
HR	Hazard Ratio
HVA	Homovanillic Test
GCIG	Gynecologic Cancer Intergroup
HRCT	High-Resolution Computed Tomography
IEC	Independent Ethics Committee
¹²³ I-MIBG	¹²³ I-metaiodobenzylguanidine
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
IWRS	Interactive Web Response System
KD, KDR	Kinase insert Domain (Receptor)
LC/MS/MS	Liquid Chromatography/Tandem Mass Spectrometry
LFT	Liver Function Test
LPFV	Last Patient First Visit
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple-Gated Acquisition
NCI	National Cancer Institute

NSCLC	Non-Small Cell Lung Cancer
NOAEL	No-Observed-Adverse-Effect-Level
ORR	Objective Response Rate
OS	Overall Survival
PIGF	Placental Growth Factor
PD	Progressive Disease
PDGF, PDGFR	Platelet Derived Growth Factor (Receptor)
PFS	Progression-Free Survival
PfOS	Powder for Oral Suspension
PHI	Protected Health Information
PK	Pharmacokinetic
PNET	Primitive Neuro Ectodermal Tumor
PPI	Proton Pump Inhibitor
PPTP	Pediatric Preclinical Testing Program
PR	Partial Response
QTc	Corrected QT
QTcB	Corrected QT using the Bazett's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SPM	Study Procedure Manual
STS	Soft Tissue Sarcoma
TBI	Total Body Irradiation
TDM	Therapy Delivery Map
TOC	Table Of Content
TTP	Time To Progression
TUNEL	Terminal deoxynucleotidyl transferase dUTP Nick End Labeling
ULN	Upper Limit of Normal
UPC	Urine Protein to Creatinine Ratio
VEGF, VEGFR	Vascular Endothelial Growth Factor (Receptor)
VMA	Vanillylmandelic Acid
XRT	Radiotherapy

ABSTRACT

Anti-angiogenic therapy via vascular endothelial growth factor (VEGF) blockade has been shown in several studies to be an effective cancer therapy. VEGF is a potent mediator of endothelial proliferation, survival, and vascular permeability¹ and is present in most malignancies; higher VEGF expression has been correlated with advanced stage or poor prognosis disease.²⁻⁸ Platelet derived growth factor (PDGF) signaling via PDGFR also plays a key role in angiogenesis by recruiting vascular mural cells, which stabilize vessels when VEGF levels decline.⁹ There are a number of preclinical studies identifying VEGFR, PDGFR¹⁰⁻²⁰ and stem cell factor receptor (KIT) in a wide range of pediatric tumors.^{17,21}

Pazopanib (GW786034) is a small-molecule tyrosine kinase inhibitor that has been shown to prevent ligand induced receptor autophosphorylation of VEGFR-1,-2,-3, PDGFR- α , - β and c-Kit. In addition, a number of *in vivo* murine xenograft studies demonstrate growth inhibition of tumors by pazopanib. This study will examine the efficacy of pazopanib in children with a variety of relapsed solid tumors. The study will also seek to further define the toxicities of pazopanib in children, as well as examine biologic markers that may help to further define the response characteristics of pazopanib.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule

<u>Time</u>	<u>Agent</u>
Days 1 – 28	Oral Pazopanib once daily

This is an open label phase II trial designed to primarily assess the efficacy of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Patients will receive pazopanib monotherapy and the term “protocol therapy” will be used throughout this document to designate pazopanib monotherapy.

Pazopanib will be dosed daily as an oral tablet (450 mg/m²/dose, maximum 800 mg) or as an oral powder for suspension (225 mg/m²/dose, maximum 400 mg). Each cycle will be defined as 28 days, with no rest periods between cycles.

The first patients enrolled who receive powder suspension will be expected to complete extended pharmacokinetic (PK) sampling (Section 7.3.2) in order to obtain PK and safety data in 6 evaluable patients. If the 225 mg/m²/dose is not tolerated (≥ 2 patients with dose limiting toxicities (DLTs) in the first 6 evaluable patients), subsequent new patients will be enrolled at the 160 mg/m²/dose level until 6 evaluable patients are available for the safety review and the PK analysis.

Patients with benefit (stable disease or an objective response) may continue therapy unless there is evidence of progressive disease, unacceptable treatment-related toxicity, until death or until study closure [defined as 1 year after Last Patient First Visit (LPFV)], whichever occurs first.

1. GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the investigator- assessed objective response rate of pazopanib in children, adolescents and young adults (patients) with relapsed or refractory solid tumors of the following types (each defining a cohort):

1. rhabdomyosarcoma,
2. non-rhabdomyosarcomatous soft tissue sarcoma, or
3. Ewing sarcoma/peripheral Primitive Neuro Ectodermal Tumor (PNET).

1.2 Secondary Aims

1.2.1 To determine the investigator- assessed objective response rate of pazopanib in children, adolescents, and young adults (patients) with relapsed or refractory solid tumors of the following types (each defining a cohort):

1. osteosarcoma,
2. neuroblastoma (measurable),
3. neuroblastoma (evaluatable), or
4. hepatoblastoma

- 1.2.2 To further define and describe the toxicities of oral pazopanib in patients with recurrent/refractory solid tumors.
- 1.2.3 To further characterize the pharmacokinetics (PK) of pazopanib after administration of the powder suspension formulation in children, adolescents and young adults with cancer
- 1.2.4 To determine progression free- survival in patients with relapsed or refractory solid tumors, per cohort (described under Section 1.1.1 and 1.2.1).
- 1.2.5 To determine the time to progression in patients with relapsed or refractory solid tumors, per cohort (described under Section 1.1.1 and 1.2.1).
- 1.2.6 To determine the therapeutic activity (a confirmed complete or partial response or stable disease for at least 4 cycles) per cohort (described under Section 1.1.1 and 1.2.1).
- 1.2.7 To assess duration of response in patients with relapsed or refractory solid tumors, per cohort.
- 1.2.8 To further examine the biologic relationship between tumor response and angiogenic cytokines.
- 1.2.9 . To assess the genotype/phenotype relationships of VEGF or other members of the VEGF signaling pathway in children with soft tissue sarcoma.
 - 1.2.10 To further explore pazopanib pharmacokinetic/pharmacodynamic relationships with biomarkers and clinical outcomes, including hypertension.
 - 1.2.11 To assess overall survival (OS) in patients with relapsed or refractory solid tumors per cohort (described under Section 1.1.1 and 1.2.1).

2 BACKGROUND

2.1 Rationale for Development

Vascular endothelial growth factor (VEGF) is a potent mediator of endothelial proliferation, survival, and vascular permeability exerting its effects principally by induction of VEGFR-2 auto-phosphorylation.¹ VEGF is present in most malignancies; higher VEGF expression has been correlated with advanced stage or poor prognosis disease.²⁻⁸ Platelet derived growth factor (PDGF) signaling via PDGFR also plays a key role in angiogenesis by recruiting vascular mural cells, which stabilize vessels when VEGF levels decline.⁹ A number of preclinical studies have identified VEGFR and PDGFR as potential therapeutic targets in a wide range of pediatric solid tumors; these include osteosarcoma, synovial sarcoma, Ewing sarcoma, rhabdomyosarcoma, hepatoblastoma, Wilms' tumor, and neuroblastoma.¹⁰⁻²² The presence of the stem cell factor receptor (KIT) has also been demonstrated by immunohistochemistry in osteosarcoma, synovial sarcoma, Ewing sarcoma, rhabdomyosarcoma, Wilms' tumor, and neuroblastoma.^{17,23}

Pazopanib (GW786034B) is a novel 2H-indazolpyrimidine orally bioavailable, ATP competitive small-molecule tyrosine kinase inhibitor²⁴ that has been shown to prevent ligand induced receptor autophosphorylation of VEGFR-1, -2, -3, PDGFR- α , - β and c-Kit with an IC₅₀ < 0.085 μ mol/L in *in vitro* studies. It also has modest activity against FGFR1, -R3 and c-fms but is otherwise highly selective. Pazopanib is highly protein bound (> 99.9%) thus in *in vivo* studies, steady state concentrations exceeding 18 μ g/mL were required to prevent VEGFR2 signaling.²⁴ Pharmacokinetic studies in adults have shown that these concentrations are readily achievable.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Pazopanib treatment has been shown to inhibit the growth of a variety of established (100-250 μ L) human tumor xenografts in mouse models including renal cell carcinoma (Caki-2), colon carcinoma (HT29), non-small-cell lung carcinoma (NCI-H322), melanoma (A375), prostate carcinoma (PC3), and breast carcinoma (BT474). Pazopanib demonstrated a wide therapeutic index as it had no effect on mouse body weight and all animals appeared active and healthy throughout preclinical studies. Histological analysis following pazopanib administration demonstrated apoptosis or necrosis of tumor cells; TUNEL assays confirmed increased apoptosis. This effect correlated with reduced angiogenesis as measured by decreased concurrent endothelial (CD31) staining. The anti-angiogenic activity of pazopanib has also been demonstrated in mouse corneal micropocket and Matrigel plug analyses.²⁴

There has been limited pediatric pre-clinical testing of pazopanib; however, growth delay was observed in one subcutaneous model of neuroblastoma and was significantly enhanced by concomitant administration of metronomic topotecan.²⁵ The pediatric preclinical testing program (PPTP) also tested the activity of pazopanib against a limited panel of pediatric sarcoma xenografts and observed delayed time to progression, but no tumor regression.²⁶ Other multi-targeted tyrosine kinase inhibitors have been screened by the PPTP using a more complete solid tumor xenograft panel. The pan-VEGFR inhibitor cediranib demonstrated broad *in vivo* antitumor activity (78%; primarily tumor growth delay) including: 3/3 rhabdoid, 2/3 Wilms', 3/3 Ewing, 5/5 rhabdomyosarcoma, 1/3 medulloblastoma, 2/4 glioblastoma, 5/6 neuroblastoma, 4/5 osteosarcoma, with one complete response each in a rhabdoid and osteosarcoma xenograft. Similarly the multi-tyrosine kinase inhibitor sunitinib (VEGFR-1,-2,-3, PDGFR- α , - β , c-Kit,

and FLT3 receptors) showed intermediate (13/34) and high (1/34) levels of activity against 14 of 34 evaluable solid tumor xenografts, including 4 of 6 rhabdomyosarcoma, 4 of 5 Ewing tumor, and 2 of 3 rhabdoid tumor. The overlapping spectrum of receptors targeted by these agents suggests the broad potential of pazopanib for pediatric anti-tumor activity.

2.2.2 Animal Toxicology

In monkeys, no specific toxic effects were seen after 1 month with oral doses of up to 500 mg/kg/day, a dose resulting in a C_{max} and AUC_{0-t} of 36 $\mu\text{g/mL}$ and 316 $\mu\text{g}\cdot\text{h/mL}$ respectively. However, a dose of 500 mg/kg/day could not be tolerated for more than 34 weeks due to severe toxicity, consisting of diarrhea, anorexia, moribundity and accumulation of crystalline material in a number of organs. Monkeys were given 5 or 50 mg/kg/day pazopanib for 1 year, without observed toxicity. The no observed adverse effect level (NOAEL) after 1 year was 50 mg/kg/day. Mean plasma C_{max} and AUC_{0-t} values at 50 mg/kg/day were 31.8 $\mu\text{g/mL}$ and 235 $\mu\text{g}\cdot\text{h/mL}$, respectively, in male monkeys and 44.0 $\mu\text{g/mL}$ and 289 $\mu\text{g}\cdot\text{h/mL}$, respectively, in female monkeys after 1 year (Pazopanib GW786034 Investigator's Brochure).

There are no published data describing the toxicity of pazopanib in juvenile primates. However, doses ≥ 30 mg/kg/day were not tolerated in juvenile rats with marked reductions in body weight as well as mortality seen. These effects occurred at exposures that were similar to or below those expected in pediatric cancer patients. The specific nature of the effects in these animals is not currently known but is presumed to be related to vasculogenesis in critical organs such as the heart, liver, or kidney. In the two surviving groups, 0.3 and 3 mg/kg/day there did not appear to be an effect on body weight although one animal at 3 mg/kg/day had bilateral broken incisors. Hypertrophy of epiphyseal growth plates, and tooth abnormalities (including excessively long, brittle, broken and missing teeth, and dentine and enamel degeneration and thinning) were also observed during repeated dose administration in mature rat and murine models but notably not in adult monkeys (Pazopanib GW786034 Investigator's Brochure).

These findings are consistent with previous observations of physeal dysplasia and ovarian and uterine changes in juvenile animals, including cynomolgus monkeys, during the preclinical testing of other potent VEGF blocking agents raising concern of potential pediatric-specific adverse effects on long-term growth and development.^{27,28} Nonetheless, at least in murine models, the changes in bone growth appeared reversible after cessation of therapy.²⁷ Consistent with the known roles of VEGF in follicle maturation and corpus luteum formation there were significant reductions in female rat fertility at pazopanib doses > 30 mg/kg/day. In males, reductions in testicular and epididymal weights were observed at ≥ 30 mg/kg/day and sperm production, motility and concentration were reduced at 100 mg/kg/day, but this did not result in a functional effect on mating or male fertility. Consistent with the critical role of VEGF in embryogenesis, cardiac malformations were observed in rat fetuses at maternal doses of 3 and 10 mg/kg/day. Delayed ossification (≥ 3 mg/kg/day), embryo lethality and reduced fetal body weight were observed at 10 mg/kg/day. The NOAEL for developmental toxicity in the rat was 1 mg/kg/day (Pazopanib GW786034 Investigator's Brochure).

2.2.3 Preclinical Pharmacology

¹⁴C-pazopanib demonstrates wide tissue distribution. The majority of pazopanib measured in plasma is unmodified, minor metabolites including mono-oxygenated

and de-methylated forms. In rats and monkeys, pazopanib is predominately excreted in the feces with a small amount eliminated in the urine. Following absorption in the monkey, pazopanib is principally metabolized in the liver by oxidation and di-demethylation with glucuronidation. In vitro studies indicate that the oxidative metabolism of pazopanib in human liver microsomes is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. There appears to be minimal potential for inductive effects on CYP enzyme activities in rats or monkeys after oral doses (300 and 500 mg/kg, respectively) of pazopanib for 1 month. (Pazopanib GW786034 Investigator's Brochure)

In order to optimize in vivo dosing for pazopanib and determine whether C_{steady} state or C_{max} best correlated with activity, once and twice daily p.o. dosing was compared with a continuous infusion of a pazopanib analogue (GW771806). Both HT29 tumor growth inhibition and anti-angiogenic activity in the Matrigel plug assay correlated with steady state concentrations of pazopanib and not with C_{max} or exposure (AUC). Complete tumor growth inhibition was achieved with a steady-state plasma concentration of 2.67 μ Mol/L pazopanib. This value corresponded with a pazopanib steady-state concentration of 18 μ g/mL. At this level, pazopanib also demonstrated inhibition of VEGF-induced VEGFR2 phosphorylation in vivo, but if the concentration dropped below this level, inhibition was minimal, again indicating the need to sustain effective levels.²⁴

2.3 Adult Studies

As of 09 September 2012, approximately 5000 patients have received pazopanib as monotherapy or in combination out of approximately 7000 patients enrolled in pazopanib oncology clinical studies. Data collected to date show that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings. Pazopanib is approved for the treatment of adult patients with advanced renal cell carcinoma (RCC) and for the treatment of adult patients with soft tissue sarcoma who have received prior chemotherapy. Results of pharmacokinetic and pharmacodynamic analyses demonstrate that (a) pazopanib is absorbed after oral administration; (b) a plateau is reached in steady-state systemic exposure at a dose of 800 mg daily; (c) a maximum tolerated dose has not been reached at pazopanib doses up to 2000 mg daily; and (d) doses of pazopanib that maintain plasma pazopanib concentrations above 15 μ g/mL (i.e., 800 mg daily and 300 mg twice daily [BID]) are associated with pharmacodynamic and clinical effects. Pazopanib administered as oral doses up to 800 mg daily is being developed by Novartis for the treatment of a variety of cancers.

2.3.1 Pharmacokinetic and Pharmacodynamic Data in Adults with Cancer

The oral bioavailability of pazopanib reflects absorption that is limited by solubility above doses of 800 mg once daily; therefore, increases in doses above 800 mg, up to the highest dose evaluated (2000 mg), in the fasted state will not result in increased systemic exposure. Geometric mean pazopanib $t_{1/2}$ values ranged from 18.1 to 52.3 hours. The geometric mean $t_{1/2}$ was 30.9 hours in the 800 mg once daily dose group, the monotherapy dose selected for administration in Phase II and Phase III clinical trials. The t_{max} was 3 to 4 hours. The oral bioavailability of pazopanib may also be affected by its substrate affinity for gut efflux transporters. Oral absorption is significantly enhanced when pazopanib is dosed with food; therefore, it is recommended to administer pazopanib on an empty stomach, at least 1 hour before or 2 hours after a meal.

The absolute bioavailability of pazopanib (median 21%) suggests that the majority

(67%) of the oral dose recovered unchanged in feces represents unabsorbed drug. Pazopanib is not extensively metabolized and first-pass metabolism is minor, consistent with its low plasma clearance and small volume of distribution.

Age, race, and gender had no effect on pazopanib PK. Mild/moderate renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary. Based on baseline hepatic function, 400 mg pazopanib is recommended for patients with mild impairment (defined as either normal bilirubin and any degree of alanine aminotransferase [ALT] elevation or as an elevation of bilirubin up to 1.5x upper limit of normal [ULN] regardless of the ALT value), and 200 mg for patients with moderate impairment (defined as an elevation of bilirubin >1.5 to 3xULN regardless of the ALT values). The maximum dose of pazopanib (200 mg) administered to patients with severe hepatic impairment did not achieve therapeutic plasma concentrations. Therefore, pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3xULN regardless of any level of ALT).

In clinical studies with pazopanib, events of QT prolongation or torsade de pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of ECGs and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

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 (i.e., increases in VEGF and decreases in soluble VEGFR2). Concentration-effect relationships were observed between trough plasma pazopanib concentrations and an increase in blood pressure in the First Time in Human study, as well as in the percent change from baseline in soluble VEGFR2 nadir in the Phase II study in renal cell carcinoma. The trough plasma pazopanib concentrations associated with one-half the maximal effect (EC50) in both concentration effect relationships were similar (12 to 15.3 µg/mL for hypertension and 21.3 µg/mL for soluble VEGFR2), which demonstrates that there is a consistent inhibition of VEGF receptor(s) in patients with cancer when plasma pazopanib concentrations are maintained above 15-20 µg/mL.

2.3.2 Safety Data in Adults with Cancer (adverse events and serious adverse events)

In a randomized, double-blind, placebo-controlled Phase III study of pazopanib monotherapy in patients with advanced RCC, the median time on treatment was approximately twice that on placebo (7.4 months versus 3.8 months).²⁹ The overall frequency of adverse events (AEs) reported during the study was higher in the pazopanib arm (92%) compared with placebo (74%). Most common AEs reported in >20% patients in the pazopanib arm (as of 23 May 2008) were diarrhea (52%), hypertension (40%), hair color change (depigmentation; 38%), nausea (26%), anorexia (22%), and vomiting (21%). These AEs were all reported at a higher incidence in the pazopanib arm than in the placebo arm. Most of these events were Grade 1 or 2 using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) Version 3.0. More Grade 3 AEs were reported in the pazopanib arm (33%) compared with the placebo arm (14%). The frequency

of Grade 4 AE and Grade 5 events was similar between the pazopanib and placebo arms: Grade 4 in 7% and 6%, respectively; Grade 5 in 4% and 3%, respectively.²⁹ At the time of the final overall survival (OS) analysis, a subsequent review of safety data did not reveal any changes to the previously observed safety profile; no new safety signals were detected.

Based on the analysis of the safety data integrated across 3 RCC studies, including a Phase II study of pazopanib monotherapy in patients with advanced RCC and a single arm Phase III extension study of pazopanib monotherapy in patients with advanced RCC as of January 9, 2009 (N=593), the most common AEs and serious adverse events (SAEs) were similar to those observed in the pazopanib arm of the monotherapy Phase III study.

In a randomized placebo-controlled Phase III study of pazopanib monotherapy in patients with soft tissue sarcoma [STS]), the median time on pazopanib was 19.4 weeks, as compared with 8.1 weeks in the placebo arm. The most common AEs ($\geq 20\%$) reported in the pazopanib arm (as of May 23, 2011) were fatigue (65%), diarrhea (59%), nausea (56%), weight decreased (51%), hypertension (42%), decreased appetite (40%), hair color changes (39%), vomiting (33%), tumor pain (30%), dysgeusia (28%), headache (23%), musculoskeletal pain (23%), myalgia (23%), gastrointestinal pain (23%), and dyspnea (20%). Twenty-eight percent of patients on placebo and 63% of patients on pazopanib experienced an AE of maximum Grade 3 or higher. The proportion of patients who experienced maximum Grade 4 and Grade 5 AEs was similar in both treatment arms.³⁰

An analysis of integrated safety data from a Phase III study in patients with STS and a single arm Phase II study of pazopanib monotherapy in patients with STS showed a safety profile similar to that observed in the pazopanib arm of the Phase III study alone. Increased rates of myocardial dysfunction, venous thromboembolic events, and pneumothorax were newly observed in the STS studies as compared to RCC. Rare but severe AEs previously described for VEGFR inhibitors, such as cardiac/cerebral ischemia, hemorrhage, and bowel perforation, were observed with pazopanib treatment.

A review of SAEs across oncology studies revealed that the most frequently reported SAEs (≥ 70 events), regardless of causality and treatment regimen, as of September 9, 2011 in decreasing order of frequency were increased ALT, dyspnea, vomiting, abdominal pain, pyrexia, diarrhea, anemia, pneumonia, dehydration, and aspartate aminotransferase (AST) increased.

2.3.3 Efficacy Data in Adults with Cancer

Pazopanib 800 mg once daily has shown efficacy and/or encouraging efficacy signals in the following settings:

- **RCC:** The primary analysis of the primary endpoint, progression-free survival (PFS), revealed a large and highly statistically significant improvement in PFS in the pazopanib-treated patients compared to placebo-treated patients (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.34 to 0.62, $p < 0.0000001$). The median PFS in the pazopanib arm was more than double that in the placebo arm: 9.2 months (95% CI, 7.4, 12.9) versus 4.2 months (95% CI, 2.8, 4.2), respectively. The response rate (RR), defined as the percentage of patients who achieved either a confirmed complete response (CR) or partial response (PR)

according to Response Evaluation Criteria in Solid Tumors (RECIST) was significantly higher for the pazopanib arm compared with the placebo arm by Independent Review Committee (IRC) assessment (30% vs. 3%, $p < 0.001$). In the pazopanib arm, the median duration of response was 58.7 weeks (95% CI, 52.1 to 68.1 weeks) and the median time to response was 11.9 weeks (95% CI, 9.4 to 12.3 weeks) by IRC assessment.²⁹ The median OS at final analysis was 22.9 months in the pazopanib arm and 20.5 months in the placebo arm. The final OS was not statistically different between the pazopanib arm and the placebo arm in (HR = 0.91, stratified log-rank p -value, 0.224). Of note, 54% of patients in the placebo arm received pazopanib, many starting early in the study, and an additional 12% received other systemic therapies.

- **Soft Tissue Sarcoma:** In a Phase III study a statistically significant improvement in PFS but not OS was observed in the pazopanib arm compared with the placebo arm. Median progression-free survival was 4.6 months for pazopanib compared with 1.6 months for placebo (hazard ratio [HR] 0.31, 95% CI 0.24-0.40; $p < 0.0001$). Overall survival was 12.5 months with pazopanib versus 10.7 months with placebo (HR 0.86, 0.67-1.11; $p = 0.25$).³⁰ In a Phase II Study, the PFS rate at 12 weeks, based on investigator assessment, was 18 of 41 patients (43.9%) for leiomyosarcoma; 18 of 37 patients (48.6%) for synovial sarcoma; 5 of 19 (26.3%) for adipocytic sarcoma; and 16 of 41 patients (39.0%) for other types of sarcoma.³¹
- **Ovarian cancer:** 11 of 36 patients (31%) experienced a cancer antigen-125 (CA-125) response to pazopanib, with a median time to CA-125 response of 29 days and median duration of response of 113 days. Excluding one patient whose CA-125 decreased before she received the first dose, the biochemical response was 28% (10 patients). Overall response rate based on modified Gynecologic Cancer Intergroup (GCIg) criteria (incorporating CA-125, RECIST, and clinical assessment) was 18% in patients with measurable disease at baseline, and was 21% in patients without measurable disease at baseline. Median PFS was 84 days.³²
- **Early-stage Non-Small Cell Lung Cancer (NSCLC):** 30 of 35 patients (86%) experienced a reduction in tumor volume after short-term use of pazopanib (median duration of 16 days) as assessed by high-resolution computed tomography (HRCT) after preoperative pazopanib treatment.³³
- **ErbB2-positive advanced or metastatic breast cancer:** A higher response rate (36.2% versus 22.2%) by independent review at Week 12 was observed in patients on combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared with lapatinib 1500 mg once daily as a monotherapy, respectively.³⁴
- **Cervical cancer:** There was a 34% reduction in risk for progression for patients receiving pazopanib relative to lapatinib (hazard ratio: 0.66; 90% CI: 0.48, 0.91). The median time to investigator-assessed PFS was 17.1 weeks in the lapatinib group and 18.1 weeks in the pazopanib (one-sided $p = 0.013$).³⁵

Pazopanib has not shown signals of efficacy in Phase II studies conducted in multiple myeloma (VEG20006)³⁶ or glioma (VEG102857).

Most important to the rationale for this current trial are the results from the study of pazopanib in adult patients with advanced or metastatic soft tissue sarcoma. These combined findings form the basis for including several cohorts for soft tissue and bone sarcoma as well as the embryonal tumors specific to pediatrics, which are of mesenchymal origin.

To date, results of correlative biologic assays specific to pazopanib are limited. Most studies sample platelet-poor plasma and serum for cytokine/angiogenic factor profiling which include VEGF, sVEGFR1, and sVEGFR2 and whole blood for circulating endothelial cell subsets (CECs). In two separate Phase II studies of renal cell and NSCLC presented at the 2008 annual meeting of the American Society for Clinical Oncology (ASCO) a decrease in sVEGFR2 compared with baseline was significantly correlated with tumor response ($p < 0.05$).^{37,38} In adult patients with metastatic imatinib-refractory gastrointestinal stromal tumors treated with sunitinib, another VEGF and c-kit targeting multityrosine kinase inhibitor, biomarker analysis of CECs, monocytes, VEGF, and sVEGFR-2 were consistently modulated by treatment. In this study, changes in CECs and monocytes rather than plasma markers differed between the patients with clinical benefit and those with progressive disease.³⁹ In pediatric patients with refractory solid tumors treated with pazopanib, baseline levels of plasma soluble VEGFR-2 and endoglin levels were significantly decreased when measured after 2 weeks of treatment, while placental growth factor levels were significantly increased over the same time points. There was no significant change in VEGF or plasma soluble VEGFR-1 levels with pazopanib therapy.⁴⁰

This study will continue to examine the effects of pazopanib therapy on cytokines and angiogenic factors.

In part, genetic predisposition may account for the variability in biomarker or clinical response to anti-VEGF treatment. Three lines of ongoing investigation justify voluntary collection of DNA in this trial to evaluate relationships between discovered associations in the adult population and pazopanib effects in the pediatric population, and to assess age as a covariate in these relationships.

- 1) Recently, Dr. [REDACTED] and [REDACTED] colleagues identified a single nucleotide polymorphism in KDR (the gene that encodes VEGFR2) that is reproducibly associated with the baseline levels of circulating soluble VEGFR2 in three separate cohorts: healthy volunteers of the Old Order Amish community; 128 unrelated cancer patients at the [REDACTED]; and adult RCC patients enrolled on the phase II trials of pazopanib. Subsequently, they demonstrated that in the RCC patients treated with pazopanib for 4 weeks, this polymorphism is associated with a greater magnitude decline in plasma sVEGFR2 (Late Breaking Abstract, 2011 Am Soc Clin Pharm & Therapeutics Meeting). This genotype/phenotype relationship is currently being studied by another cooperative group (the CALGB Pharmacology and Experimental Therapeutics Committee) in adult patients who are taking agents in this class. Determination of the effect of this KDR polymorphism and sVEGFR2 degree of change on disease response to therapy is ongoing.
- 2) Several genotypes at the VEGFA locus have been associated with increased or decreased VEGF production and prognostic and predictive marking of treatment outcomes. In most VEGF signaling pathway inhibitor trials analyzed so far, 4 SNPs in the promoter region have been evaluated for associations with clinical outcomes: -2578, -1498, -1154, and -634. These studies have yielded inconsistent findings. In amyotrophic lateral sclerosis, similar inconsistencies led to confusion on the predictive role of VEGF alleles until a meta-analysis by Lambrechts, et al.⁴¹ revealed only -2578 to have a clinically relevant and consistent effect. Such studies in oncology are ongoing.

We propose to evaluate all common variation across the VEGFA locus with tagging SNPs representing all common variation in the haplotype analyzed for association with changes in VEGF-A post pazopanib exposure, response rate, and progression-free survival.

- 3) GlaxoSmithKline has recently published results of a candidate gene association study in adult RCC patients treated with pazopanib.²⁵ Several polymorphisms in candidate genes demonstrated associations with response rate and progression-free survival. Validation and elaboration of these findings will become available prior to completion of this trial. Based on the adult findings, additional markers may be explored in the pediatric population.

2.4 Pediatric Studies

2.4.1 Pediatric Phase I Studies

The Children's Oncology Group (COG) conducted a phase I study of pazopanib in children with STS or other refractory solid tumors (ADV0815). This study was performed to determine the maximum tolerated dose (MTD) of two formulations of oral pazopanib; to define and describe the toxicities, pharmacodynamics and pharmacokinetics (PK) of pazopanib administered as a tablet (Part 1) or powder suspension (Part 2a); and to explore pazopanib induced changes in tumor blood volume and vascular permeability (Ki) using dynamic contrast enhanced MRI (DCE-MRI) in a subset of patients with STS (Part 2b). During part 1, pazopanib (tablet formulation) was administered once daily in 28 day cycles at 4 dose levels (275 to 600 mg/m²) using the rolling-six design. Dose determination for a powder suspension (Part 2a) was initiated at 50% of the MTD for the intact tablet. Ten patients with STS underwent DCE-MRI scanning at baseline and 15 ± 2 days after initiation of pazopanib at the tablet MTD (Part 2b). A total of 53 patients were enrolled; 51 were eligible [26 male, median age 12.9 yrs (range 3.8-23.9)].

Hematologic and non-hematologic toxicities were generally mild. Diarrhea, nausea, vomiting, fatigue, proteinuria and hypertension were the most commonly reported side effects. Only cycle 1 DLTs were considered for determination of the MTD and included Grade 3 lipase, amylase and ALT elevation, proteinuria and hypertension. One patient with occult brain metastasis in the imaging expansion cohort also had Grade 4 intracranial hemorrhage. The MTD was 450 mg/m²/dose for tablets, and 160 mg/m²/dose for powder suspension; two isolated and reversible Grade 3 ALT elevations were seen at the powder suspension dose of 225 mg/m²/dose. Toxicities requiring dose modification and/or discontinuation in later cycles included tumor pain (n=2), ALT elevation (n=2), diarrhea, myalgia associated with microangiopathic hemolytic anemia, hand foot syndrome, weight loss, fistula formation at a site of prior RT, growth plate abnormality and recurrent neutropenia (each n=1). Three of 27 patients treated at the MTD had asymptomatic decreases in left ventricular systolic function; all were reversible and the drug was successfully reintroduced in two. Asymptomatic sinus bradycardia was noted in 4 patients, all ≥ 12 years. No QTc prolongation was observed.

Steady state trough concentration (C_{trough}) was reached by day 15 and exceeded 15µg/ml at all dose levels. There was marked inter-patient variability in PK parameters resulting in substantial overlap between dose levels and trough concentrations did not appear dose-dependent. Patients received 1-22⁺ cycles

(median = 2). One patient each with hepatoblastoma or desmoplastic small round and all 5 who received therapy for a year or more had Ctrough ≥ 30 $\mu\text{g/ml}$. All patients with evaluable DCE-MRI (n=8) experienced decreases in tumor blood volume and permeability (Ki; $p<0.01$). PlGF increased, whereas endoglin and soluble VEGFR2 decreased ($p<0.01$; n=31).⁴⁰

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Hypertension was seen in several patients in the pediatric Phase I dose escalation study, which is a class effect seen with other VEGF blocking agents. Such hypertension has been treatable with anti-hypertensives and may ultimately be a biomarker of treatment effect. Pediatric specific guidelines for the management of VEGF blocking agent-induced hypertension have been developed for other COG Developmental Therapeutics studies (e.g. ADVL0413, ADVL0612, ADVL0714, and ADVL0815) and will be used for this trial. In the adult Phase I pazopanib trial, a relationship between steady-state trough concentrations and the occurrence of hypertension could be described by a logistic regression model. Twenty (77%) of the 26 patients with Ctrough values > 15 $\mu\text{g/mL}$ on Day 22 developed hypertension, versus 11 (39%) of the 28 patients who had lower Ctrough values.⁴² In the pediatric phase I trial, the mean Ctrough in patients with drug related hypertension (n=13) was 42 ± 13 g/ml versus 29 ± 13 g/ml in normotensive patients (n=27; $p=0.008$), suggesting a relationship between blood pressure elevation and drug exposure. In addition pediatric patients with a best response of stable disease had a 30% incidence of blood pressure elevation within the first two cycles, and 47% incidence over all cycles. This trial will seek to expand our understanding of the relationship of pazopanib Ctrough to hypertension, and the utility of hypertension as a pharmacodynamic or predictive marker.

2.5 Overview of Proposed Pediatric Phase II Trial

This is a two-stage open label phase II trial of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Tumors of primary interest are rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma (including synovial sarcoma, alveolar soft part sarcoma and desmoplastic small round cell tumor) and Ewing sarcoma/peripheral PNET. Tumors of secondary interest include hepatoblastoma, neuroblastoma (measurable and evaluable), and osteosarcoma.

Each tumor type defines a cohort resulting in 7 total cohorts. The first stage of the study involves enrolling an initial 10 patients into each cohort. The response rate will be determined for each cohort after the target enrollment of 10 patients is reached for that cohort. If one or more confirmed responses are observed in the first 10 evaluable patients in a cohort, an additional 10 patients will be enrolled into that cohort in the second stage of study. Thus, for cohort(s) with one or more confirmed responses in the first stage of study, a total of 20 patients will be enrolled and evaluated to determine efficacy.

Eligible patients will receive pazopanib monotherapy. Pazopanib will be dosed daily as an oral tablet ($450 \text{ mg/m}^2/\text{dose}$, maximum 800 mg) or as a powder for oral suspension ($225 \text{ mg/m}^2/\text{dose}$, maximum 400 mg) in 28 day cycles.

The MTD for pazopanib tablets was $450 \text{ mg/m}^2/\text{dose}$ as determined by ADVL0815/PZP114411, the COG Phase I study in children with relapsed or refractory solid tumors. For the powder suspension formulation, the selected starting dose is higher than the protocol-defined MTD of $160 \text{ mg/m}^2/\text{dose}$ established in ADVL0815. This decision is driven by the considerations that the 160

isolated and reversible laboratory-defined DLTs were observed at the 225 mg/m²/dose.

The first patients who are enrolled to receive pazopanib as powder suspension at 225 mg/m²/dose daily will be closely monitored for safety and for the occurrence of dose-limiting toxicity during the first cycle (28 days) of therapy. Patients who either receive 225 mg/m²/dose daily for at least 24 days (85% of the dose for a 28-day cycle with powder suspension at 225 mg/m²/dose) or are withdrawn from dosing due to one or more protocol-defined dose-limiting toxicities (Section 5.1) during the first cycle will be considered evaluable for the purpose of this safety review. Six evaluable patients are required.

The first patients enrolled to receive powder suspension at 225 mg/m²/dose will also be expected to complete extended PK sampling (Section 7.3.2) with blood samples collected prior to dosing, and 30 min, 1, 2, 4, 6, and 8 hours after the pazopanib dose on Day 1 and Day 15 ± 1 day of Cycle 1 (with no pazopanib dose modification or adjustment in the 10 days before Cycle 1 Day 15 sample collection). Patients who can provide adequate blood samples for the 2 scheduled extended PK collections will be considered to be evaluable patients for the purpose of this PK analysis, and PK data are required from 6 evaluable patients. If one or more of the first 6 patients fails to provide blood samples as specified in the protocol or if it is known that for some reason a patient's collected blood sample(s) cannot be analyzed, that patient will be determined to be non-evaluable for this analysis, and one or more additional patients will be enrolled for treatment with pazopanib as powder suspension for the purpose of obtaining the extended PK samples.

Because patients receiving the powder suspension enrolled in the safety review group may be different from those in the PK analysis group, enrollment onto powder suspension may follow several different paths:

- If ≥ 2 out of 6 evaluable patients have dose-limiting toxicities (DLT and as defined in Section 5.1) within the first cycle, then enrollment onto 225 mg/m²/dose pazopanib will be halted. Subsequent new patients will be enrolled at the 160 mg/m²/dose level until 6 evaluable patients from this dose group are available for the safety review and 6 patients are available for PK analysis at 160 mg/m²/dose.
- If 6 PK evaluable patients are enrolled prior to enrollment of 6 patients who are evaluable for the safety review, the extended PK sample collection may be suspended.
- If < 2 DLTs are observed during the first cycle in 6 patients evaluable for safety at 225 mg/m²/dose and these 6 patients are not all evaluable for the PK analysis, then enrollment will continue until 6 PK evaluable patients are available.

All patients will be closely monitored with clinical and laboratory observations for adverse events.

Tumor response will be evaluated using appropriate imaging assessments at baseline, prior to Cycle 3, Cycle 5, Cycle 8, Cycle 11 and then every 3rd cycle thereafter.

[REDACTED]

In addition, we will assess KDR polymorphism and pazopanib-induced change in soluble VEGFR2; VEGF-A genotype and changes in VEGF-A concentration; KDR and VEGF-A genotypes and response rate, and progression-free survival; and candidate SNPs and clinical endpoints as identified in the adult population.

The primary analysis will be performed 20 weeks after the last patient's first visit in the three cohorts of primary interest (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma and Ewing sarcoma/peripheral PNET).

The study will be completed one year from the date of the last patient's first visit and the end of study analysis will be performed at the time of study completion.

For patients who are still on treatment and continue to derive benefit from it at the time of study completion, and for whom no other treatment options are available, Novartis will discuss individual patient cases with investigators to identify possible access to study treatment after termination of the VEG116731/ADVL1322/PZP034X2203 trial.

A patient will be considered to have completed the study if the patient:

- Dies while on study and prior to study completion
- Stays on study in follow-up until the time of study completion

3 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

3.1.1 Patient Registration

No study-specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines), defining the study entry.

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with registration, please refer to the online help.

Upon completion of all required baseline assessments, the investigator or authorized site staff will assign each eligible patient a Sponsor study-specific patient identification number. Each site will be assigned a range of patient numbers, and this information is provided in the Study Procedure Manual (SPM). The patient ID number consists of 6 digits including leading zeros. Using this patient ID number and patient's histology cohort (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma, Ewing sarcoma/peripheral PNET, osteosarcoma, neuroblastoma (measureable), neuroblastoma (evaluable) or hepatoblastoma), each patient will then be registered into the interactive webresponse system (IWRS). The IWRS will then provide a randomization number consistent with the patient's tumor type.

All sessions to IWRS are confirmed with an onscreen confirmation which will be also sent via e-mail to the site upon completion of each call. **Study-specific instructions will be provided for the use of IWRS in the Study Procedures Manual and in the user manual.**

3.1.2 Patient Rescreening

Patients may be rescreened if the reasons for the initial screen failure were non-medical or if the medical issues leading to screen failure have resolved. Approval by the Study Chair is required prior to rescreening. A new informed consent form must be signed. Please refer to detailed instructions in the Study Procedure Manual for rescreening.

3.1.3 Institutional Review Board (IRB) Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients.

Sites must submit the following documents to Novartis prior to approval to enroll subjects and receive study drug:

- FDA 1572 (for U.S. sites)
- Investigator Agreement Page in Protocol
- Financial Disclosure Forms

- IRB approval (ICF, protocol, subject related materials)
- CV's (Investigator and sub-investigators)
- Laboratory Certifications and Normal Lab Values

IRB/REB approval documents may be faxed, e-mailed, or mailed to Novartis. Further details will be provided in the Study Procedures Manual.

3.1.4 Study Enrollment Status

The study will remain open for enrollment into any of the 7 cohorts until the following:

1. The cohorts with the tumors of primary interest have completed enrollment

and
2. All patients with tumors in the primary interest cohorts have either discontinued from study treatment or have completed a minimum of 5 cycles of treatment

While the study remains open for enrollment, enrollment into each cohort will proceed independently from the other cohorts (see Section 9.2 for details). The enrollment in the cohorts of secondary interest may remain open if after review of the data, an efficacy signal is seen.

The Sponsor in agreement with COG may consider the option of closing recruitment of further patients in a given study cohort in the case that no objective responses are observed in the first 10 evaluable patients in two out of the 3 cohorts of primary interest during stage 1 of the study.

3.1.5 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Specific procedures related to the requirements for patient enrollment are described in protocol Section 3 and in the Study Procedures Manual. Sites will be required to complete a session into the (IWRS) to record patient information as described in Section 3.1.1.

3.1.6 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **5 calendar days** after the date of study enrollment. See Section 3.2 for timing requirements for eligibility studies. See Section 3.1.7 for timing requirements for baseline studies to be obtained prior to start of therapy. **Note: Repeat laboratory and imaging studies may be required if enrollment and start of therapy do not occur on the same day.**

3.1.7 Requirements to Initiate Protocol Therapy

- 3.1.7.1 Laboratory Studies: If more than 7 calendar days elapse between the date laboratory studies to determine eligibility were obtained

(Section 3.2.8) and the start date of treatment, then the following studies must be repeated prior to initiating protocol therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory assessments are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is not eligible for protocol therapy.

Note: For hepatoblastoma patients, blood for serum alpha fetoprotein (AFP) must be drawn within 48 hours prior to initiating protocol therapy. It is not required that the results be known prior to enrollment.

- 3.1.7.2 Imaging Studies: Imaging studies must be performed within 14 calendar days prior to initiating protocol therapy. If more than 14 calendar days have elapsed between the date imaging studies to determine eligibility were obtained (Section 3.2) and the enrollment date, then repeat imaging assessments must be obtained prior to initiating protocol therapy.
- 3.1.7.3 Cardiac studies: Cardiac ECHO and electrocardiogram (ECG) must be performed within 14 calendar days prior to initiating protocol therapy. If more than 14 days have elapsed between the date cardiac studies to determine eligibility were obtained (Section 3.2.8.4) and the enrollment date, then repeat cardiac studies must be obtained prior to initiating protocol therapy.
- 3.1.7.4 Bone Marrow (BM) Evaluations (Solid Tumors with known Marrow Involvement): Bone Marrow aspirate and/or biopsy must be performed within 14 calendar days prior to initiating protocol therapy. If the Bone Marrow evaluation was performed more than 14 days prior to enrollment date and if it was negative, then BM aspirate and/or biopsy must be repeated prior to initiating protocol therapy. If the Bone Marrow evaluation was obtained more than 14 calendar days prior to enrollment and it was positive, and there was no intervening treatment provided to the patients, then there is no need to repeat the Bone Marrow evaluation.

3.2 Eligibility: Inclusion Criteria

Important note: The inclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to the date of enrollment. Imaging studies must be performed within 14 days prior to the date of enrollment. The cardiac ECHO, electrocardiogram (EKG) and baseline knee radiograph must be obtained within 14 days prior to the date of enrollment.

- 3.2.1 Age: Patients must be at least 1 year and less than or equal to 18 years of age at the time of study entry.
- 3.2.2 Diagnosis: Patients must have had histologic verification of one of the malignancies listed below at original diagnosis or at relapse.
1. Rhabdomyosarcoma
 2. Non-rhabdomyosarcomatous Soft Tissue Sarcoma (including desmoplastic small round cell tumor)
 3. Ewing Sarcoma/Peripheral PNET
 4. Osteosarcoma
 5. Neuroblastoma (Measurable)
 6. Neuroblastoma (Evaluable)
 7. Hepatoblastoma



- 3.2.3 Patient must have disease that has either relapsed or is refractory to prior therapy
- 3.2.4 Body Surface Area (BSA) (for subjects taking tablet formulation only): Patients who will be receiving the tablet formulation must have a BSA ≥ 0.84 m² at baseline. The same method should be used to calculate a given patient's BSA throughout their study participation.
- 3.2.5 Disease Status

- 3.2.5.1 Patients must have radiographically measurable disease (with the exception of neuroblastoma – see Section 3.2.5.2).

Measurable disease is defined as the presence of at least one lesion on MRI or CT scan that can be accurately measured with the longest diameter a minimum of 10 mm in at least one dimension (CT scan slice thickness no greater than 5 mm).

Note: The following do not qualify as measurable disease:

- malignant fluid collections (e.g. ascites, pleural effusions)
- bone marrow infiltration
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans)
- elevated tumor markers in plasma
- previously radiated lesions that have not demonstrated clear progression post radiation

- 3.2.5.2 Patients with **neuroblastoma** who do not have measurable disease but have metaiodobenzylguanidine (MIBG+) evaluable disease are eligible.

Note: If the patient has only one MIBG positive lesion and that lesion was irradiated, a biopsy must be or have been done at least 4 weeks after radiation was completed and must show viable neuroblastoma (see Section 10.4.1).

3.2.6 Performance Level

Patients must have a Lansky or Karnofsky performance status score of ≥ 50 , corresponding to ECOG categories 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

3.2.7 Prior Therapy

3.2.7.1 Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

- a. Myelosuppressive chemotherapy: Must not have received myelosuppressive chemotherapy within 3 weeks of enrollment onto this study (6 weeks if prior nitrosourea).
- b. Hematopoietic growth factors: At least 7 days must have elapsed since the completion of therapy with a growth factor that supports platelet or white cell number or function. At least 14 days must have elapsed after receiving peg-filgrastim.
- c. Biologic (anti-neoplastic agent):
 - At least 7 days must have elapsed since the completion of therapy with a biologic agent.
 - For biologic agents that have known adverse events occurring beyond 7 days after administration, the period prior to enrollment must be extended beyond the time during which adverse events are known to occur.
 - Patients may have received bevacizumab, VEGF-Trap, or other VEGF blocking tyrosine kinase inhibitors, provided that they did not progress while receiving one of these agents. Patients may not have previously received pazopanib.
 - At least 21 days must have elapsed since the completion of the last dose of VEGF-Trap, and at least 7 days since a VEGF blocking tyrosine kinase inhibitor. Patients must have recovered from any VEGF blocking drug-related toxicity (e.g., proteinuria).
- d. Monoclonal antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must have recovered to Grade ≤ 1 .
- e. Radiotherapy (XRT): ≥ 2 weeks must have elapsed since local palliative XRT (small port); ≥ 3 months must have elapsed if prior total body irradiation (TBI), craniospinal XRT or if $\geq 50\%$ radiation of pelvis; ≥ 6 weeks must have elapsed if other substantial bone marrow irradiation was given.

- f. Stem Cell Transplantor Rescue without TBI: No evidence of active graft vs. host disease and ≥ 2 months must have elapsed since transplant or rescue

3.2.8 Organ Function Requirements

3.2.8.1 Adequate Bone Marrow Function defined as:

- Peripheral absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
- Platelet count $\geq 75,000/\mu\text{L}$ (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment); and
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

Note: Patients with bone marrow involvement will be eligible for study (provided they meet the criteria above) but will not be evaluable for hematologic toxicity.

3.2.8.2 Adequate Renal and Metabolic Function defined as:

- a. Creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥ 70 mL/min/1.73 m², or
- b. A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this table were derived from the Schwartz formula ⁴³ for estimating GFR utilizing child length and stature data published by the CDC.		

- c. Urine protein:creatinine (UPC) ratio of <1 ; or a urinalysis that is negative for protein; or 24-hour urine protein level < 1000 mg/dL (see [Appendix IV](#)).
- d. Adequate thyroid function: either normal TSH or on a stable dose of thyroid replacement for at least 4 weeks (see [Section 3.3.2.8](#))
- e. No more than Grade 1 abnormalities of:
 - a. Potassium
 - b. Calcium (confirmed by ionized calcium)
 - c. Magnesium
 - d. Phosphorous
 Oral supplementation is allowed.

3.2.8.3 Adequate Liver Function defined as:

- a. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age;
- b. SGPT (ALT) ≤ 2.5 x ULN (for the purpose of this study, the ULN for SGPT is 45 U/L);

- c. Serum albumin ≥ 2 g/dL.
- d. Must not have active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).
 - NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.
- e. No known positivity of hepatitis B surface antigen (HBsAg) or of positive hepatitis C antibody

3.2.8.4 Adequate Cardiac Function defined as:

- a. Shortening fraction of $\geq 27\%$ by echocardiogram (while not receiving medications for cardiac function), or
- b. Ejection fraction of $\geq 50\%$ by gated radionuclide study (while not receiving medications for cardiac function)
- c. Corrected QT according to the Bazett's formula QTcB must be < 450 msec (See Section 5.4.6.2 to determine QTcB)
- d. Must not have a history of myocardial infarction, severe or unstable angina, peripheral vascular disease or familial QT prolongation.

3.2.8.5 Adequate Blood Pressure Control defined as:

A blood pressure (BP) \leq the 95th percentile for age, height, and gender ([Appendix V](#)) measured as described in Section 5.4.1.

- Patients on stable doses of no more than one anti-hypertensive medication, with a baseline BP \leq 95th percentile for age, height and gender ([Appendix V](#)), will be eligible.

3.2.8.6 Central Nervous System Function defined as:

- a. Patients with a known history of seizures must have well-controlled seizures and may not be receiving enzyme-inducing anti-convulsants (See [Appendix IIIA](#))
- b. CNS toxicity \leq Grade 2.

3.2.8.7 Adequate Coagulation defined as:

PT and PTT ≤ 1.2 x upper limit of normal and an INR ≤ 1.2 .

3.3 Exclusion Criteria

Important note: The exclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.

3.3.1 Pregnancy or Breast Feeding/contraception

Pregnant or breast-feeding women are not eligible for this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Negative

pregnancy tests must be obtained in girls who are post-menarchal. Females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method beginning at the signing of the informed consent until at least 2 weeks after the last dose of the study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate. Study drug may also potentially be secreted in milk and therefore breastfeeding women are excluded.

Males (including those who have had vasectomies) with partners who can become pregnant will need to use birth control while on this study, as will their partner. Men are advised to use condoms during sexual intercourse while on study drug and continue to use adequate contraception for at least 2 weeks after the last dose of protocol therapy.

3.3.2 Concomitant Medications

3.3.2.1 Corticosteroids: Patients requiring corticosteroid who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to enrollment are not eligible.

3.3.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

3.3.2.3 Anti-Cancer Agents or Radiation Therapy: Patients who are currently receiving other anti-cancer agents or radiation therapy are not eligible.

3.3.2.4 Anti-hypertensive: Patients who are currently receiving more than one anti-hypertensive medication (Grade 3) or whose blood pressure is not controlled (i.e. as defined in Section 3.2.8.) are not eligible for study enrollment.

3.3.2.5 Anti-coagulation: Patients must not be on therapeutic anticoagulation. ((Warfarin (coumadin®) and/or low molecular weight heparin are prohibited.) Prophylactic anticoagulation (ie intraluminal heparin) of venous or arterial access devices is allowed.

3.3.2.6 CYP3A4 Substrates and drugs causing QTc prolongation: Patients receiving drugs with a known risk of torsades de pointes are not eligible. See [Appendices IIIA](#) and [IIIB](#) and Section 4.8 for a list of enzyme inducing, enzyme inhibiting and other adversely interacting drugs and the appropriate washout periods required prior to study enrollment

Note: This list includes the prohibition of grapefruit juice for 14 days prior to enrollment and while receiving pazopanib.

3.3.2.7 Thyroid Replacement Therapy: Patients who require thyroid replacement therapy are not eligible if they have not been receiving a stable replacement dose for at least 4 weeks prior to study enrollment.

3.3.3 Patients who are unable to swallow tablets or liquid are not eligible. Pazopanib cannot be administered via NG tube or G-tube.

3.3.4 Infection: Patients who have an uncontrolled infection are not eligible.

- 3.3.5 Bleeding and Thrombosis: Patients will be excluded if any of the following are present:
 - 3.3.5.1 Evidence of active bleeding, intratumoral hemorrhage, or bleeding diathesis.
 - 3.3.5.2 History (within 6 months prior to study enrollment) of arterial thromboembolic events, including transient ischemic attack (TIA) or cerebrovascular accident (CVA).
 - 3.3.5.3 History (within 6 months prior to study enrollment) of pulmonary embolism, DVT, or other venous thromboembolic event.
 - 3.3.5.4 History of clinically significant bleeding (grade 3 hemorrhage) within 6 weeks prior to study enrollment, including CNS, pulmonary, or GI hemorrhage.
- 3.3.6 Patients with known involvement of the CNS by malignancy will be excluded.
- 3.3.7 Surgery: Patients who have had or are planning to have the following invasive procedures will be excluded:
 - a. Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 therapy. (Subcutaneous port placement or central line placement is not considered major surgery but must be placed greater than 48 hours from planned Day 1 of therapy.)
 - b. Core biopsy within 7 days prior to Day 1 therapy
Note: Routine bone marrow aspirate and biopsy for the purposes of disease staging are **not** part of these exclusion guidelines.
 - c. Fine needle aspirate or central line placement within 48 hours prior to Day 1 therapy.
- 3.3.8 Patients with serious or non-healing wound, ulcer, or bone fracture.
- 3.3.9 History of abdominal fistula, gastrointestinal perforation, pneumothorax, or intra- abdominal abscess within 28 days of study enrollment.
- 3.3.10 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible

3.4 Regulatory

- 3.4.1 All patients and/or their parents or legal guardians must sign a written informed consent (and assent according to institutional guidelines).
- 3.4.2 All institutional, FDA and Health Canada requirements for human studies must be met.

4 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol). This does NOT apply to eligibility requirements; but to therapy and evaluations post consent and post the start of protocol directed care. Novartis will not grant protocol waivers.

4.1 Overview of Treatment Plan

Pazopanib will be dosed daily as an oral tablet at 450 mg/m²/dose or as a powder for oral suspension at 225 mg/m²/dose.

For the tablet formulation, the maximum tolerated dose (MTD) was 450 mg/m²/dose as determined by ADVL0815/PZP114411, the COG Phase I study. The maximum dose to be administered daily for tablets is 800 mg.

For the powder suspension formulation, the selected starting dose is 225 mg/m²/dose, higher than the protocol-specified MTD of 160 mg/m²/dose established in study ADVL0815. This decision is driven by the considerations that the 160 mg/m²/dose may result in exposure that is suboptimal to demonstrate efficacy and that only two isolated and reversible laboratory- defined dose-limiting toxicities (DLTs) were observed at the 225 mg/m²/dose. The maximum dose to be administered daily for oral suspension is 400 mg.

Note: The first patients enrolled who receive powder suspension will be reviewed for safety and will be expected to complete extended PK sampling (Section 7.3.2). A minimum of 6 evaluable patients for safety and 6 evaluable patients for PK are required as described in section 2.5. Safety and PK data from these patients will be reviewed prior to further enrollment of patients requiring powder suspension to determine if the 225 mg/m²/dose is tolerated and if the PK exposure is similar to exposure in adults associated with clinical efficacy. If 225 mg/m²/dose is not tolerated (≥ 2 patients with DLTs in the first 6 evaluable patients during their first cycle), all subsequently enrolled patients will receive 160 mg/m²/dose, and an additional 6 subjects will be assessed for safety and PK.

Patients will take pazopanib continuously, once daily. A cycle will be defined as 28 days with no rest periods between cycles. Patients with benefit (stable disease or an objective response) may continue therapy unless there is evidence of progressive disease or unacceptable treatment-related toxicity, death or until study closure defined as 1 year after Last Patient First Visit.

Patients must remain on the same formulation of pazopanib throughout the duration of their protocol therapy.

Drug dosing for the tablet formulation should be determined using the dosing nomogram in [Appendix II](#). For patients receiving powder for suspension (50 mg/mL), the dose will be rounded to the nearest 5 mg. Drug doses should be adjusted based on the BSA as determined by the height and weight obtained within 1 week prior to the beginning of each cycle.

Pazopanib should be taken on an empty stomach (at least 1 hour before a meal or 2 hours after a meal) at approximately the same time each day. Pazopanib tablets should be taken with clear liquids (approximately 4 ounces for children < 12 years of age and 4-8 ounces for children ≥ 12 years of age). Pazopanib suspension should be taken according to instructions in [Appendix VII](#).

The pazopanib suspension should be swirled for at least 30 seconds prior to removal of the dose from the bottle, which should be given immediately. If a patient vomits after a dose of pazopanib, the dose should not be repeated.

A patient diary (see [Appendices IA](#) and [IB](#)) should be completed by the patient or their guardian and collected at the end of each cycle.

See Section 5 for Dose Modifications in Response to Toxicities

4.1.1 Dose Reduction

For patients who receive pazopanib tablets: Dose reduction(s) in response to toxicity may be implemented according to guidance in Sections 5.2, 5.3, and 5.4 of the protocol. Outside the specific management guidance described in these sections, patients who recover from an adverse event to starting criteria as outlined in Section 4.2 within 14 days following planned administration will also be permitted to receive protocol therapy at a reduced dose. Dose reduction(s) will be based on the starting dose and should follow the Dosing Nomogram in [Appendix II](#).

Note: For patients receiving pazopanib tablets at a starting dose of 400 mg, there will only be one allowed dose reduction due to tablet size.

For patients who receive pazopanib as oral powder for suspension: Dose reduction(s) in response to toxicity may be implemented according to guidance in Sections 5.2, 5.3 and 5.4 of the protocol. Outside the specific management guidance described in these sections, patients who recover from an adverse event to starting criteria as outlined in Section 4.2 within 14 days following planned administration will also be permitted to receive protocol therapy at a reduced dose. Dose reduction(s) will be based on the starting dose and should follow the guidance in [Table 1](#) and [Table 1a](#).

Table 1: Dose Reduction for Toxicity if powder suspension starting dose is 225 mg/m²

Starting Dose	225 mg/m ² /dose
First Dose Reduction	160 mg/m ² /dose
Second Dose Reduction	135 mg/m ² /dose

Table 1a: Dose Reduction for Toxicity if powder suspension starting dose has been reduced to 160 mg/m²

Starting Dose	160 mg/m ² /dose
First Dose Reduction	135 mg/m ² /dose

Any subsequent dose reduction would need to be discussed and agreed by the Study Chair.

4.1.2 Dose Escalation

Dose escalations will not be allowed.

4.1.3 Treatment Interruptions

If the protocol therapy has been interrupted for more than 14 days due to toxicity or

for reasons other than toxicity (unplanned travel or vacation, or lack of transportation to the site), the Study Chair must be notified to review the patient's condition in order to resume treatment. In cases of toxicity, re-challenge at a reduced dose is possible if the patient's condition has been stable and has not deteriorated and the patient must have recovered from the toxicity (Section 4.2).

If the protocol therapy has been interrupted for more than 28 days, the patient should be permanently discontinued from protocol therapy and will continue to be followed for survival.

4.1.4 Missed Doses

Missed doses should be documented in the electronic case report form (eCRF).

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

4.1.5 Study Specific Supportive Care

4.1.5.1 Management of Hypertension: The algorithm in Section 5.4.1 will be used to grade and manage pazopanib-related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, which are permissible without notifying the Study chair) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 5.4.1.

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section 5.4.1.

4.1.5.2 Management of Hypothyroidism: Patients with Grade 2 hypothyroidism should be evaluated by an endocrinologist for further management. Patients with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol therapy. Patients with Grade 3 or greater hypothyroidism attributable to pazopanib will be considered to have had a dose-limiting toxicity. These patients should be managed according to Section 5.3 and should also be evaluated by an endocrinologist for further management. If Grade 3 or greater hypothyroidism is adequately managed with thyroid hormone replacement and improves to grade 2 or less, pazopanib may be restarted.

4.1.5.3 Treatment of palmar-plantar erythrodysesthesia (Hand-foot syndrome): Oral administration of vitamin B 6 (pyridoxine) may be considered for patients who develop palmar-plantar erythrodysesthesia (hand-foot) syndrome:

- BSA <0.5 m²: 50 mg per day
- BSA 0.5-1.0 m²: 100 mg per day
- BSA >1.0-1.5 m²: 200 mg per day
- BSA >1.5 m²: 300 mg per day

Other supportive care measures for the treatment of hand-foot syndrome should be instituted as needed. If steroids are used, they must fall within the

dosing parameters in Section 4.8.

4.1.5.4 Blood-product Support: Patients should be supported with transfusion of blood and blood products (including platelet transfusion) per institutional standards.

4.1.5.5 Supportive Care: General supportive care should be provided according to institutional standards. The COG Study Chair or Novartis Medical Lead can be contacted for specific questions regarding supportive care.

4.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease or progressive disease is ruled out based on clinical or laboratory evidence and met the clinical and laboratory parameters as defined by the guidelines for dose modification and toxicity management (Section 5) and does not have a dose limiting toxicity requiring permanent removal from protocol therapy (Section 5.1). A patient may resume protocol therapy at the same or a reduced dose if they have a toxicity that is adequately managed (eg: myelosuppression, hypertension, hepatotoxicity, electrolyte abnormality, bleeding, wound healing, etc) as outlined in Sections 5.2, 5.3, and 5.4.

4.3 Concomitant Therapy

If new data become available showing an interaction between a concomitant medication and pazopanib that is considered significant enough to impact the risk/benefit balance of pazopanib, the list of permitted/prohibited medications in the Investigator Brochure will be updated either during the annual update or within an IB supplement. Any such changes will be communicated to the site via a letter which should be stored in the site's study file.

4.4 Permitted Medications

All patients will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to 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 post-treatment follow-up visit.

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration.

Patients should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT₃ antagonists) may be administered prophylactically in the event of nausea. However, it is important to note that 5-HT₃ blockers that are given daily for a prolonged period of time may prolong QTc and should be used with caution. (Appendix IIIB). Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤ 2 g/day is permitted, it should be used with caution in patients with impaired liver function.

4.5 Permitted Medications – Use with Caution

4.5.1 Specific recommendations regarding anticoagulants:

Results from drug-drug interaction studies conducted in patients 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, if the investigator decides to continue pazopanib and anticoagulants use concomitantly, it should be used with caution in patients with increased risk of severe bleeding or who are benefitting from treatment and require the initiation of concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) while on study. Note: Patients are excluded from enrolling on the study if they are taking therapeutic doses of S-warfarin at the time of screening. Patients 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.

4.5.2 Specific recommendations regarding hypoglycemic therapy including insulin:

Results from drug-drug interaction studies conducted in patients 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 reported in patients treated with another small molecule tyrosine kinase inhibitor, sunitinib (British Journal of Cancer 2008: 99, 1380). Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Patients should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, and sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

4.5.3 Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for pazopanib or consider discontinuing simvastatin.

4.5.4 Concomitant administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by 40% (AUC and C_{max}). Co-administration of pazopanib with Proton Pump Inhibitors (PPIs) should be avoided. **Co-administration of pazopanib with PPIs is PROHIBITED from 24 hours before the first dose of pazopanib until after the final PK blood sample is collected on Day 15 ± 1 day of Cycle 1.** After this, if the concomitant use of a proton-pump inhibitor (PPI) is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI (Section 4.8). If the concomitant administration of an H₂-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H₂-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids.

4.5.5 Concurrent Anti-Hypertensive Therapy: The algorithm in Section 5.4.1 will be used to grade and manage pazopanib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine) may be started without notifying the study chair.

- 4.5.6 Anti-inflammatory and anti-platelet agents (e.g. aspirin, and/or ibuprofen, or other NSAIDs) could result in elevated blood pressure or increased bleeding episodes when co-administered with pazopanib and therefore should be used with caution.
- 4.5.7 Patients' medications should be reviewed at eligibility, before treatment initiation, and during treatment. Any concomitant medications that are "generally accepted" to cause a risk of Torsade de pointes are prohibited (see [Appendix IIIB](#)). Those "associated" with a risk of QTc prolongation and/or Torsades de pointes should be discontinued or replaced with drugs that do not carry these risks, if possible. Patients who must take these medications should be watched carefully for symptoms of QTc prolongation, such as syncope. Performing additional EKGs on patients who must take one or more of these medications is recommended but not required, at the investigator's discretion.

4.6 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 patients 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, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

4.7 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 and for breast cancer resistance protein. 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. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section 4.8); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

Medications that induce CYP3A4 may result in decreased plasma pazopanib concentrations and a loss of efficacy and therefore are prohibited (See Section 4.8). Anticonvulsant drugs that do not induce CYP enzymes are allowed. Refer to Appendix IIIA for a list of anticonvulsant drugs with little or no enzyme induction. The use of azithromycin or fluconazole is discouraged but allowed.

4.8 Prohibited Medications

Patients should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] while on treatment in this study. Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning 14 days prior to the first dose of protocol therapy until discontinuation of the protocol therapy.

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

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

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

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

- Glucocorticoids for greater than 2 weeks duration: cortisone (>50 mg/day), hydrocortisone (>40 mg/day), prednisone (>10 mg/day), methylprednisolone (>8 mg/day), dexamethasone (>1.5 mg/day)
- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, oxcarbazepine, primidone, fosphenytoin
- HIV antivirals: efavirenz, nevirapine, tipranavir
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

Grapefruit or grapefruit juice is prohibited as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

As noted above, co-administration of pazopanib with PPIs should be avoided and is prohibited from 24 hours before the first dose of pazopanib until after the final PK blood sample is collected on Day 15 ± 1 day of Cycle 1.

The therapy delivery maps (TDMs) are on the next 2 pages.

4.9 Therapy Delivery Map (TDM) - Cycle 1

This therapy delivery map relates to Cycle 1: Pazopanib treatment given once daily continuously for 28 days. See Section 4.10 for the therapy delivery map for subsequent cycles. 1 cycle = 28 days. Dosing is continuous. There is no interruption between cycles.		Patient name/initials	DOB
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Criteria to start Cycle 1 are described in Section 3.2. Extensive details are in Section 4.1 (treatment overview). Cycle 1 lasts 28 days.

DRUG	ROUTE	DOSAGE Circle applicable formulation and strikethrough unused formulation to avoid confusion	DAYS	IMPORTANT NOTES	OBSERVATIONS OBTAIN OTHER ASSESSMENTS AS REQUIRED FOR GOOD PATIENT CARE
Pazopanib (GW786034) IND# 065747	PO	If tablets: 450 mg/m ² /dose given once daily (Max dose: 800 mg) If powder in suspension: 225 mg/m ² /dose given once daily (Max dose: 400 mg)	1-28	Take on an empty stomach (at least 1 hour before a meal or 2 hours after a meal). See Section 4.1 for further details.	a History, physical exam, vital signs, blood pressure b Urinalysis (including UPC) and/or 24 hour urine for protein c Ht, Wt, BSA, performance status d CBC, differential, platelets, electrolytes including K ⁺ , Ca ⁺⁺ , PO ₄ ³⁻ , Mg ⁺⁺ , creatinine, total protein, albumin, ALT, bilirubin, amylase, lipase e PT/PTT/INR, pregnancy test, TSH f ECHO, EKG, plain x-ray of knee (see Section 7.2.1) g Disease evaluation including BMA/Bx, Urine VMA/HVA, AFP as indicated (see Section 7.1). h PK (see Section 7.3 & Appendix VI). i PD (see Sections 7.1 and 7.4)

Ht _____ cm Wt _____ kg

BSA _____ m²

Date Due	Date Given	Week	Day	Pazopanib _____ mg	Assessments	Comments (Include any held doses, or dose modifications)
Please refer to the Visit Schedule in Section 7 for Screening assessments.						
				Enter calculated dose above and then dose administered below		
		1	1	mg	a, b, c ¹ , d ² , h ³ , i ³	
			2	mg		
			3	mg		
			4	mg		
			5	mg		
			6	mg		
			7	mg		
		2	8	mg	a, d ²	
			9	mg		
			10	mg		
			11	mg		
			12	mg		
			13	mg		
			14	mg		
		3	15	mg	a, d ² , h ⁴	
			16	mg		
			17	mg		
			18	mg		
			19	mg		
			20	mg		
			21	mg		
		4	22	mg	a, d ²	
			23	mg		
			24	mg		
			25	mg		
			26	mg		
			27	mg		
			28	mg		
			See Section 4.2 for criteria for starting a subsequent cycle. See section 5 for dose modifications			

¹Evaluations obtained for screening will ONLY be repeated at Cycle 1 Day 1 if they are older than 7 days.

²If Grade 4 neutropenia or thrombocytopenia, CBCs should be checked at least twice a week (every 3 to 4 days) until ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (transfusion independent).

³Prior to the first dose

⁴Obtain at the same time as safety labs.

4.10 Therapy Delivery Map – Subsequent Cycles of Therapy

This therapy delivery map applies to all cycles given after Cycle 1: Pazopanib treatment given once daily continuously for 28 days (1 cycle = 28 days). Patient may receive additional cycles (if they meet requirements described in Section 4.2.

Patient name/initials

DOB

See Section 4.2 for criteria for starting next cycle.

DRUG	ROUTE	DOSAGE Circle applicable formulation and strikethrough unused formulation to avoid confusion	DAYS	IMPORTANT NOTES	OBSERVATIONS OBTAIN OTHER ASSESSMENTS AS REQUIRED FOR GOOD PATIENT CARE
Pazopanib (GW786034) IND# 065747	PO	If tablets: 450 mg/m ² /dose given once daily (Max dose: 800 mg) If powder in suspension: 225mg/m ² /dose given once daily (Max dose: 400 mg)	1-28	Take on an empty stomach (at least 1 hour before a meal or 2 hours after a meal). See Section 4.1 for further details.	a History, physical exam, vital signs, blood pressure b Urinalysis (including UPC) and/or 24 hour urine for protein c Ht, Wt, BSA, performance status d CBC, differential, platelets, electrolytes including K ⁺ , Ca ⁺⁺ , PO ₄ ³⁻ , Mg ⁺⁺ , creatinine, total protein, albumin, ALT, bilirubin, amylase, lipase e Pregnancy test f TSH g PT/PTT/INR h ECHO, EKG, plain x-ray of knee (see Section 7.2.1) i Disease evaluation including BMA/Bx, Urine VMA/HVA, AFP as indicated (see Section 7.1). j PK (see Section 7.3 & Appendix VI). k PD (see Sections 7.1 and 7.4)

Cycle of Therapy: _____ Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Week	Day	Pazopanib _____mg	Assessments	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and then dose administered below		
		1	1	mg	a ¹ , b ² , c ² , d ³ , e ² , f ⁴ , g ⁵ , h ⁶ , i ⁴ , j ⁷ , k ⁸	
			2	mg		
			3	mg		
			4	mg		
			5	mg		
			6	mg		
			7	mg		
		2	8	mg	d ³	
			9	mg		
			10	mg		
			11	mg		
			12	mg		
			13	mg		
			14	mg		
		3	15	mg	a ¹ , d ³	
			16	mg		
			17	mg		
			18	mg		
			19	mg		
			20	mg		
			21	mg		
		4	22	mg	d ³	
			23	mg		
			24	mg		
			25	mg		
			26	mg		

			27	mg		
			28	mg		
				See Section 4.2 for criteria for starting next cycle. See section 5 for dose modifications.		

¹ Every other week for Cycle 2 and 3, and then prior to the start of each subsequent cycle.

² Prior to the start of each subsequent cycle.

³ Weekly during Cycle 2, every other week in Cycle 3, and then prior to the start of each subsequent cycle.

⁴ Prior to Cycle 3, 5, 8, and 11 and every 3rd cycle thereafter

⁵ Prior to Cycle 3 and every 6 cycles thereafter

⁶ Prior to Cycle 2 and Cycle 5, and then every 6 cycles.

⁷ Pre-dose at every odd cycle.

⁸ Pre-dose on either Day 1 of Cycle 2 or Day 1 of Cycle 3.

5 DEFINITIONS AND DOSE MODIFICATION FOR TOXICITY

All dose modifications should be based on the worst preceding toxicity. The severity of adverse events will be graded utilizing the National Cancer Institute (NCI) CTCAE, version 4.

The cycle duration remains 28 consecutive days in patients who have dose interruption.

5.1 Definition of Dose Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are at least possibly, probably, or definitely attributable to pazopanib. See Section 5.4 for the Potential Pazopanib Specific Side Effects. Dose-limiting hematological and non-hematological toxicities are defined differently.

5.1.1 Hematological Dose-Limiting Toxicity

- a) For patients who are evaluable for hematologic toxicity assessment (patients **without** bone marrow involvement)
 - Grade 4 Thrombocytopenia (platelet count < 25,000/mm³) or Grade 4 neutropenia
 - Any hematologic toxicity requiring dose reduction or treatment interruption for >14 days
- b) For all patients:
 - ≥ Grade 2 arterial thromboembolic events (visceral arterial ischemia, peripheral ischemia, or ischemia cerebrovascular)
 - Grade 3 or 4 venous thromboembolic event
 - Any thrombotic event (other than central venous line [CVL] associated thrombosis) requiring systemic anticoagulation

5.1.2 Non-Hematological Dose-Limiting Toxicity

- 5.1.2.1 Any Grade 4 non-hematologic toxicity
- 5.1.2.2 Any Grade 3 non-hematological toxicity, with the specific exclusion of the following:
 - Grade 3 nausea and vomiting of less < 3 days duration
 - Grade 3 fever or infection,
 - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation within 7 days of start of supplement (see Section 5.4.4 for dose modifications)
- 5.1.2.3 Grade 2 allergic reactions that necessitate discontinuation of protocol therapy will not be considered a dose-limiting toxicity.
- 5.1.2.4 Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption may also be considered a DLT following discussion with the Study chair and a Novartis Medical Lead.
- 5.1.2.5 Hypertension will be graded according to the NCI CTCAE; however, dose limiting hypertension will be considered as the following:

- Grade 4 hypertension
- A blood pressure >25 mmHg above the 95th percentile for age, height, and gender (see [Appendix V](#)) confirmed by repeated measurement on the same day (See Sections [5.4.1](#) and [4.1.5.1](#) for management)
- In patients already on anti-hypertensive therapy due to previous hypertension (see Section [3.2.8.5](#)), any blood pressure 1-25 mmHg above the 95th percentile for age, height, and gender ([Appendix V](#)) for > 14 days (See Sections [5.4.1](#) and [4.1.5.1](#) for management)

5.2 Dose Modifications for Hematologic Toxicity

All dose modifications should be based on the worst preceding toxicity.

Pazopanib tablets: For step-wise dose reductions, see [Appendix II](#) for the dosing nomogram.

Pazopanib powder in suspension: For step-wise dose reductions see [Tables 1](#) and [1a](#) (Section [4.1.1](#)).

5.2.1 For **all** patients:

If Grade 4 neutropenia occurs,

- a) Pazopanib should be held.
- b) CBCs should be checked at least twice a week (every 3 to 4 days) until $ANC \geq 750/\mu L$.
- c) Subsequent doses of pazopanib should be given at a reduced dose, when $ANC \geq 750/\mu L$.

If Grade 4 thrombocytopenia occurs,

- a) Pazopanib should be held.
- b) CBCs should be checked at least twice a week (every 3 to 4 days) until platelet count $\geq 75,000/\mu L$ without need for platelet transfusion in the preceding 7 days.

Subsequent doses of pazopanib should be given at a reduced dose, when platelet count $\geq 75,000/\mu L$ without need for platelet transfusion in the preceding 7 days.

5.2.1.1 If dose-limiting myelosuppression occurs as noted in Section [5.1.1](#),

- a) The dose of pazopanib should be resumed at a reduced dose, once $ANC \geq 750/\mu L$ and platelet count $\geq 75,000/\mu L$ without need for platelet transfusion in the preceding 7 days.

5.2.2 For patients who have a dose limiting hematological toxicity that does not resolve to the parameters defined in Section [5.2.1](#) within 14 days of holding pazopanib: if re-challenge is to be considered the Study Chair must be contacted and provide approval prior to re-challenge.

5.3 Dose Modifications for Non-Hematological Toxicity

Specific instructions for the management of potential pazopanib side effects are included in Section [5.4](#).

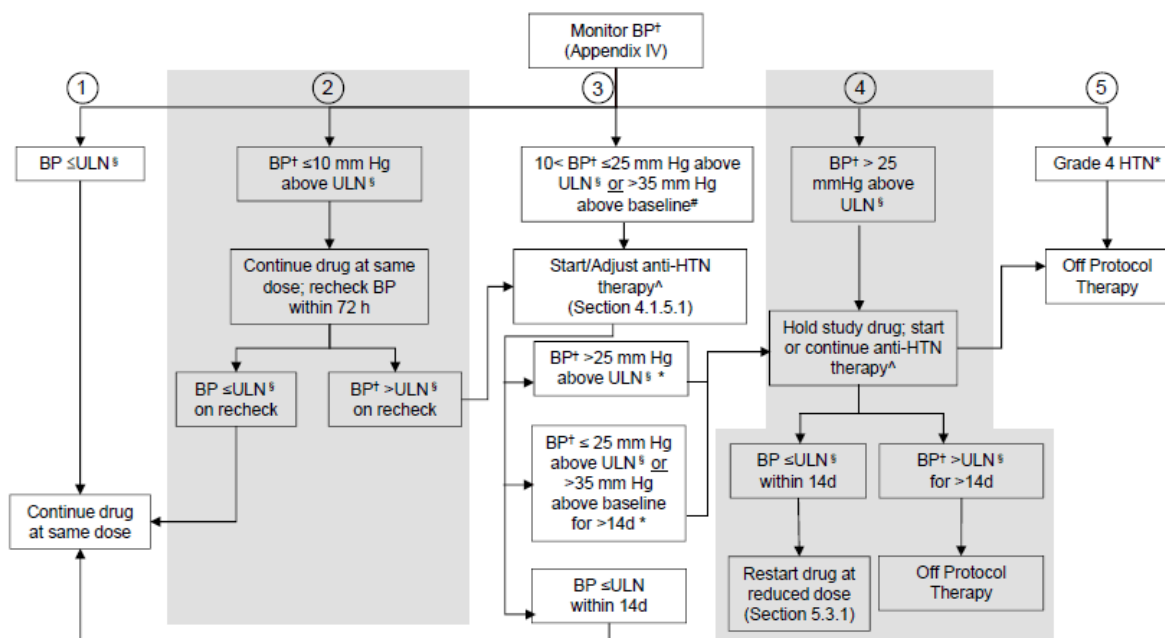
5.3.1 For any non-hematologic dose limiting toxicity as detailed in Section 5.1.2:

- a) Pazopanib should be held
- b) If the non-hematologic DLT is a pazopanib specific toxicity, the dosing guidelines in Section 5.4 should be followed
- c) If the non-hematologic DLT returns to baseline within 14 days of holding pazopanib, subsequent doses of pazopanib should be given at a reduced dose.
 - If toxicity does not resolve to meet continued treatment parameters within 14 days of drug discontinuation, and if re-challenge is to be considered, the Study Chair must be contacted as outlined in Section 4.2 to discuss.
 - If DLT recurs in a patient who has resumed treatment after the maximum allowed dose reductions, the patient must be removed from protocol therapy, unless the patient has been approved for a further dose reduction following discussion with the Study Chair.

5.4 Potential Pazopanib Specific Side Effects

5.4.1 Hypertension

- **Baseline blood pressure (BP)** is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:
 - 1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
 - 2) Average the systolic blood pressure from the 2nd and 3rd measurements.
 - 3) Average the diastolic blood pressure from the 2nd and 3rd measurements.
 - 4) The baseline BP is the average of the systolic over the average of the diastolic measurements.
- **Elevation** in either the systolic or diastolic blood pressure should be considered when following the algorithm below.
- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. If ≥ 18 yrs of age, ULN will be defined as a BP of 140/90. See [Appendix V](#).
- The NCI CTCAE version 4.0 will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with an elevated BP should have BP measurements performed at least twice weekly until BP is \leq ULN.
- The algorithm below will be used to manage pazopanib related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.
- For patients who were on one anti-hypertensive medication at study enrollment and hypertension worsens while on study, further anti-hypertensive therapy may include dose adjustment of the current medication or the addition of a second anti-hypertensive medication.



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix VIII)

* If BP > 25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 5.4.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95thile for age, height, and gender: continue pazopanib at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue pazopanib at the same dose and recheck the BP within 72 hours.
 - If the BP is ≤ ULN on recheck, continue pazopanib at the same dose.
 - If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy (Section 4.1.5.1) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start/adjust anti-hypertensive therapy (see Section 4.1.5.1) and continue pazopanib at the same dose. Monitor BP at least twice weekly.
 - If the BP returns to ≤ ULN within 14 days, continue pazopanib at the same dose and continue anti-hypertensive therapy.
 - If the BP remains elevated ≥ 25 mm Hg above the ULN or > 35 mm Hg above baseline for more than 14 days after the institution/adjustment of anti-hypertensive therapy, **hold** pazopanib, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that pazopanib is held. The anti-hypertensive therapy should be continued until the BP is less than the ULN.
- If the BP returns to ≤ ULN within 14 days, restart pazopanib at a reduced

- dose.
- If the BP remains $> \text{ULN}$ for more than 14 days, patient must be removed from protocol therapy.
 - If the BP increases to $> 25 \text{ mm Hg}$ above the ULN despite anti-hypertensive therapy, **hold** pazopanib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that pazopanib is held.
 - If the BP is $\leq \text{ULN}$ within 14 days, pazopanib may be restarted at a reduced dose.
 - If the BP is $> \text{ULN}$ for > 14 days, the patient must be removed from protocol therapy (Section 8.1).

Arm 4 of algorithm:

- If BP is $> 25 \text{ mm Hg}$ above the ULN **hold** pazopanib, monitor BP, and administer/adjust anti-hypertensive therapy as clinically indicated.
 - If the BP returns to $\leq \text{ULN}$ within 14 days, pazopanib may be restarted at a reduced dose.
 - If the BP is $> \text{ULN}$ for > 14 days, the patient must be removed from protocol therapy (Section 8.1).

Arm 5 of algorithm:

If the participant develops Grade 4 hypertension, **discontinue** pazopanib, monitor BP and administer anti-hypertensive therapy as clinically indicated. A nephrology and/or cardiology consult is recommended. The patient must be removed from Protocol Therapy (Section 8.1).

5.4.2 Abdominal pain:

Abdominal pain is a common symptom with vascular endothelial growth factor (VEGF) receptor antagonists such as pazopanib. Bowel perforations have been reported in clinical trials of pazopanib and with other agents in this class. Bowel perforations have been associated in some patients with tumor in the bowel wall, or diverticulitis, while in others there has been no clear explanation.

Although bowel perforation is a rare event, investigators and study staff at the site are advised to be vigilant of this potential complication in patients receiving pazopanib. Abdominal complaints should be assessed during AE review at every visit. In addition, every physical exam should include a complete abdominal exam. For patients with abdominal complaints and/or abnormal findings on clinical exam, follow the dose modifications and evaluations described below.

Adverse events & descriptions	Dose Modifications & Evaluations
Mild to Moderate abdominal pain or other abdominal complaints with no associated abnormal findings on physical exam	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Implement supportive care as indicated and per institutional standards; consider imaging studies 3. Advise the patient to seek medical attention should their complaints worsen 4. Appropriate follow-up until complaints resolve or origin of the pain is identified. Imaging studies to confirm the absence of abdominal pathology should be performed based on the investigator judgment.
Severe abdominal pain or a concerning abdominal exam	<ol style="list-style-type: none"> 1. Hold pazopanib 2. Recommend obtaining appropriate imaging studies to evaluate the patient's specific complaints or exam findings 3. Resume pazopanib at previous dose if imaging studies confirm the absence of abdominal pathology
Confirmed diagnosis of abdominal perforation	<ol style="list-style-type: none"> 1. Remove from protocol therapy

Contact the Study Chair if you need further guidance or would like to discuss an event involving abdominal pain or bowel perforations.

5.4.3 Hepatotoxicity:

Adverse events & descriptions	Dose Modifications & Evaluations
Grade 1 ALT/AST elevation	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Check liver function tests (LFTs)¹ as per Evaluations table in Section 7.1
Grade 2 ALT/AST elevation without bilirubin elevation (defined as total bilirubin ² ≤ 1.5 x ULN or direct bilirubin ≤ 35% of total bilirubin) and without hypersensitivity symptoms (eg: fever, rash)	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Consider performing the following to exclude hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • Eosinophil count • Viral serology⁴ for hepatitis A, B and C • Liver imaging (ultrasound) 3. Monitor patient closely for clinical signs and symptoms 4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until AST/ALT ≤ Grade 1

<p>≥Grade 3 ALT elevation without bilirubin elevation (defined as total bilirubin² ≤ 1.5 x ULN or direct bilirubin ≤35% of total bilirubin) and without hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>Liver Event Interruption/Stopping Criteria³:</u></p> <ol style="list-style-type: none"> 1. Hold pazopanib. Repeat LFTs¹ within 72 hrs to confirm ≥Grade 3 ALT elevation; if confirmed: 2. Perform the following assessments to exclude hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Liver imaging (Ultrasound) 3. Monitor patient closely for clinical signs and symptoms 4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until ALT reduced to ≤ Grade 1 5. Pazopanib may be held for up to 14 days, if ALT returns to ≤ Grade 1 and patient is benefitting from treatment, pazopanib may be resumed at a reduced dose following Novartis / Study Chair approval (contact the Sponsor Medical Lead and the Study Chair via email or phone to start the approval process). If approval for re-treatment is granted, the patient must be re-consented (with a separate informed consent) specific to hepatotoxicity. <ul style="list-style-type: none"> • For patients on tablets dose reductions are as follows: <ul style="list-style-type: none"> ○ If on 800 mg, then reduce to 400 mg daily ○ If on 600 mg, then reduce to 400 mg daily ○ If on 400 mg, reduce to 200 mg daily • For patients on powder suspension: <ul style="list-style-type: none"> ○ Follow the sequential dose reduction (Section 4.1.1.), one dose level reduction is required (e.g. from 225 mg/m2 to 160 mg/m2) 6. Following re-introduction of pazopanib, continue to monitor ALT weekly for 2 cycles, if ALT ≥ Grade 2 recurs permanently discontinue pazopanib
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<p>≥ Grade 2 ALT <u>AND</u> elevation in bilirubin² (defined as total bilirubin > 1.5 x ULN and direct bilirubin > 35% of total bilirubin) or with hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>Liver Event Stopping Criteria</u>³:</p> <ol style="list-style-type: none"> 1. Discontinue pazopanib permanently 2. Recheck LFT's¹, serum creatinine phosphokinase (CPK) and collect PK sample. Also check: <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein-Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Anti-nuclear antibody⁴, anti-smooth muscle antibody⁴, anti-mitochondrial antibody⁴ • Liver imaging (Ultrasound) 3. Recommend referral to (consult) a pediatric gastroenterologist/hepatologist. 4. Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs¹ weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
<p>For isolated total bilirubin² elevation without concurrent ALT increase (defined as Grade 1 ALT ≤ 3 x ULN).</p>	<ol style="list-style-type: none"> 1. Isolated hyperbilirubinemia (in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Study treatment inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury 2. If total bilirubin is >1.5 ULN in the absence of ALT elevation, fractionation of bilirubin should be performed. <ul style="list-style-type: none"> • If the bilirubin is predominantly indirect (≥65%) indirect (unconjugated), continue study treatment at the same dose. • If bilirubin is >35% direct (conjugated), study treatment may also be continued however, further evaluation should be undertaken for underlying cause of cholestasis.

¹LFTs include: AST, ALT, alkaline phosphatase, GGT and total bilirubin.

²Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a patient meets the criterion of total bilirubin > 1.5 x ULN, then the event should be promptly reported as defined.

³When a liver chemistry event meets the Liver Event Interruption Criteria, or Liver Event Stopping Criteria, blood samples should be obtained for clinical laboratory testing by the central laboratory (Liver Event Kits will be provided for this purpose).

⁴These extra tests will be performed centrally

5.4.4 Electrolyte Abnormalities:

Serum K⁺, Ca⁺⁺, Mg⁺⁺, phosphate levels should be monitored given the risk of prolonged QTc. If serum Ca⁺⁺ is abnormal, ionized calcium should be obtained and interventions based on ionized calcium only.

Pazopanib should be **held** and an EKG obtained for

- Hypokalemia or hyperkalemia \geq Grade 2
- Hypocalcemia or hypercalcemia \geq Grade 3
- Hypophosphatemia or hyperphosphatemia \geq Grade 3
- Hypomagnesemia or hypermagnesemia \geq Grade 3

These laboratory values should be corrected as soon as possible in a manner consistent with good medical judgment. Pazopanib may be resumed at a reduced dose when:

- Hypokalemia or hyperkalemia is Grade 1 or within institutional limits
- Hypocalcemia or hypercalcemia is \leq Grade 2
- Hypophosphatemia or hyperphosphatemia is \leq Grade 2
- Hypomagnesemia or hypermagnesemia is \leq Grade 2.

Even though pazopanib administration is allowed at these lower laboratory toxicity grades, every effort should be made to correct the abnormal lab values to normal if possible.

5.4.5 Proteinuria:

- If urinalysis shows \geq trace protein then obtain a urine protein: creatinine ratio (UPC).
- If the UPC is ≥ 1 , then obtain a 24-hour urine collection for protein estimation.
- If the urine protein is ≥ 3.5 g/24-hours then hold pazopanib and re-assess urine protein weekly.
- If the urine protein decreases to < 3.5 g/24 hours in < 21 days then resume pazopanib at a reduced dose.
- Monitor the 24 hour urine protein or UPC weekly for 2 consecutive weeks once pazopanib is resumed.
- If pazopanib is held for ≥ 28 days then the patient must be removed from protocol therapy.

5.4.6 Cardiac Function:

5.4.6.1 Left Ventricular Systolic Dysfunction:

Adverse events & descriptions	Dose Modifications & Evaluations
LV EF $<$ LLN but $\geq 50\%$ OR LV SF $<$ LLN but $\geq 24\%$ without symptoms of cardiac dysfunction	Continue drug and repeat Echo on Day 28 of subsequent cycle
LV EF 40 – 49% OR LV SF 15 – 23% OR Absolute decrease in SF ≥ 8 percentage points from baseline	Hold pazopanib and obtain repeat Echo in 7 days. If toxicity confirmed, then remove from protocol therapy. If not confirmed, then resume drug at reduced dose and repeat Echo 14 and 28 days after resuming pazopanib. If any 2 Echos demonstrate LV EF 40 - 49% OR LV SF 15 - 23% OR ≥ 8 percentage point decrease in SF then remove from protocol therapy and refer to pediatric cardiologist
Grade 3 LV EF decreased OR Grade 3 LV SF decreased	Remove from protocol therapy – refer to pediatric cardiologist

- Cardiac evaluation by Echo but MUGA (Multiple-Gated Acquisition) may be used if clinically indicated

5.4.6.2 QT Prolongation:

Guidelines for the management of prolonged QT interval are as follows: Measure the QT interval (from the start of the Q wave to the end of the T wave) and the preceding RR interval. The corrected QT interval using the Bazett's formula (QTcB interval) will be calculated as the QT interval (msec) divided by the square root of the RR interval (msec). Only the Bazett's formula should be used to calculate the corrected QT interval.

- QTcB interval < 500 msec: No specific therapy needed. Continue pazopanib at the same dose. Serum K⁺, Ca⁺⁺, Mg⁺⁺, and Phos should be monitored and repleted if low (see Section 5.4.4).
- QTcB interval ≥ 500 msec: Hold pazopanib, review concomitant medications, and replete serum K⁺, Ca⁺⁺, Mg⁺⁺, and Phos as needed. The EKG should be repeated within 7 days and if the QTcB interval is < 500 msec then resume pazopanib at a reduced dose. If the QTcB interval remains ≥ 500 msec, the patient must be removed from protocol therapy.

5.4.7 Delays in Wound Healing:

Patients treated with VEGF blocking agents appear to have an increased risk of wound healing complications. Therefore, if patients require elective major surgery on study, pazopanib should be held for 14 days prior to surgery and for 14 days after surgery (see Section 3.3.7). Pazopanib should not be restarted if there is evidence of wound healing complications such as a wound infection. Patients who require surgery less than 14 days from treatment with pazopanib should be monitored closely for wound complications. Patients who require major surgery during Cycle 1 of therapy must be removed from protocol therapy.

5.4.8 Bleeding:

	Dose Modifications & Evaluations
Grade 1	Continue pazopanib at the current dose and monitor as clinically indicated.
Grade 2	1. Hold pazopanib until bleeding resolves to ≤ Grade 1 2. Restart pazopanib at a reduced dose; monitor as clinically indicated
Grade 3 or higher <u>OR</u> Recurrent ≥ Grade 2 event after dose interruption/reduction	Discontinue pazopanib permanently and remove from protocol therapy

5.4.9 VascularThrombosis:

	Dose Modifications & Evaluations
Grade 2	Continue pazopanib at the current dose and monitor as clinically indicated.

Grade 3 (CVL associated only)	<ol style="list-style-type: none">1. Hold pazopanib2. Treat thrombosis according to institutional standards; would consider removal of the CVL.3. Resume pazopanib when all symptoms have resolved. If anticoagulation is required, use with caution.
All non-CVL associated Grade 3 AND all Grade 4	Discontinue pazopanib permanently and remove from protocol therapy

6

DRUG INFORMATION

6.1 PAZOPANIB

(Votrient™, GW786034, Pazopanib HCl, GW786034B (monohydrochloride salt))
NSC# 737754, IND# 065747

Source and Pharmacology:

The chemical name for pazopanib is 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. The molecular formula is C₂₁H₂₃N₇O₂S·HCl. The molecular weight is 474.0 (monohydrochloride salt) and 437.5 (free base). The monohydrochloride salt is very slightly soluble in 0.1 M HCl (0.65 mg/mL), practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL), and practically insoluble in pH 11 piperidine buffer (0.0002 mg/mL).

Pazopanib is a multi-targeted inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3), platelet-derived growth factor receptor kinases (PDGFR- α and - β), fibroblast growth factor receptor-1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR- β receptors. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

In adults, pazopanib is orally absorbed with median time to peak concentration of 2 to 4 hours after the dose. Also in adults, the administration of a single, crushed pazopanib 400 mg tablet increased AUC₍₀₋₇₂₎ by 46%, increased C_{max} by approximately 2 fold, and decreased T_{max} by approximately 2 hours compared to administration of the whole tablet. Due to this potential for increased exposure (increased bioavailability, increased rate of absorption), tablets of pazopanib should not be crushed. Systemic exposure is increased when pazopanib is administered with food. Administration with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal. Pazopanib is more than 99% bound to human plasma protein in vivo. In vitro studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

In vitro studies demonstrated that pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8. In vitro data also indicate that pazopanib is an inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1,

and CYP3A4 with its most potent inhibition for the isoenzyme CYP2C9. In vivo, however, pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 with no effect on probes for CYP2C19, CYP2C9, and CYP1A2. Therefore, medications that are potent inducers or inhibitors of CYP3A4 are prohibited (refer to Section 4.8). Washout periods are specified in Sections 4.6, 4.7 and 4.8. If not specifically mentioned, it is at the discretion of the clinician based on the pharmacokinetic properties of each individual agent. Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2C8, or CYP2D6 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

In adults, pazopanib has a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose. Based on baseline hepatic function, 800 mg pazopanib is recommended for adult patients with mild impairment (defined as either normal bilirubin and any degree of alanine aminotransferase [ALT] elevation or as an elevation of bilirubin up to 1.5x upper limit of normal [ULN] regardless of the ALT value), and 200 mg for adult patients with moderate impairment (defined as an elevation of bilirubin >1.5 to 3xULN regardless of the ALT values). The maximum dose of pazopanib (200 mg) administered to adult patients with severe hepatic impairment did not achieve therapeutic plasma concentrations. Therefore, pazopanib is not recommended in adult patients with severe hepatic impairment (defined as total bilirubin >3xULN regardless of any level of ALT).

Pazopanib may cause prolongation of the QT interval and torsades de pointes. Refer to [Appendix IIIB](#) for agents to avoid during administration of pazopanib.

Pregnancy and lactation:

Pregnancy Category D

Pazopanib can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, pazopanib is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥ 3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was reduced fetal body weight, and pre- and post-implantation embryoletality in rats administered pazopanib at doses ≥ 3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥ 30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥ 100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥ 3 mg/kg/day (AUC not calculated).

There are no adequate and well-controlled studies of pazopanib in pregnant women. Protocol therapy should be immediately discontinued if pregnancy occurs while the patient is on therapy. Women of childbearing potential should be advised to avoid becoming pregnant while taking pazopanib and for up to 30 days after stopping pazopanib.

Excretion in breast milk unknown and breast-feeding while on pazopanib is not recommended.

Formulation and Stability:

Tablets

Pazopanib is supplied as a series of aqueous film-coated tablets containing, 200 mg, and 400 mg of the free base:

- 200 mg, oval-shaped, white, packaged in bottles containing 34 tablets each
- 400 mg, oval-shaped, white, packaged in bottles containing 68 tablets each

Tablet excipients in all tablet sizes include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film coating consists of titanium dioxide, hypromellose, polyethylene glycol, and polysorbate 80. Store the intact bottles at controlled room temperature (20°C-25°C). Excursions are permitted between 5°C and 25°C. Do not store pazopanib tablets above 25°C.

Pazopanib Suspension (to be prepared in pharmacies)

Pazopanib Powder for Oral Suspension is a white to slightly colored powder supplied to the clinical sites in amber glass (USP Type III) bottles with child-resistant closures. Each bottle contains 5 grams of pazopanib.

Pazopanib Powder for Oral Suspension should be reconstituted with 90 mL of sterilized or purified water to provide a white oral suspension containing 50 mg/mL of GW786034 as free base as detailed below.

1. Tap the sides to the bottle to loosen the powder.
2. Add 90 mL of room temperature sterilized or purified water for injection to the bottle.
3. Replace the cap tightly and shake vigorously by inversion for at least 2 minutes to ensure complete powder reconstitution.
4. Allow the bottle to sit for at least 3 minutes to allow any foam to dissipate. Suspension is then ready for use as a white, lemon-flavored, 50 mg/mL suspension.

Pazopanib oral suspension should be stored refrigerated (2°-8° C). Do not freeze. The powder suspension is designed for multiple use and may be used for up to 35 days when refrigerated (2°-8° C).

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Also, see [Appendix VII](#) for Patient Instructions for Pazopanib suspension.

Pazopanib should be taken on an empty stomach at least 1 hour before or 2 hours after a meal. The tablets should be swallowed whole and cannot be crushed or broken.

Avoid concomitant strong CYP3A4 inhibitors as these may increase pazopanib concentrations. Avoid concomitant strong CYP3A4 inducers as these may decrease

pazopanib concentrations. Refer to Sections 4.5, 4.6, 4.7 and 4.8 for agents that should be avoided or used with caution. The consumption of grapefruit and its juice are not allowed for the duration of treatment with pazopanib. Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

If a dose is missed, refer to section 4.1.4 Missed doses. If a patient vomits the dose, do not repeat the dose.

Dosing Instructions for Pazopanib (50mg/mL) multiple use oral powder suspension:

- Insert a Baxa 28 mm Press-In-Bottle Adapter (PIBA®) (these supplies will be provided to the site by Novartis) into the neck of the bottle. Check to ensure that the lip of the Adapter fits snugly with the top of the bottle.
- Swirl gently for at least 30 seconds to ensure homogeneity of the suspension immediately prior to the removal of the required dose for administration.
- Remove the required dose using a suitable graduated syringe (recommend Exacta- Med® Baxa) as follows:
 1. Ensure that the syringe plunger is fully pushed into the barrel.
 2. Insert the syringe tip into the Adapter, then invert the bottle and dispense at least 5 mL of suspension into the syringe and then pump the entire suspension back into the bottle to purge the syringe of any air bubbles. Repeat this step until the syringe is free from air bubbles.
 3. Withdraw the required dose. Then re-invert the bottle and remove the syringe from the Adapter and administer the dose as soon as possible.

Supplier:

Pazopanib suspension is supplied and distributed by Novartis.

Obtaining the Agent

Agent Ordering:

Sites will be provided the information for ordering drug supplies in the Study Procedures Manual.

Agent Accountability

The investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of Novartis investigational product dispensed and/or administered to study patients, the amount returned by study patients (if applicable), and the amount received from Sponsor and, when applicable, the amount returned to Novartis. Product accountability records must be maintained throughout the course of the study.

After completion of the study, a final inventory of accountability records and unused study medications will be performed by the study monitor and site personnel.

A record of the number of tablets dispensed to and returned by each patient at each visit must be maintained and reconciled with the study medication and compliance

records in the eCRF. At each site visit, the cause of any missed doses should be discussed and documented.

A record of the number of milligrams (determined by weight) of pazopanib in oral powder suspension dispensed to and returned by each patient at each visit must be maintained and reconciled with the study medication and compliance records in the eCRF. At each site visit, the cause of any missed doses should be discussed and documented.

After completion of the study, a final review of accountability records and inventory of unused study medications will be performed by the study monitor and site personnel. If the site has received documented approval from Sponsor, unused study medication may be destroyed, prior to inventory by the study monitor. In this case, the study monitor would review only study medication accountability records at the end of study visit. Additional information on the drug accountability process is provided in the Study Procedure Manual.

Any AE(s) associated with missed doses must be recorded in the eCRF. Patients should be instructed for the importance of compliance to study treatments.

Agent Destruction:

If allowed per site policy and procedures, unused study medications will be destroyed according to site-specific guidelines and proof of destruction will be forwarded to Novartis.

7 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol). This policy does NOT apply to eligibility requirements; but to therapy and evaluations post consent and post the start of protocol-directed care. Novartis will not grant protocol waivers.

7.1 Required [REDACTED] Clinical, Laboratory and Disease Evaluations

See Section 3.2 and Section 3.3 for eligibility requirements. See Section 3.1.7 for requirements to initiate protocol therapy. Laboratory tests used to determine eligibility may be counted as the Week 1 studies if the tests were drawn within 7 days of treatment start and there have been no significant changes in the patient's clinical status (Section 3.1.7.1)

Obtain indicated studies prior to the start of cycle unless otherwise indicated.

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles ¹	During Subsequent Cycles	End of Therapy ²	Survival Follow-up
History	X	Weekly	X	Every other week for Cycles 2 & 3, then prior to each subsequent cycle	X	
Physical Exam, Vitals (including BP ³)	X	Weekly	X	Every other week for Cycles 2 & 3, then prior to each subsequent cycle	X	
Height, weight, BSA	X	Cycle 1 Day 1 ⁴	X			
Performance Status	X	Cycle 1 Day 1 ⁴	X		X	
CBC, differential, platelets	X	Weekly ^{5,6}	X	Weekly for Cycle 2; every other week for Cycle 3; then prior to each subsequent cycle	X	
Electrolytes including K ⁺ , Ca ⁺⁺ (ionized Ca ⁺⁺), PO ₄ , MG ⁺⁺	X	Weekly	X	Weekly for Cycle 2; every other week for Cycle 3; then prior to each subsequent cycle	X	
Creatinine, ALT ⁷ , bilirubin, Amylase, Lipase	X	Weekly	X	Weekly for Cycle 2; every other week for Cycle 3; then prior to each subsequent cycle	X	

Total protein/albumin	X	Weekly	X	Weekly for Cycle 2; every other week for Cycle 3; then prior to each subsequent cycle	X	
TSH ⁸	X		Prior to Cycle 3, 5, 8, 11 and every 3 rd cycle thereafter			
PT, PTT, and INR	X		Prior to Cycle 3 and every 6 cycles thereafter			
Urinalysis (UPC and/or 24 hour urine for protein) ⁹	X	X	X		X	
Disease Evaluation ¹⁰ (including bone marrow aspirate/biopsy ¹¹)	X		Prior to Cycle 3, 5, 8, 11 and every 3 rd cycle thereafter ¹²		X	
Serum AFP (for hepatoblastoma patients only) ¹³	X		Prior to Cycle 3, 5, 8, 11 and every 3 rd cycle thereafter ¹²		X	
Urine VMA/HVA (for neuroblastoma patients only) ¹⁴	X		Prior to Cycle 3, 5, 8, 11 and every 3 rd cycle thereafter ¹²		X	
Serum Pregnancy Test ¹⁵	X	-	X	-		
Patient Diary		X	X			
ECHO ¹⁶	X		Prior to Cycle 2, 5 and then every 6 cycles			
EKG (including QTcB) ¹⁷	X		Prior to Cycle 2, 5 and then every 6 cycles			
Plain radiograph of tibial growth plates ¹⁸	X		Prior to Cycle 2, 5 and then every 6 cycles			
Pharmacokinetics ¹⁹		X	Prior to every odd cycle			
Survival status ²⁰						X
Antineoplastic therapies since protocol therapy discontinuation ²⁰						X

1. Window for assessment is Day 25-28 of the preceding cycle for any assessment with the exception of disease evaluations. See footnote 12 for assessment window on disease evaluation.
2. Should be performed, if possible, at the time the patient comes off protocol therapy regardless of the reason, unless the test or procedure has been performed within the past 2 weeks.
3. Blood pressures will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (> the 95th percentile for age, height, and gender). If both BP measurements are > 95th percentile for age, height, and gender, follow the guidelines in Section 5.4.1. Patients with elevated BP (that is, BP greater than the 95th percentile for age, height, and gender) at any time should have BP measurements performed at least twice weekly until BP is within the 95th percentile for age, height, and gender (see Appendix V). Guidelines for the grading and management of hypertension are in Section 5.1.2.5, 5.4.1, and Appendix V.
4. Evaluations obtained for screening will ONLY be repeated at Cycle 1 Day 1 if they are older than 7 days.
5. If patients have Grade 4 neutropenia, then CBCs should be checked every 3 to 4 days until recovery to Grade ≤3.
6. If patients have Grade 3 or 4 thrombocytopenia, then CBCs should be checked twice a week until recovery to Grade ≤2.
7. If patient has LFT elevation, monitor LFTs as described in Section 5.4.3.

8. Patients found to have an abnormal TSH level at baseline and/or at subsequent visits should have a free T4 level measured (See Section 7.2.2). Management of hypothyroidism is described in Section 4.1.5.2.
9. See Appendix IV for UPC rationale and calculation and Section 5.4.5 for dose modifications if $UPC \geq 1$. UPC assessment is adequate to follow-up prior proteinuria. If a 24-hour urine for protein is obtained, UPC is not required.
10. A confirmatory disease evaluation should be obtained, if possible, on the next consecutive cycle after initial documentation of either a PR or CR. This confirmatory evaluation is in addition to the schedule as noted (eg: if confirmatory scans are done prior to Cycle 4, the next disease evaluation should be done as scheduled prior to Cycle 5)
11. Bone marrow evaluation to be done only in patients with known marrow involvement.
12. Disease evaluation should be performed during Days 24 – 28 of the cycle for the first 2 assessments (prior to Cycles 3 and 5) and during Days 21 – 28 of subsequent indicated cycles. Patients who achieve a PR or CR should undergo the appropriate disease evaluation on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, the investigator can remove the patient from protocol therapy, he/she may opt not to confirm this finding radiographically. ; however an end of study disease assessment should be completed.
13. For hepatoblastoma patients only – perform no more than 48 hours prior to starting treatment on Day 1 of Cycle 1 (results do not need to be known) and then with each disease evaluation if the initial value is elevated.
14. For neuroblastoma patients only - VMA = vanillylmandelic acid; HVA = homovanillic test.
15. Females of childbearing potential require a negative serum pregnancy test prior to starting treatment. Patients of childbearing potential must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.
16. See Section 5.4.6 for dose modifications regarding Left ventricular systolic dysfunction or decrease in shortening fraction.
17. More frequent EKG monitoring is recommended for patients receiving drugs “associated” with Torsades de pointes (See Appendix IIIB) and required for Grade 2 potassium and Grade 3 calcium (confirmed by ionized calcium), magnesium and phosphorous abnormalities. See Sections 5.4.4 and 5.4.6.2.
18. Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to the first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 7.2.1.
19. See Section 7.3 for timing of required PK sampling, and Appendix VI for the PK worksheet. No PK samples are required beyond Cycle 11
20. Survival follow-up will be completed every 3 months

Obtain Other Studies As Needed For Good Patient Care.

7.2 Monitoring for Specific Toxicities

7.2.1 Growth Plate Toxicity

Patients will have a plain AP radiograph of a single proximal tibial growth plate obtained prior to the first dose of protocol therapy.

- a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.
- b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained prior to starting Cycle 2, Cycle 5 and then every 6 months (prior to cycle 11, 17, etc).
 - Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and undergo more frequent x-ray follow up. MRI should be performed without contrast. If no MRI changes are seen, x-rays may be performed approximately every 2 months.
 - Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of pazopanib should take into account the presence of any symptoms referable to the knee as well as the patient's response to pazopanib. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue pazopanib or not. Consultation with orthopedics and with the Study Chair is advised.

7.2.2 Thyroid Toxicity

Patients will have a TSH level measured prior to initial treatment, prior to starting Cycle 3, 5, and then every 3rd cycle thereafter (eg: prior to Cycle 8, Cycle 11, etc). Patients found to have an abnormal TSH level should have a free T4 level measured. Thyroid toxicity will be handled like any other non-hematological toxicity. Guidance on the management of patients who develop hypothyroidism is included in Section 4.1.5.2.

7.2.3 Cardiac Toxicity

Patients will have a baseline echocardiogram and EKG obtained pre-treatment, prior to Cycles 2 and 5, and then every 6 months (prior to Cycle 11, 17, etc) and as clinically indicated. See Section 5.4.6 for management of changes in left ventricular function and prolonged QTcB while on protocol therapy.

7.2.4 Pregnancy Testing and Reporting

The need for a screening pregnancy test depends on whether a female patient is of childbearing potential or non-childbearing potential. If a female patient is of childbearing potential, she must have a serum β -Human Chorionic Gonadotropin (β -HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). Patients with a positive pregnancy test result must be excluded from the study. Patients with a negative pregnancy test result must agree to use an adequate contraception method as described below during the study until 2 weeks following the last dose of study treatment(s). Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure patient safety, each pregnancy must

be reported to Novartis within 24 hours of learning of its occurrence. Study treatment should be immediately discontinued if pregnancy occurs during study participation. 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 (Section 11.8). Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study treatment(s) must be promptly reported to Novartis.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to the Sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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.

7.3 Pharmacokinetic studies

7.3.1 Description of Studies and Assay

Plasma samples will be collected and analyzed for pazopanib levels using a validated LC/MS/MS (Liquid Chromatography/Tandem Mass Spectrometry) method under the control of Novartis.

7.3.2 Sampling schedule:

All patients (whether receiving pazopanib as tablet or as oral powder suspension) will have a blood sample for analysis of the plasma pazopanib concentration collected prior to the first dose on Day 1 of Cycle 1. In addition, all patients will have 2 blood samples collected on Day 15 \pm 1 day of Cycle 1: one sample prior to the dose and one sample 3-4 hours after dosing.

Blood samples for analysis of steady-state trough plasma pazopanib concentrations will also be obtained prior to the start of every subsequent odd-numbered cycle (that is, pre-dose prior to Cycle 3, pre-dose prior to Cycle 5, etc). These steady-state trough plasma concentration samples can be collected between Day 22 of the previous cycle to Day 1 of the odd-numbered cycle, and the actual date and time of sample collection recorded on the PK sample collection form. No PK samples are required beyond Cycle 11.

The pre-dose sample on Day 15 \pm 1 day of Cycle 1 and the trough plasma concentration samples taken prior to dosing for every odd-numbered cycle should be obtained between 22-26 hours after the previous dose of pazopanib. Patients should be instructed to hold their dose of pazopanib on the day that a pre-dose PK sample is to be collected. Collection of these PK samples should correspond to the timing of routine laboratory evaluations.

Extended PK sampling will be done during Cycle 1 in the first patients who receive the powder suspension formulation, until 6 patients are considered evaluable for the PK analysis. These patients will have a blood sample for analysis of the plasma pazopanib concentration collected at the following time points on Day 1 of Cycle 1: pre-dose and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. Samples will also be obtained on Day 15 \pm 1 day of Cycle 1: pre-dose and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. If one or more of these 6 patients fail to provide blood samples as specified in the protocol or if it is known that for some reason a patient's collected blood sample(s) cannot be analyzed, that patient(s) will be determined to be non-evaluable for this analysis and one or more additional patients will be enrolled for treatment with pazopanib as powder for oral suspension and provision of the extended PK samples. These patients will also provide blood samples for analysis of steady-state trough plasma pazopanib concentrations prior to the start of every subsequent odd-numbered cycle as described in the preceding paragraph.

Pazopanib dosing of either tablet or powder suspension must have continued uninterrupted and at the same dose level for at least 10 days prior to acquisition of the Cycle 1 Day 15 PK samples. If pazopanib dosing has been interrupted or modified <10 days prior to Cycle 1 Day 15, then the PK samples should be taken between Cycle 1 Day 15 and Cycle 1 Day 22 on a study day that meets the condition of at least 10 consecutive days of dosing at the same dose level. The Cycle 1 Day 15 PK kit should be used and the actual date and time of sample collections should be recorded in the eCRF.

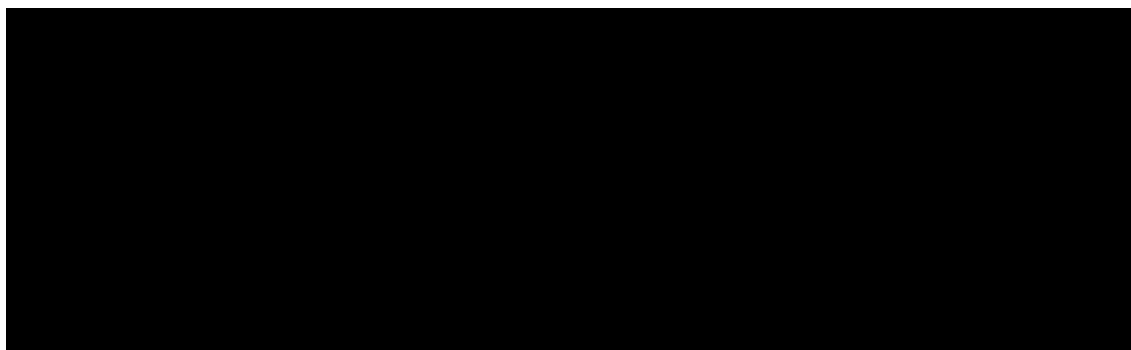
If ≥ 2 out of 6 evaluable patients have dose-limiting toxicities as defined in Section 5.1) during the first cycle, then enrollment at the 225 mg/m²/dose dose level of pazopanib oral suspension will be halted. Subsequent new patients will be enrolled at the 160mg/m²/dose level until 6 evaluable patients from this dose group are available for the safety review and 6 patients are available for PK analysis.

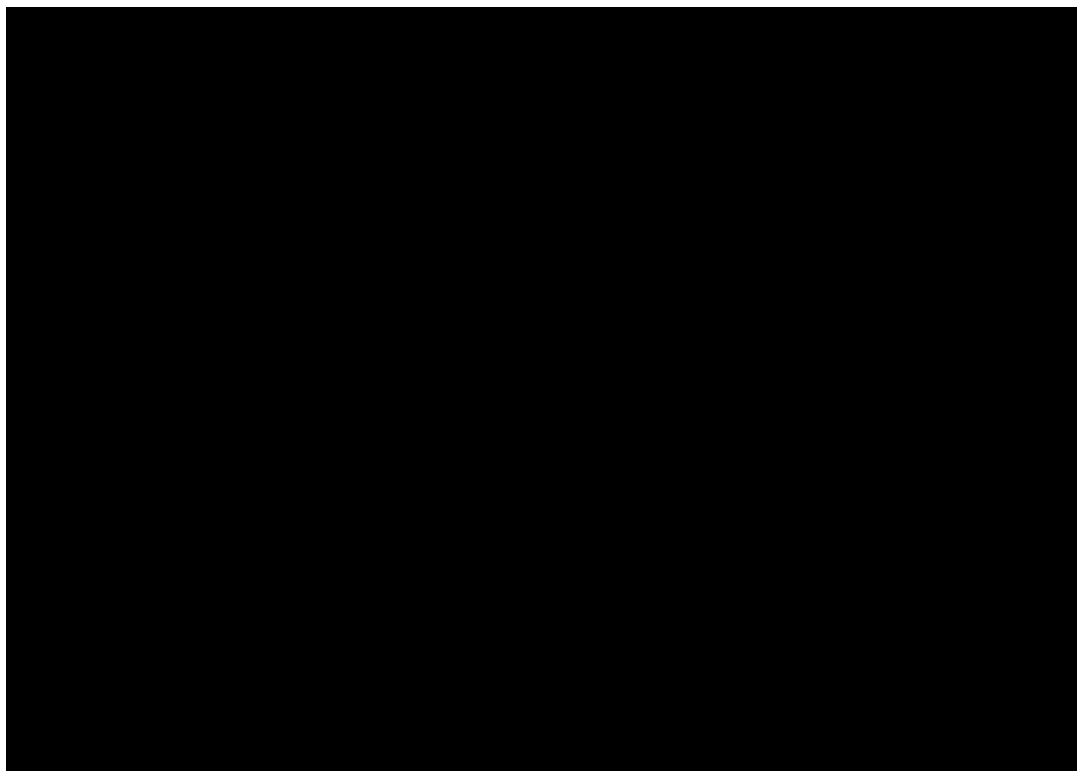
7.3.3 Sample Collection and Handling Instructions:

Blood samples (2 mL for each sample) will be collected for PK into tubes containing potassium EDTA as an anticoagulant. See the corresponding Pharmacokinetic Study Form ([Appendix VI](#)) for specific details of Sample Collection, Processing, Handling, and Shipping.

7.3.4 Instructions for Ordering PK Kits:

Please refer to the Study Procedures Manual for PK kit ordering instructions.





8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal From Protocol Therapy

Patients will be permanently discontinued of protocol therapy if any of the following occur:

- a) Progressive disease
- b) Adverse Events requiring removal from protocol therapy, as stated in Section 5.
- c) Concurrent use of other anticancer or investigational therapy, as stated in Section 3.3.2.
- d) Requirement for major surgery during Cycle 1, as stated in Section 5.4.7.
- e) Refusal of further therapy by patient/parent/guardian
- f) Physician determines it is in patient's best interest
- g) Major protocol deviations including non-compliance
- h) Development of a second neoplasm
- i) Pregnancy

8.2 Follow-up assessments after Removal From Protocol Therapy

Patients who are removed from protocol therapy are to be followed until they meet at least one of the criteria for withdrawal from study (see Section 8.3). Survival Follow-up data will be required unless consent was withdrawn.

Safety follow-up:

All patients will be followed for adverse events and serious adverse events for 28 days after last dose.

Survival follow-up:

The following information will be collected and reported every 3 months:

- Survival status
- Antineoplastic therapies taken since discontinuation of protocol therapy

The primary reason protocol therapy was permanently discontinued must be documented in the patient's medical records and eCRF. If the patient discontinues from protocol therapy due to toxicity, AE will be recorded as the primary reason for permanently discontinuation on the eCRF. Once a patient has permanently discontinued protocol therapy, the patient will not be allowed to be retreated.

8.3 Criteria for Withdrawal from Study

Patients will be withdrawn from the study if any of the following occur:

- Death
- Lost to follow-up
- Withdrawal of consent
- The study is closed/ terminated
- Investigator discretion

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

9.1.1 Review of patient accrual onto recent Phase II solid tumor studies indicates the following entry rates for the various tumors under study can be expected:

<u>DiseaseGroup/Cohorts</u>	<u>Patients/Year</u>
Osteosarcoma	24
Ewing sarcoma	18
Rhabdomyosarcoma	18
Neuroblastoma (measurable disease)	12
Neuroblastoma (evaluatable disease)	12
Non-rhabdomyosarcomatous soft tissue sarcomas (including synovial sarcoma, alveolar soft part sarcoma)	10
Hepatoblastoma	7

With these entry rates, the probability of accruing 10 patients to complete the initial stage of evaluation in the seven named categories within 24 months is 88%. The corresponding probability for enrolling 20 patients in the seven named disease categories in 48 months is 95%. The study will likely require 2 to 3.5 years for sufficient patient enrollments to evaluate pazopanib in the stated disease groups. A minimum of 77 patients and a maximum of 154 patients are anticipated, after accounting for historical rates of patient inevaluability for the primary endpoint in phase II studies.

9.2 Study Design

The primary endpoint will be objective response by protocol-specified, disease-specific

response criteria. The best response of disease to pazopanib will be examined separately in each of the seven disease cohorts. The following two stage design will be used in each cohort.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 patients	0	Terminate the cohort: agent ineffective
	1 or more	Inconclusive result, continue the cohort (proceed to Stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the cohort: agent ineffective
	3 or more	Terminate the cohort: agent effective

We will consider the agent not of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If the agent has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (1-sided type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If the agent has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis $P = 0.25$).

9.3 Analysis Populations

The modified Intent-to-Treat (mITT) population is the primary analysis population. The mITT will consist of all patients who have received at least one dose of protocol therapy.

The Safety population will comprise all patients in the mITT population. The safety population will be used for the analysis of safety data.

The Per Protocol (PP) population is a subset of the mITT population who meet all eligibility criteria.

The Pharmacokinetic (PK) population will comprise all patients in the mITT population for whom a pharmacokinetic sample is obtained and analyzed. The Pharmacokinetic Extended Sampling (PKES) population will comprise all subjects in the Pharmacokinetic population who received powder suspension and have at least one non-predose sample collected and analyzed using the extended sampling schedule in Section 7.3.2. PK analysis summaries, figures and listings will be based on PK and PKES populations.

9.4 Analysis Data Sets

The primary data set for assessing efficacy will comprise the mITT population. The PP and mITT populations will be used for objective response analysis. All other efficacy analyses will be based on mITT only.

The primary data set for assessing safety will comprise the safety population defined in Section 9.3 (Analysis Populations).

9.5 Treatment Comparisons

There will be no treatment comparisons as there is only one treatment arm. No comparisons across cohorts will be conducted.

9.6 Primary Analysis and End of Study Analysis

No formal interim analysis is planned outside of the study design. The study team will review safety data periodically over the course of the study.

Expansion of tumor specific cohorts will be done when there is at least one investigator determined confirmed response in that cohort within the first 10 enrolled patients. A given tumor specific cohort will not be expanded if all the patients in the cohort have:

- Progressed
- Discontinued therapy
- Withdrawn consent
- Been determined to be lost-to-follow-up
- Or have been treated for at least 20 weeks without a response, making it unlikely that a response will occur.

The primary analysis will be performed 20 weeks after the last patient's first visit in the three cohorts of primary interest (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma and Ewing sarcoma/peripheral PNET).

The study will be completed one year from the date of the last patient's first visit and the end of study analysis will be performed at the time of study completion.

Any additional data collected after the primary analysis will be included in a supplementary analysis and reported in a final Clinical Study Report.

9.7 Key Elements of Analysis Plan

9.7.1 Study Withdrawal

All patients who withdraw from the study will be included in analyses up to the time of withdrawal, regardless of the duration of treatment.

9.7.2 Missing Data

As the period of treatment for any patient will be dependent on treatment efficacy and toxicity, the duration of follow-up will vary between patients. Consequently, there will be no imputation for missing data. Where appropriate, available data will be summarized over specified intervals (e.g. from study entry until withdrawal from the study) using suitable summary statistics. Details will be given in the Reporting and Analysis Plan (RAP).

For the secondary PFS endpoint, the date associated with the last adequate disease assessment will be used for those patients who are alive and have not progressed at the time of analysis; such patients will be considered censored in the analysis.

9.7.3 Other Issues

Data from all participating centers will be pooled prior to analysis. It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative and will not, therefore, be provided.

Demographic and baseline characteristics will be summarized.

Two-sided 90% confidence limits will be used in the estimation of response rates and viewed as descriptive.

Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

9.8 Methods of Analysis

9.8.1 Primary Endpoint: Objective Response Rate (ORR)

This is defined as the percentage of patients achieving either a complete or partial tumor response as per response criteria. The response rate will be calculated from the investigator review. Confirmation will be based on the disease assessment performed 1 cycle after the initial response. The objective response rate will be computed for the 3 tumor types of primary interest.

Patients in the mITT population with unknown or missing response will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage).

In other words, $ORR = (\text{number of patients with a confirmed best overall response of CR} + \text{number of patients with a confirmed best overall response of PR}) / \text{total number of patients in the cohort}$.

The assessment of activity of treatment within each histology cohort will be based on the decision rule outlined in Section 9.2.

90% confidence intervals will be provided to characterize the variability around the response rate. The data will be presented for each cohort.

9.8.2 Secondary Endpoints:

9.8.2.1 The objective response rate will be computed for the 4 tumor types of secondary interest. The analysis method will be the same as that described in Section 9.8.1.

9.8.2.2 If recruitment is stopped in the non-primary histology group(s) and it has less than 10 patients, the response data will display summary statistics and the rule in the table under Section 9.2 will not apply.

9.8.2.3 Progression-free survival (PFS) and overall survival (OS)

The analysis will evaluate the mITT population on PFS using data from the investigator review. PFS is defined as the interval between the date of first dose of protocol therapy and the earliest date of disease progression or death due to any cause. Patients are considered to have progressive disease if they have documented progression based on radiologic assessment as determined by investigator review (defined in Section 10). For patients who do not progress or die, progression-free survival will be censored at the date of last adequate assessment or date of last adequate assessment prior to initiation of new anti-cancer therapy if applicable. PFS will be summarized using a Kaplan-Meier

survival curve. The Kaplan-Meier estimate for the median progression-free survival time and the first and third quartiles will be presented, along with a naive approximate 90% confidence interval if there are a sufficient number of progressions or deaths.

Overall survival is defined as the time from the first dose of the study medication until death due to any cause. The OS analysis will be performed on the mITT population and summarized using a Kaplan-Meier survival curve. The Kaplan-Meier estimate for the median OS time and the first and third quartiles will be presented, along with a naive approximate 90% confidence interval if there are a sufficient number of deaths.

Details on how event and censoring times are assigned to a patient will be provided in the RAP.

9.8.2.4 Duration of response (DoR)

For the subset of patients with a confirmed CR/PR, DoR is defined as the time from first documented evidence of complete or partial response to the earliest date of disease progression or death due to any cause. For confirmed responders who have not experienced progression or death prior to the date of data cut-off for analysis or starting other anticancer therapy, duration of response will be right-censored on the date of their last adequate post-baseline tumor assessment prior to the cut-off or start of other anticancer therapy.

Duration of response will be summarized descriptively for each cohort using medians and quartiles if there are 5 or more responders (confirmed CR/PR) in one cohort, otherwise, only a listing with subject level details will be provided.

9.8.2.5 Clinical Benefit

This is defined as the percentage of patients achieving either a complete or partial tumor response or stable disease for at least two protocol scheduled disease assessments as per RECIST criteria. 90% confidence intervals will be produced to characterize the variability around the point estimate.

Time to Progression (TTP)

The analysis will evaluate the mITT population on TTP using data from the investigator review. TTP is defined as the interval between the date of first dose of protocol therapy and the earliest date of disease progression or death due to disease under study. Patients are considered to have progressive disease if they have documented progression based on radiologic assessment as determined by investigator review (defined in Section 10). TTP will be summarized using a Kaplan-Meier survival curve. The Kaplan-Meier estimate for the median time to progression and the first and third quartiles will be presented, along with a naive approximate 90% confidence interval if there are a sufficient number of events.

Details on how event and censoring times are assigned to a patient will

be provided in the RAP.

9.8.2.6 Safety Measures:

Safety data will be presented for all patients in the safety population (mITT) regardless of cohort. If there are multiple dose levels for the powder suspension formulation group, then data for each dose level will be presented in separate columns.

Clinical Laboratory Evaluations

Hematology, coagulation parameters, clinical chemistry, lipase and amylase, thyroid function tests, and UPC data will be summarized at each scheduled assessment. Hematology, coagulation parameters and clinical chemistry will be summarized by NCI-CTCAE version 4.0 and by data outside the reference range for each scheduled assessment.

Other Safety Measures

Vital signs (blood pressure, heart rate, temperature), height and weight will be listed for each patient and change from baseline will be included for blood pressure and heart rate. A descriptive summary including change from baseline pre-dose will also be presented. Individual profiles of blood pressure will be plotted by time.

The corrected QTcB interval (QTcB) will be listed for each patient and summarized at each scheduled assessment time. Change from baseline will be summarized and an analysis of central tendency (means, medians) will be presented. A categorical analysis for each QTcB parameter will be performed to determine the number of patients at each time point for the following categories:

- QTcB. <450, 450 to <480, 480 to 500, and >500 msec.
- QTcB change from baseline, 30 to <60 msec, and ≥ 60 msec.

9.9 Evaluability for Response

Response will be determined on the modified intent to treat (mITT) population consisting of all patients who are eligible and received at least one dose of protocol therapy.

For hepatoblastoma patients, RECIST criteria as described below will be used to provide an evaluation of RECIST-based response. For patients without serum alpha fetoprotein (AFP) elevated beyond the institutional upper limit of normal for age at the time of the start of protocol therapy, the RECIST-based response will determine the response for the application of the statistical rule described in Section 9. Patients whose serum AFP level is elevated beyond the institutional upper level of normal for age at the start of protocol therapy will also be assessed for AFP-based response. Any such patient considered evaluable for response as described in Section 9.8 will be considered: (1) an AFP complete responder (AFP-CR) if any serum AFP obtained on or after the start of Cycle 3 but before the start of Cycle 7 is considered at or below the institutional upper limit of normal for age; or (2) an AFP partial responder (AFP-PR) if any serum AFP obtained on or after the start of Cycle 3 but before the start of Cycle 7 is 50% or less than that individual's initial AFP but is still considered above the institutional upper level of normal age; and (3) AFP-non-responder in any other case. The initial AFP obtained on Day 1 of protocol therapy or

the AFP obtained during enrollment (see Note in Section 3.1.7.1), if the Day 1 AFP is not available.

For patients evaluable for both RECIST-based and AFP-based response, the overall response for application of the statistical rule will be calculated as: (1) RECIST-CR or RECIST-PR, AFP-any response category – response; (2) RECIST-SD, AFP-CR or AFP-PR – response; (3) Any other combination of RECIST and AFP response – non-responder.

9.10 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	15	11	26
Not Hispanic or Latino	48	80	128
Ethnic Category: Total of all patients	63	91	154
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	8	5	12
Black or African American	9	16	24
Native Hawaiian or other Pacific Islander	0	0	0
White	46	70	116
Racial Category: Total of all patients	63	91	154

* These totals must agree

This distribution was derived from ADVL0524 (Phase II trial of Ixabepilone (BMS-247750), an Etoposide B Analog in Children and Young Adults with refractory Solid tumors.

9.11 Analysis of the Pharmacokinetic Parameters

Plasma pazopanib concentrations observed in the first 6 patients who receive pazopanib as powder for oral suspension and are evaluable for pharmacokinetics will be analyzed with standard non compartmental methods using WinNonlin version 5.2 or higher. Parameter values for maximum plasma pazopanib concentration (C_{max}), the time to C_{max} (t_{max}), and the area under the curve (AUC) from zero to the time of the last quantifiable concentration (AUC(0-t)) will be calculated. The AUC from zero to 24 hours after administration (AUC (0-24)) on Day 15 will be calculated by using the predose plasma pazopanib concentration as the concentration 24 hours after dosing. The analysis to assess pazopanib pharmacokinetics after administration of the suspension prior to continuing enrollment on suspension may be performed using scheduled time. Calculations of noncompartmental parameter values for the final analysis will be based on actual sampling times.

Plasma pazopanib concentration values at each sampling occasion will be summarized by cohort as well as after combining the data from all cohorts, separately for each formulation and each dose level, if needed. In addition, plasma pazopanib concentration values at each sampling occasion will be summarized by age subgroups (28 days to <2 years, 2 to <12 years of age, and 12 to 18 years of age) for each formulation and dose level, if needed. This analysis

will combine data across all disease cohorts unless pharmacokinetic differences between the cohorts are observed.

The pharmacokinetic parameter values in the patients with extended sampling will be summarized for Cycle 1 Day 1 and Cycle 1 Day 15, combining data from all patients, separately by dose level, if needed.

9.12 Analysis of Biological and Correlative Endpoints

The secondary analyses for examining the biologic relationship between tumor response and angiogenic cytokines as well as the effects on toxicity (including hypertension) of pharmacokinetic parameters (secondary objectives 1.2.7 and 1.2.9) will be conducted [REDACTED] For the response outcome measure, patients will be classified as responders or non-responders according to paragraphs 2 and 3 of the **Primary Endpoint** (Section 9.8.1) above. If response occurs in 10% or more of patients, the following logistic model will be fitted:

[REDACTED]

The initial analysis will be carried out with the Day 15 trough plasma concentration. [REDACTED]

[REDACTED]

Toxicities, which occur in a frequency of 10% or more of toxicity evaluable courses, will be analyzed for association between the risk of toxicity and the particular biological parameter. The data will be presented as a cross tabulation of the presence of frequency of the toxicity of interest in toxicity-evaluable cycles [REDACTED]

[REDACTED]

[REDACTED]

accounting for possible patient frailty will be fitted to the data. This analysis will not be segregated by disease type.

The precision attendant with these analyses will depend on the overall frequency of response and toxicity amongst patients enrolled on the study. The precision observed will be quantified by 95% confidence intervals. Adjustment for multiple testing will not be used for these secondary objectives.

10 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. The descriptions and grading scales found in the revised CTCAE version 4.0 will be utilized for reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0, which can be downloaded from the CTEP web site (<http://ctep.cancer.gov>). Additionally, toxicities are to be reported on the appropriate case report forms.

10.2 Response Criteria

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor and measurable disease (Section 10.3); b) neuroblastoma with MIBG positive lesions (Section 10.4) c) hepatoblastoma (Section 10.6)

Note: Neuroblastoma patients who do not have MIBG positive lesions should be assessed for response as solid tumor patients with measurable disease.

10.3 Response Criteria for Patients with Solid Tumors and Measurable Disease

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009].⁴⁵ Key points are that 5 target lesions are identified and that changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v 1.1 criteria.

10.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm (CT scan slice thickness no greater than 5 mm). The investigator will identify up to 5 measurable lesions to be followed for response. Previously irradiated lesions must demonstrate clear evidence of progression to be considered measurable.

Serial measurements of lesions are to be done with appropriate imaging modalities (e.g., CT or MRI). Bone scans cannot be used to measure lesions. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

10.3.2 Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

10.3.3 End-of-Cycle Response

Note: Please also see Table 1 in Section 10.7.

a. Complete Response (CR)

Disappearance of all target and non-target lesions. Normalization of urinary catecholamines (for patients with neuroblastoma), immunocytologic findings, or other tumor markers if abnormal or elevated at study enrollment.

b. Partial Response (PR)

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment. No new lesions or progression of any non-target measurable lesion.

c. Stable Disease

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

d. Progressive Disease (PD)

At least a 20% increase in the sum of the disease measurements for measurable lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

10.3.4 Overall Best Assessment Response

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described in [Table 1](#) and [2](#) in Section [10.7](#).

10.4 Response Criteria for Neuroblastoma Patients with 123I-MIBG Positive Lesions

10.4.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ¹²³I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was irradiated, a biopsy must be done at least 4 weeks after radiation was completed and must show viable neuroblastoma.

10.4.2 The following criteria will be used to report MIBG response by the treating institution:

- **Complete Response:** Complete resolution of all MIBG positive lesions
- **Partial Response:** Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions.
- **Stable Disease:** No change in MIBG scan in number of positive lesions (includes patients who have same number of positive lesions but decreased density).
- **Progressive Disease:** Development of new MIBG positive lesions.

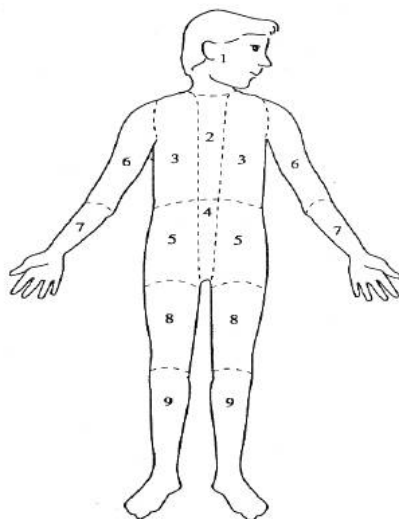
10.4.3 The response of MIBG lesions will be assessed using the Curie scale as outlined below.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan. In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

- 0 = no site per segment,
- 1 = 1 site per segment,
- 2 = more than one site per segment,

3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, the patient will be determined to have a complete response when no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies which are done at least 3 weeks apart.
2. **Partial response:** Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease:** Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease:** New lesions on MIBG scan

10.4.4 Overall Best Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in [Table 3](#) in Section [10.7](#).

10.5 Response Criteria for the Bone Marrow in Neuroblastoma Patients

10.5.1 Bone Marrow Response

Bone Marrow response is determined by H&E staining of bilateral bone marrow biopsies and aspirates.

- Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 3 weeks apart.
- ProgressiveDisease:

- Patients who enroll with neuroblastoma in the bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND have a minimum of 25% tumor in the bone marrow by morphology. (For example, a patient entering with 5% tumor in the bone marrow by morphology must increase to $\geq 25\%$ tumor to have progressive disease; a patient entering with 30% tumor must increase to $\geq 60\%$).
- Patients who enroll without evidence of neuroblastoma in the bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 3 weeks apart.
- Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

10.5.2 The above Bone marrow response criteria will be utilized for Neuroblastoma patients when determining the Overall Best Response in Section 10.7.

10.6 Response Criteria for Hepatoblastoma

10.6.1 For hepatoblastoma patients, RECIST criteria as described above will be used to provide an evaluation of RECIST-based response. For patients without serum alpha fetoprotein (AFP) elevated beyond the institutional upper limit of normal for age at the time of the start of protocol therapy, the RECIST-based response will determine the response for the application of the statistical rule described in Section 9. Patients whose serum AFP elevated beyond the institutional upper level of normal at the start of protocol therapy will also be assessed for AFP- based response. Any such patient considered evaluable for response as described in Section 9.4 above will be considered: (1) an AFP complete responder (AFP- CR) if any serum AFP obtained on or after the start of Cycle 3 but before the start of Cycle 7 is considered at or below the institutional upper limit of normal for age; or (2) an AFP partial responder (AFP-PR) if any serum AFP obtained on or after the start of Cycle 3 but before the start of Cycle 7 is 50% or less than that individual's initial AFP but is still considered above the institutional upper level of normal for age; and (3) AFP-non-responder in any other case. The initial AFP is the AFP obtained on Day 1 of protocol therapy or the AFP obtained during enrollment, if the Day 1 AFP is not available.

For patients evaluable for both RECIST-based and AFP-based response, the overall response for application of the statistical rule will be calculated as: (1) RECIST-CR or RECIST-PR, AFP-any response category – response; (2) RECIST-SD, AFP-CR or AFP-PR – Response; (3) Any other combination of RECIST and AFP response – non-responder.

10.6.2 Measurement of serum AFP markers

The serum AFP should be collected immediately prior to starting therapy on the first day of treatment, and again at each scheduled disease evaluation if the initial value is elevated. The value must be reported as a precise number, and not as an estimate (e.g., $> 50,000$ ng/mL). This may require serial dilutions of samples in order to obtain an accurate value. In addition, values that are unexpectedly low should also be confirmed by serial dilutions.

10.6.3 Overall Response Assessment

The overall response assessment for hepatoblastoma patients takes into account response in the measurable and non-measurable disease, and the appearance of new lesions, where applicable, and decline of AFP according to the criteria described in [Table 4](#) below.

10.7 Best Response (Solid Tumors)

Two objective status determinations of disease status, by CT or MRI, obtained on two consecutive determinations, separated by at least a 3 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

Table 1: Sequences of objective statuses with corresponding best response.

1 st Status	2 nd Status	3 rd or subsequent Status	Best Response
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

Table 2: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow¹	Catecholamines	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

¹ Bone marrow does not need to be routinely done for disease assessment if Negative at the start of protocol therapy

Table 3: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow¹	Catecholamines	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

¹ Bone marrow does not need to be routinely done for disease assessment if Negative at the start of protocol therapy

Table 4: Overall Response Assessment for Hepatoblastoma Patients

Target Lesions	Non-target Lesions	New Lesions	AFP¹	Overall Response
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD
SD	Non-PD	No	Stable	SD
Non-PD	Non-PD	No	≥ 50% decrease from highest AFP prior to treatment	PR
PR	Non-PD	No	Decreased	PR
CR	Incomplete response/SD	No	Decreased	PR
CR	CR	No	Normalized ²	CR ²

¹ AFP is not part of the overall response assessment if it was NOT elevated at the start of protocol therapy

² An overall response of CR MUST include a normal AFP. Until the AFP has normalized, a patient can only be considered PR at best.

10.8 Survival Follow-Up

Patients who have discontinued protocol therapy will be followed for Survival status. The investigator site will collect and report Survival follow-up in the eCRF every 3 months, which would include the patient's survival status and any antineoplastic therapies taken since discontinuation of protocol therapy, until death, lost to follow-up, or withdrawal of consent from survival follow-up occurs or final cut-off for survival analysis.

The date and cause of death should be recorded in the eCRF.

11 ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

- AEs will be collected from the start of protocol therapy and until 28 days following last dose of protocol therapy.
- SAEs will be collected over the same time period as stated above for AEs. From the time a patient consents to participate in and completes the study, all SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) will be reported promptly to Novartis as indicated in Section 11.8.
- Medical occurrences that begin prior to the start of protocol therapy but after obtaining informed consent should be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any new primary cancer must be recorded as an SAE and will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to Novartis and COG within 24 hours, as indicated in Section 11.8.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator should promptly notify Novartis and COG.

11.1 Definition of Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. CTCAE criteria version 4.0 will be used to grade severity of adverse events.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and 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 study treatment 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 study treatment or a concomitant medication. (Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.)
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient'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 patient'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.

11.2 Definition of Serious Adverse Events (SAEs)

Refer to Section 11.8 for reporting requirements including the within 24 hour time limit for all SAEs as defined below.

If an event is not an AE per Section 11.1 then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize

the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT > 3xULN **and** bilirubin > 1.5x ULN (>35% of total bilirubin is direct) or ALT > 3xULN and INR>1.5, if INR measured termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a patient meets the criterion of total bilirubin \geq 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

11.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?" or "How does your child seem to feel?"
- "Have you had any (other) medical problems since your last visit/contact?" or
- "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

11.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

11.5 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the patient's medical records to Novartis or COG in lieu of completion of the Novartis AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are

requested by Novartis and COG. In this instance, all patient identifiers, with the exception of the patient number (both COG and Novartis study numbers), will be blinded on the copies of the medical records prior to submission to Novartis.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

11.6 Evaluating AEs and SAEs

11.6.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

11.6.2 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

11.7 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by Novartis to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a patient dies during participation in the study or during a recognized follow-up period, the investigator will

provide Novartis with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to Novartis within the designated reporting time frames

11.8 Prompt Reporting of SAEs to Novartis and COG

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Novartis and COG **within 24 hours**. Any follow-up information on a previously reported SAE will also be reported to Novartis and COG within 24 hours. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying Novartis and COG of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 11.6.2, Assessment of Causality.

The primary mechanism for reporting SAEs to Novartis and COG will be the electronic data collection tool. If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the number included in the Study Procedures Manual. Then the site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool (e.g., DataLabs™ system) will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to their Novartis protocol contact by telephone.

Novartis contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor Information page.

11.9 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to Novartis is essential so that legal obligations and ethical responsibilities towards the safety of patients are met. Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/Independent Ethics Committees (IECs) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

12 STUDY REPORTING AND MONITORING

For this study, patient data will be entered into electronic case report forms (eCRFs), transmitted electronically to Novartis or designee and be combined with data provided from other sources in a validated data system.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures with the objective of resolving errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. All AEs and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom dictionary. eCRFs (including queries and audit trails) will be retained by Novartis, and copies will be sent to the investigator to maintain as the investigator copy.

12.1 Data and Safety Monitoring

A formal data safety monitoring board will not be utilized for this open-label study. The following procedures will be followed to provide appropriate data and safety monitoring for this study:

- The study team, which includes the Medical Lead, representatives from the Clinical Pharmacology Group, and the COG protocol chair will review and discuss safety data at periodic intervals throughout the duration of the study.

13 APPENDICES

13.1 APPENDIX IA: PATIENT DIARY FOR PAZOPANIB TABLETS

COG Patient ID: _____ ACC #: _____ Institution: _____

Please do not write patient name on this form.

Sponsor Patient ID: _____

Please write the date, time and dose of pazopanib given. Please make note of all prescription medications, nonprescription medications, and herbal remedies you take. Also, please remember to take the tablets at least 1 hour before or 2 hours after a meal. Return the completed diary to your institution after each treatment cycle along with any unused study medication or empty study medication bottles.

EXAMPLE				Number of tablets taken		
WEEK 1	Date	Time (Circle AM or PM)		200 mg	400 mg	Comments
Day 1	1/15/08	8:30	am/pm	1	1	He felt nauseated an hour after taking the drug but did not vomit.

Cycle #: _____						Start Date: []/[]/[]		End Date: []/[]/[]	
Daily dose: _____ mg = _____ × 200 mg + _____ × 400 mg									
WEEK 1	Date	Time (Circle AM or PM)		200 mg	400 mg	Comments			
Day 1			am/pm						
Day 2			am/pm						
Day 3			am/pm						
Day 4			am/pm						
Day 5			am/pm						
Day 6			am/pm						
Day 7			am/pm						
WEEK 2	Date	Time		200 mg	400 mg	Comments			
Day 8			am/pm						
Day 9			am/pm						
Day 10			am/pm						
Day 11			am/pm						
Day 12			am/pm						
Day 13			am/pm						
Day 14			am/pm						
WEEK 3	Date	Time		200 mg	400 mg	Comments			
Day 15			am/pm						
Day 16			am/pm						
Day 17			am/pm						
Day 18			am/pm						
Day 19			am/pm						
Day 20			am/pm						
Day 21			am/pm						
WEEK 4	Date	Time		200 mg	400 mg	Comments			
Day 22			am/pm						
Day 23			am/pm						
Day 24			am/pm						
Day 25			am/pm						
Day 26			am/pm						
Day 27			am/pm						

Day 28			am/pm			
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13.2 APPENDIX IB: PATIENT DIARY FOR PAZOPANIB POWDER IN SUSPENSION

COG Patient ID: _____ ACC #: _____ Institution: _____

Please do not write patient name on this form.

Sponsor Patient ID: _____

Please write the date, time and dose of pazopanib given. Please make note of all prescription medications, nonprescription medications, and herbal remedies you take. Please remember to swirl the suspension for 30 seconds prior to withdrawing the dose from the bottle. Also, **please remember to take the suspension on an empty stomach either 1 hour before or 2 hours after meals.** Return the completed diary to your institution after each treatment cycle along with all the bottles of study medication, even empty.

<i>EXAMPLE</i>				<i>Suspension Taken</i>	
<i>WEEK 1</i>	<i>Date</i>	<i>Time</i> (Circle AM or PM)		<i>Amount (ml)</i>	<i>Comments</i>
<i>Day 1</i>	<i>1/15/08</i>	<i>8:30</i>	<i>am/pm</i>	<i>4 ml</i>	<i>He felt nauseated an hour after taking the drug but did not vomit.</i>

Cycle #: _____		Start Date: []/[]/[] End Date: []/[]/[]			
Daily dose: _____ mL					
WEEK 1	Date	Time (Circle AM or PM)		Suspension Taken Amount (mL)	Comments
Day 1			am/pm		
Day 2			am/pm		
Day 3			am/pm		
Day 4			am/pm		
Day 5			am/pm		
Day 6			am/pm		
Day 7			am/pm		
WEEK 2	Date	Time			Comments
Day 8			am/pm		
Day 9			am/pm		
Day 10			am/pm		
Day 11			am/pm		
Day 12			am/pm		
Day 13			am/pm		
Day 14			am/pm		
WEEK 3	Date	Time			Comments
Day 15			am/pm		
Day 16			am/pm		
Day 17			am/pm		
Day 18			am/pm		
Day 19			am/pm		
Day 20			am/pm		
Day 21			am/pm		
WEEK 4	Date	Time			Comments
Day 22			am/pm		
Day 23			am/pm		
Day 24			am/pm		
Day 25			am/pm		
Day 26			am/pm		
Day 27			am/pm		
Day 28			am/pm		

13.3 APPENDIX II: PAZOPANIB DOSING NOMOGRAM FOR TABLETS

Dosing Nomogram for Target Starting Dose of 450 mg/m²/dose and for Dose Reductions if required

	Starting Dose	Dose Reduction #1	Dose Reduction #2
	Target : 450 mg/m ² /dose		
BSA*	Dose (mg) [†]		
0.84-1.16	400	200	0
1.17 -1.61	600	400	200
≥ 1.62	800	600	400

* BSA, body surface area in m².

† Actual dose is in mg (tablets sizes 200 mg and 400 mg) to be administered daily.

13.4 APPENDIX IIIA: LIST OF ANTICONVULSANT DRUGS THAT ARE ALLOWED

Anticonvulsant drugs with little or no enzyme induction: ELIGIBLE/ALLOWED
Lamotrigine (Lamictal) Levetiracetam (Keppra) Tigabine (Gabitril) Topiramate (Topamax) Valproic Acid, Depakote (Depakene) Zonisamide (Zonegran)

13.5 APPENDIX IIIB: MEDICATIONS THAT MAY CAUSE QTc PROLONGATION

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: ...azcert.org/medical-pros/drug-lists/drug-lists.cfm.

<p><i>Drugs that are generally accepted to have a risk of causing Torsades de pointes</i></p> <p>PROHIBITED DRUGS (See Appendix III-A)</p>	<p><i>Drugs that in some reports have been associated with Torsades de pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de pointes</i></p> <p>CONSIDER MORE FREQUENT EKG MONITORING (Unless otherwise noted as prohibited)</p>	<p><i>Drugs that, in some reports, have been <u>weakly associated</u> with Torsades de pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).</i></p> <p>EKG MONITORING AS PER INVESTIGATOR DISCRETION (Unless otherwise noted as prohibited)</p>
<u>Generic/Brand Name</u>	<u>Generic/Brand Name</u>	<u>Generic/Brand Name</u>
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril® (prohibited)	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatol® (prohibited)	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor® (prohibited)	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx® (prohibited)	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporonax® (prohibited)
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral® (prohibited)
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil® (prohibited)
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®

<p><i>Drugs that are generally accepted to have a risk of causing Torsades de pointes</i></p> <p>PROHIBITED DRUGS (See Appendix III-A)</p>	<p><i>Drugs that in some reports have been associated with Torsades de pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de pointes</i></p> <p>CONSIDER MORE FREQUENT EKG MONITORING (Unless otherwise noted as prohibited)</p>	<p><i>Drugs that, in some reports, have been <u>weakly associated</u> with Torsades de pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).</i></p> <p>EKG MONITORING AS PER INVESTIGATOR DISCRETION (Unless otherwise noted as prohibited)</p>
<u>Generic/Brand Name</u>	<u>Generic/Brand Name</u>	<u>Generic/Brand Name</u>
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Levofloxacin /Levaquin®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Lithium /Lithobid®	Sertraline /Zoloft®
Methadone /Dolophine®	Lithium /Eskalith®	Solifenacin /VESicare®
Methadone /Methadose®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moxifloxacin /Avelox®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Nicardipine /Cardene®	Trimipramine /Surmontil®
Pimozide /Orap®	Nilotinib /Tasigna®	
Probucol /Lorelco®	Octreotide /Sandostatin®	
Procainamide /Pronestyl®	Ofloxacin /Floxin®	
Procainamide /Procan®	Ondansetron /Zofran®	
Quinidine /Cardioquin®	Oxytocin /Pitocin®	
Quinidine /Quinaglute®	Paliperidone /Invega®	
Sotalol /Betapace®	Perflutren lipid microspheres/ Definity®	
Sparfloxacin /Zagam®	Quetiapine /Seroquel® (prohibited)	
Terfenadine /Seldane®	Ranolazine /Ranexa®	
Thioridazine /Mellaril®	Risperidone /Risperdal® (prohibited)	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf® (prohibited)	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek® (prohibited)	

<p><i>Drugs that are generally accepted to have a risk of causing Torsades de pointes</i></p> <p>PROHIBITED DRUGS (See Appendix III-A)</p>	<p><i>Drugs that in some reports have been associated with Torsades de pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de pointes</i></p> <p>CONSIDER MORE FREQUENT EKG MONITORING (Unless otherwise noted as prohibited)</p>	<p><i>Drugs that, in some reports, have been <u>weakly associated</u> with Torsades de pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).</i></p> <p>EKG MONITORING AS PER INVESTIGATOR DISCRETION (Unless otherwise noted as prohibited)</p>
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend® (prohibited)	
	Ziprasidone /Geodon®	

13.6 APPENDIX IV: URINE PROTEIN TO CREATININE (UPC) RATIO

Clinical Meaning of UPC

There is a good correlation between the ratio of urine protein to urine creatinine concentrations (UPC) in a random urine sample and the amount of protein excreted in a 24-hour urine collection period.⁴⁸ Thus, the UPC ratio from a single random urine sample permits estimation of the 24-hour urine protein excretion. The 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 per 24 hours.
- The UPC ratio is roughly equal to the 24-hour urine protein excretion in g/day

Calculating UPC Ratio

UPC ratio = (Urine protein [mg/dL]) / (urine creatinine [mg/dL]) = numerically equivalent to grams (g) protein excreted in urine over 24 hours.

Example: If a patient has a urine protein concentration of 90 mg/dL and urine creatinine concentration of 30 mg/dL,

$$\text{then UPC ratio} = \frac{90(\text{mg/dL})}{30 (\text{mg/dL})} = 3$$

UPC ratio of 3 correlates to roughly 3g of protein excretion in a 24-hour period.

Units for UPC ratio

UPC is a calculated ratio. The guidelines in the protocol are based on having urine protein and urine creatinine measured in the same units (e.g., mg/dL). The International System of Units (SI) units for urine protein and urine creatinine are not the same, so these must be converted to mg/dL before calculating the ratio. For reference, the conversion factors for commonly used units for protein and creatinine are provided below.

Starting units	Conversion to mg/dL
Protein (g/L)	Multiply by 100
Creatinine (μmol/L)	Divide by 88.4
Creatinine (mmol/L)	Multiply by 11.3

13.7 APPENDIX V: BLOOD PRESSURE LEVELS FOR CHILDREN BY AGE AND HEIGHT PERCENTILE

Blood pressure (BP) levels for **BOYS**

Age (years)	BP Percentile	Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.1.2.5 for definition of dose limiting hypertension, Section 5.4.1 for management and grading of hypertension, and Section 4.1.5.1 for medical treatment of pazopanib related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Note: For patients ≥ 18 yrs, ULN BP is 140/90 mmHg.

Blood pressure (BP) levels for GIRLS

Age (years)	BP Percentile	Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95 th	5th	10th	25th	50th	75th	90th	95 th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.1.2.5 for definition of dose limiting hypertension, Section 5.4.1 for management and grading of hypertension, and Section 4.1.5.1 for medical treatment of pazopanib related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2
August 2004, pp. 555-576.

Note: For patients ≥ 18 yrs, ULN BP is 140/90 mmHg.

13.8 APPENDIX VI: PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ ACC # _____ SPONSOR Patient ID # _____

Please do not write patient names on this form or on samples.

Except for Cycle 1 Day 1, pre-dose samples should be collected between 22-26 hours after the previous dose of pazopanib.

Samples will be obtained as outlined in the tables below.

Record the exact time the sample is drawn and the exact time that the dose of pazopanib was given.

CYCLE 1:**Day 1:**Body Surface Area: ° m² Dose: mg/m² Total Dose: mgDate and time of dose given on Cycle 1, Day 1: Date: Time: :
(MM/DD/YY)**Day 15 (± 1):**Body Surface Area: ° m² Dose: mg/m² Total Dose: mgDate and time of dose given on Cycle 1, Day 15 (± 1): Date: Time: :
(MM/DD/YY)**All patients not participating in Extended PK sampling:**

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
2 ^a	Cycle 1, Day 15 (± 1)	Prior to dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
3 ^a	Cycle 1, Day 15 (± 1)	3-4 hrs after dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>

Patients receiving powder suspension formulation and participating in Extended PK sampling:

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
2	Cycle 1, Day 1	30 min after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
3	Cycle 1, Day 1	1 hr after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
4	Cycle 1, Day 1	2 hrs after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
5	Cycle 1, Day 1	4 hrs after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
6	Cycle 1, Day 1	6 hrs after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
7	Cycle 1, Day 1	8 hrs after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
10 ^a	Cycle 1, Day 15 (± 1)	Prior to dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
11 ^a	Cycle 1, Day 15 (± 1)	30 min after first dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
12 ^a	Cycle 1, Day 15 (± 1)	1 hr after dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
13 ^a	Cycle 1, Day 15 (± 1)	2 hrs after dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
14 ^a	Cycle 1, Day 15 (± 1)	4 hrs after dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
15 ^a	Cycle 1, Day 15 (± 1)	6 hrs after dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
16 ^a	Cycle 1, Day 15 (± 1)	8 hrs after dose		<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>

^a Pazopanib dosing of either tablet or powder suspension must have continued uninterrupted and at the same dose level for at least 10 days prior to acquisition of the Cycle 1 Day 15 PK samples. If pazopanib dosing has been interrupted or modified <10 days prior to Cycle 1 Day 15, then the PK samples should be taken between Cycle 1 Day 15 and Cycle 1 Day 22 on a study day that meets the condition of at least 10 consecutive days of dosing at the same dose level. The Cycle 1 Day 15 PK kit should be used, and the actual date and time of sample

collections should be recorded in the eCRF.

SUBSEQUENT CYCLES:

For patients who continue to receive protocol therapy, PK sampling is also **required** prior to subsequent odd-numbered cycles. This sample may be taken between Day 22 of the previous even-numbered cycle to Day 1 of the odd-numbered cycle (*e.g., between Day 22 of Cycle 2 and Day 1 of Cycle 3*). Please record the actual Cycle and Day on which the sample was obtained. **The timing of this sample should be between 22-26 hours after the previous dose of pazopanib.** For samples collected in Cycle 3 and greater, record the date, time, and amount of the pazopanib dose administered on the study day prior to the blood sample collection in the area below

For Cycle 3 pre-dose: Cycle # ____ Day # ____ Sample Collected: _____ Date: _____ Time: ____ : ____
(MM/DD/YY)
Date and Time of Prior Pazopanib Dose: Date: _____ Time: ____ : ____
(MM/DD/YY)
Body Surface Area: ____° ____ m² Dose: ____ mg/m² Total Dose: ____ mg

For Cycle 5 pre-dose: Cycle # ____ Day # ____ Sample Collected: _____ Date: _____ Time: ____ : ____
(MM/DD/YY)
Date and Time of Prior Pazopanib Dose: Date: _____ Time: ____ : ____
(MM/DD/YY)
Body Surface Area: ____° ____ m² Dose: ____ mg/m² Total Dose: ____ mg

For Cycle 7 pre-dose: Cycle # ____ Day # ____ Sample Collected: _____ Date: _____ Time: ____ : ____
(MM/DD/YY)
Date and Time of Prior Pazopanib Dose: Date: _____ Time: ____ : ____
(MM/DD/YY)
Body Surface Area: ____° ____ m² Dose: ____ mg/m² Total Dose: ____ mg

For Cycle 9 pre-dose: Cycle # ____ Day # ____ Sample Collected: _____ Date: _____ Time: ____ : ____
(MM/DD/YY)
Date and Time of Prior Pazopanib Dose: Date: _____ Time: ____ : ____
(MM/DD/YY)
Body Surface Area: ____° ____ m² Dose: ____ mg/m² Total Dose: ____ mg

For Cycle 11 pre-dose: Cycle # ____ Day # ____ Sample Collected: _____ Date: _____ Time: ____ : ____
(MM/DD/YY)
Date and Time of Prior Pazopanib Dose: Date: _____ Time: ____ : ____
(MM/DD/YY)
Body Surface Area: ____° ____ m² Dose: ____ mg/m² Total Dose: ____ mg

Signature: _____
(site personnel who collected samples)

Date: _____

Sample Collection, Handling, and Processing

1. Blood samples will be collected into tubes containing potassium EDTA as an anticoagulant and may be drawn from a central venous catheter.
2. The samples should be centrifuged at approximately 2500 x g at 5°C for 10 minutes. The resulting volume of plasma will be transferred in equal aliquots to two (2) corresponding pre-labeled polypropylene storage tubes. The tubes will be frozen in an upright position at -20°C until shipped to the laboratory for analysis.
3. Each tube must be labeled with the Sponsor study specific patient number, the study I.D. (ADV1322/VEG116731), and the date and time the sample was drawn. Please also see the instructions in the [REDACTED] Central Laboratory Services Manual (binder) that is provided with the initial start up PK kits from [REDACTED].

A copy of this form along with a copy of the requisition form provided in the kits from [REDACTED] should be sent with the samples. All samples should be batched and shipped with adequate amounts of dry ice. Shipments should be sent **Monday through Thursday only** for priority overnight delivery (do not ship on Friday) to the address listed in the PK kit supplied by [REDACTED].

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____
(site personnel who collected samples)

Date: _____

13.9 APPENDIX VII: INSTRUCTIONS TO PATIENT/CAREGIVER FOR ADMINISTERING PAZOPANIB ORAL SUSPENSION

Patient name: _____

Investigator/study staff: Please fill in the dose in section A.

This document provides instructions for patients/caregivers on the administration and storage of pazopanib suspension. It also details how to clean up in the event of a spill. Any leftover medication should be returned to your doctor. You should read the information on these pages before you give your child the suspension. **Please read these instructions carefully and ask your doctor about any questions you may have.**

A. Administration:

1. The pharmacist should insert the provided adapter (Baxa 28 mm Press-In-Bottle Adapter - PIBA®) into the neck of the bottle. Once the adapter has been placed into the bottle neck, DO NOT REMOVE.
2. **Immediately** before planned dose administration, mix the contents of the bottle by **swirling** for 30 seconds to one minute in order to ensure homogeneity of suspension.
3. **Note#1: Women who are pregnant or nursing should put on a suitable size of gloves** to avoid contact between the liquid and skin (Latex gloves can be used; however, for people who are sensitive to latex, it is recommended to use Nitrile gloves). Take care not to spread material to unprotected skin (such as your face) or other body surfaces by touching them with a wet glove.
Note#2: In case of spillage, see section C for Clean-up instructions.
3. Insert the tip of an appropriate syringe (recommended: Exacta-Med® Baxa) into the Adapter after ensuring that the syringe plunger is pushed fully into the barrel.
4. Tip the bottle upside down and dispense at least 3-5 mL of suspension into the syringe. Then push the suspension back into the bottle in order to purge the syringe of any air bubbles. Repeat this step until syringe is free of air bubbles.
5. Withdraw the prescribed dose. Investigator/study staff will fill in the dose below for each patient.

The dose is _____ mg, corresponding to _____ mL each day.

Please note that the number of milligrams of pazopanib and, therefore, the number of milliliters of pazopanib oral suspension may change as the body surface area of the patient changes during study participation.

6. After you have given your child the dose, pull the plungers out of all the syringes and rinse the syringes and plungers with warm water for 30 seconds. When dry, place the plungers back into their syringes and store them for the next time.
7. Pazopanib is to be given orally (by mouth) only.
8. The dose should be given on an empty stomach (1 hour before or 2 hours after a meal) once daily.
9. If your child's study doctor prescribed medicine to prevent nausea or vomiting with pazopanib, you should give your child this medicine 30-60 minutes before you give pazopanib.
10. If your child spits out or vomits a dose of pazopanib, it should not be repeated.
11. If a dose is missed, it may be given within 12 hours of the time it was due. Beyond 12 hours that dose should be skipped. The next dose should be given at its regularly scheduled time. For example, if the dose was due at 8am, then the dose may be given up to 8pm that same day.

B. Storage and returning partially used and unused bottles:

1. The pazopanib suspension should be refrigerated in its bottle (2° to 8°C, or 36° to 46°F).
2. Pazopanib must be kept out of reach of children.
3. Any used and unused bottles of pazopanib should be returned to the investigator/clinic at each study visit.

C. Clean-up Instructions in case of spillage:

Note: Women who are pregnant or nursing should avoid doing the clean-up because there is a risk of possible harm in developing human offspring or nursing infants.

4. Put on a suitable size of gloves. Latex gloves can be used; however, for people who are sensitive to latex, it is recommended to use Nitrile gloves.

Note: Use gloves for the clean-up process to avoid contact between the liquid spill and skin.

Take care not to spread spilled material to unprotected skin (such as your face) or other body surfaces by touching them with a wet glove.

5. Add enough absorbent material (eg: kitty litter, coffee grounds, or paper towels) onto the spilled material to soak it up.
6. Place the soaked absorbent material into a sealable plastic bag, and then seal the bag.
7. Wipe the spilled area with an alcohol moistened towel (paper or cloth) and allow area to dry.
12. Place the sealed bag, towels, gloves into a second sealable bag then put into the household trash.

13.10 APPENDIX VIII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1322 (for children from 7 through 12 years of age)

A study of pazopanib in children with cancer that has come back after treatment or is difficult to treat

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.
2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine to treat your cancer.
3. Children who are part of this study will be treated with a cancer-fighting medicine called pazopanib. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if pazopanib will make more children with your type of cancer get better. We don't know if pazopanib will work well to get rid of your cancer. That is why we are doing this study.
4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that pazopanib may cause your cancer to stop growing or to shrink for a period of time. However, we don't know for sure if there is any benefit of being part of this study.
5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from pazopanib than other treatments. Other things may happen to you that we don't yet know about.
6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
7. We are asking your permission to collect additional blood. We want to learn more about how pazopanib works. Sample would be taken before you start treatment and 2 weeks after you start treatment. The extra blood would be taken only at times when blood is collected for regular treatment tests, so there would be no extra needle sticks. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1322
(for teens from 13 through 17 years of age)**

**A study of pazopanib in children with cancer that has come back after
treatment or is difficult to treat**

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.
2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.
3. Children and teens who are part of this study will be given a cancer-fighting medicine called pazopanib. Pazopanib is a drug that in laboratory studies can block proteins which are thought to be important for tumors to grow. You will get pazopanib once a day (by mouth) for 28 days. This 28 day regimen may be repeated until you benefit from treatment or until study closure. You will get the pazopanib as long as you do not have bad effects from it and your cancer does not get any worse. You will also have exams and tests done that are part of normal cancer care. But, the exams and tests will be done more often while you are being treated with pazopanib. The doctors want to see if pazopanib will make more children with your type of cancer get better. We don't know if pazopanib is better than other medicines. That is why we are doing this study.
4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that pazopanib may cause your cancer to stop growing or to shrink for a period of time. However we don't know for sure if there is any benefit of being part of this study.
5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study may be a less effective treatment and more side effects than other treatments for your cancer. Other things may happen to you that we don't yet know about.
6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
7. We are asking your permission to collect additional blood. It will be helpful for us to see how your body handles the pazopanib and how pazopanib works. Sample would be taken before you start treatment and 2 weeks after you start treatment. The extra blood would be taken only at times when blood is collected for regular treatment tests, so there would be no extra needle sticks. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

13.11 APPENDIX IX AMENDMENT 01

Where the Amendment Applies

Changes included in Amendment 01 where made prior to initiation of the study. Amendment 02 applies to all sites who will conduct the study

Summary of Amendment Changes with Rationale

The IND number in the original protocol was incorrect so only change made in Amendment 01 was to correct the IND number throughout the protocol.

13.12 APPENDIX X AMENDMENT 02



Where the Amendment Applies

Changes included in Amendment 02 were made prior to initiation of the study. Amendment 02 applies to all sites who will conduct the study.

Deleted text is shown as a strikethrough and added text is shown as bold. Minor administrative changes, including section number changes and minor changes to the text that do not impact the study conduct are not included in the summary below.

Summary of Amendment Changes with Rationale

List of Specific Changes

Change	Rationale
<p>The requirement to dose patients with tablets was changed from a BSA of 0.48 to 0.84 based on the available tablet strengths.</p> <p>The starting dose for suspension was changed from 160 mg/m² to 225 mg/m²</p>	<p>The pazopanib Phase I trial (ADVL0815) established different Maximum Tolerated Doses for the PfOS (160mg/m²) and tablet formulation (450mg/m²).</p> <p>The available tablet strengths will allow for dosing of children/adolescents to have a BSA of 0.84 mg/m².</p> <p>The mg/m² starting dose will be 225 mg/m² which is greater than the MTD (160 mg/m²) established in the Phase I study (ADVL0815) where 2 isolated reversible laboratory DLTs were observed. The initial 6 patients who require suspension will have extended PK sampling and safety monitoring for DLTs. If the 225 mg/m² dose is not tolerated subsequent patients who require suspension will receive 160 mg/m²/dose.</p>
Clarification around continuation of therapy following toxicity incorporated.	To provide investigators clarification and guidance around dose interruptions and modifications required when toxicity observed.
	
Monitoring of Pregnancy incorporated	Monitoring and documentation of pregnancy required for those females and partners of male subjects that become pregnant while participating in this study.
Protocol specific SAEs that were associated with another asset were removed.	Protocol specific SAEs were incorrectly included in the protocol and are not appropriate to be included in this study.
General administrative changes including updating TOC, formatting and Appendix references changed throughout the protocol.	To ensure consistency and accuracy throughout the protocol

Experimental Design Schema Previous Text:

Pazopanib will be administered orally once daily as a tablet at a dose of 450 mg/m²/dose or as a powder in suspension at a dose of 160 mg/m²/dose (the MTDs determined by Part 1 and Part 2A respectively of ADVL0815, the COG Phase I study). The maximum dose to be administered daily is 800 mg. Each cycle will be defined as 28 days. Note: The first 10 patients enrolled will receive the suspension formulation during Cycle 1 in order to obtain pharmacokinetic data. Those patients may switch to the tablet formulation for Cycle 2 and subsequent cycles if the patient is able to swallow tablets and meets the minimum BSA requirements for tablets. Please note, the prescribed dose for the tablet and suspension formulation is different (see Section 4.1).

Patients with benefit (stable disease or an objective response) may continue therapy for up to 2 years (in the absence of unacceptable treatment related toxicity) unless there is evidence of progressive disease or unacceptable treatment-related toxicity.

Experimental Design Schema Revised Text:

Pazopanib will be administered orally once daily as a tablet at 450 mg/m²/dose or as a powder in suspension at 225 mg/m²/dose. The maximum tolerated dose (MTD) for tablets was 450 mg/m²/dose as determined by ADVL0815, the COG Phase I study, while the dose for oral suspension of 225 mg/m²/dose exceeds the protocol-specified MTD of 160 mg/m²/dose established in that study. The 225 mg/m²/dose is where two isolated laboratory-defined dose-limiting toxicities (DLTs) were observed. The maximum dose to be administered daily for tablets is 800 mg. The maximum dose to be administered daily for suspension is 400 mg. Each cycle will be defined as 28 days.

The first 6 patients enrolled who receive suspension will be expected to complete extended pharmacokinetic (PK) sampling (Section 7.3.2) in order to obtain PK and safety data. These data will be reviewed prior to further enrollment of patients requiring suspension to determine if 225 mg/m²/dose is tolerated and PK exposure is similar to exposure in adults associated with clinical efficacy. If the 225 mg/m²/dose is not tolerated (≥ 2 dose limiting toxicities (DLTs) in 6 evaluable patients), the dose for patients who require suspension may be reduced to 160 mg/m²/dose.

Secondary Aims, Added Text:

- 1.2.3 To further characterize the PK of pazopanib after administration of the oral suspension in children, adolescents and young adults with cancer

Section 2.3.1. Pharmacokinetic and Pharmacodynamic Data in Adults with Cancer, Previous Text:

There were no clinically meaningful changes in QTc interval following pazopanib in a dedicated QT Holter study.

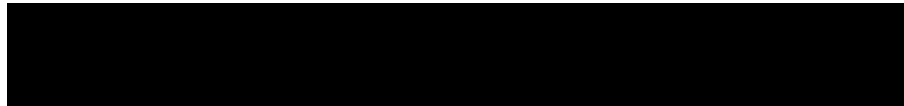
Section 2.3.1. Pharmacokinetic and Pharmacodynamic Data in Adults with Cancer, RevisedText:


~~There were no clinically meaningful changes in QTc interval following pazopanib in a dedicated QT Holter study.~~

In clinical studies with pazopanib, events of QT prolongation or torsade de pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics or other medications that may potentially prolong QT interval, or those with relevant pre-

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


Section 2.3.3 Efficacy Data in Adults with Cancer, Previous Text (Paragraphs 4 and 5):

 In two separate Phase II studies of renal cell and NSCLC presented at the 2008 annual meeting of the American Society for Clinical Oncology (ASCO) a decrease in sVEGFR2 compared with baseline was significantly correlated with tumor response ($p < 0.05$).^{37,38} In adult patients with metastatic imatinib-refractory gastrointestinal stromal tumors treated with sunitinib, another VEGF and c-kit targeting multityrosine kinase inhibitor, biomarker analysis of CECs, monocytes, VEGF, and sVEGFR-2 were consistently modulated by treatment. In this study, changes in CECs and monocytes rather than plasma markers differed between the patients with clinical benefit and those with progressive disease.³⁹ In pediatric patients with refractory solid tumors treated with the VEGF neutralizing antibody bevacizumab, patients with prolonged disease stabilization (> 3 months) had a greater contribution of apoptotic CEC to the total CEC number (aCEC/tCEC) after 4 weeks of therapy ($p=0.04$), a finding also reported in breast cancer patients who responded to metronomic therapy.^{40,41} This study will continue to examine the effects of pazopanib therapy on cytokines and angiogenic factors.

- 3) The GlaxoSmithKline genetics team led by Dr.  has recently published results of a candidate gene association study in adult RCC patients treated with pazopanib.²⁵ Several polymorphisms in candidate genes demonstrated associations with response rate and progression-free survival. Validation and elaboration of these findings will become available prior to completion of this trial. Based on the adult findings, an amendment to the protocol will be planned to study the strongest candidate SNP associations in this pediatric population.

Section 2.3.3 Efficacy Data in Adults with Cancer, Revised Text (Paragraph 4)

In pediatric patients with refractory solid tumors treated with the VEGF neutralizing antibody bevacizumab, patients with prolonged disease stabilization (> 3 months) had a greater contribution of apoptotic CEC to the total CEC number (aCEC/tCEC) after 4 weeks of therapy ($p=0.04$), a finding also reported in breast cancer patients who responded to metronomic therapy.^{40,41} **pazopanib, baseline levels of plasma soluble VEGFR-2 and endoglin levels were significantly decreased when measured after 2 weeks of treatment, while placental growth factor levels were significantly increased over the same time points. There was no significant change in VEGF or plasma soluble VEGFR-1 levels with pazopanib therapy.**⁴⁰

- 3) The GlaxoSmithKline genetics team led by Dr.  has recently published results of a candidate gene association study in adult RCC patients treated with pazopanib.²⁵ Several polymorphisms in candidate genes demonstrated associations with response rate and progression-free survival. Validation and elaboration of these findings will become available prior to completion of this trial. Based on the adult findings, ~~an amendment to the protocol will be planned to study the strongest candidate SNP associations in this~~ **additional markers may be explored in the** pediatric population.

Section 2.4.1 Pediatric Studies, Added Text (Paragraph 2, sentence 4):

The MTD for tablet was 450 mg/m²/dose, and suspension 160 mg/m²/dose; **two isolated and reversible Grade 3 ALT elevations were seen at the suspension dose of 225 mg/m²/dose.**

Section 2.4.2. Pharmacology/Pharmacokinetic/Correlative Biological Studies, Previous Text (Sentence 1):

The dose limiting toxicity in the pediatric Phase I dose escalation was hypertension, a class effect seen with

other VEGF blocking agents. Such hypertension has been treatable with anti-hypertensives and may ultimately be a biomarker of treatment effect.

Section 2.4.2. Pharmacology/Pharmacokinetic/Correlative Biological Studies, RevisedText (Sentence 1):

~~The dose limiting toxicity~~ **Hypertension was seen in several patients** in the pediatric Phase I dose escalation ~~was hypertension study, which is~~ a class effect seen with other VEGF blocking agents. Such hypertension has been treatable with anti-hypertensives and may ultimately be a biomarker of treatment effect.

Section 2.4.2. Pharmacology/Pharmacokinetic/Correlative Biological Studies, Deleted Text (paragraph 2):

~~Preliminary work in a limited number of hepatoblastoma cell lines suggests that there may be tumor specific changes in gene expression that may correlate with response to pazopanib (personal communication, Dr. [REDACTED]). To further examine this possible relationship, blood and tissue samples will be requested from consenting hepatoblastoma patients.~~

Section 2.5 Overview of Proposed Pediatric Phase II Trial, Previous Text:

This is a two-stage open label phase II trial of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Tumors of primary interest are rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma (including synovial sarcoma, alveolar soft part sarcoma and desmoplastic small round cell tumor) and Ewing sarcoma. Tumors of secondary interest include hepatoblastoma, neuroblastoma (measurable and evaluable), and osteosarcoma.

Eligible patients will receive pazopanib daily as an oral tablet (450 mg/m²/dose) or as a powder for suspension (160 mg/m²/dose) in 28 day cycles. The maximum dose to be administered daily is 800 mg. Patients will be closely monitored with clinical and laboratory observations for adverse effects. Response will be evaluated using appropriate imaging studies after the 2nd cycle of pazopanib, after the 4th cycle, and then every 3rd cycle thereafter (baseline, prior to Cycle 3, prior to Cycle 5, prior to Cycle 8, prior to Cycle 11, etc). In the absence of severe toxicity or progressive disease, patients may continue receiving pazopanib for up to 2 years.

The study will be considered complete (analysis conducted and enrollment closed) when all subjects enrolled in the tumors of the primary interest strata have completed a minimum of 6 cycles of treatment, have disease progression, or have withdrawn from the study.

The first ten subjects enrolled on this trial will receive the suspension formulation during Cycle 1 with the option to change to the tablet formulation during Cycle 2 and subsequent cycles if they are able to swallow tablets and their BSA is ≥ 0.48 m². These subjects will have extended pharmacokinetic sampling with blood samples collected prior to dosing, 30 min, 1, 2, 4, 6, and 8 hours after the pazopanib dose on Days 1 and 15 of Cycle 1. Additional blood samples for analysis of steady state trough plasma pazopanib concentrations will be collected prior to every subsequent odd cycle (in conjunction with safety labs). All subsequent subjects (regardless of formulation) will have blood samples for analysis of plasma pazopanib concentration collected prior to dosing and 3 to 4 hours after dosing on Day 15 of Cycle 1. Additional blood samples for analysis of steady state trough plasma pazopanib concentrations will be collected prior to every subsequent odd cycle (in conjunction with safety labs).

[REDACTED] In addition, we will assess KDR polymorphism and pazopanib-induced change in VEGFR2; VEGFA haplotypes and changes in VEGF-A, response rate, and overall survival;

and candidate SNPs and clinical endpoints as identified in ongoing large scale studies of pazopanib in the adult population. [REDACTED]

Section 2.5 Overview of Proposed Pediatric Phase II Trial, Revised Text:

This is a two-stage open label phase II trial of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Tumors of primary interest are rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma (including synovial sarcoma, alveolar soft part sarcoma and desmoplastic small round cell tumor) and Ewing sarcoma. Tumors of secondary interest include hepatoblastoma, neuroblastoma (measurable and evaluable), and osteosarcoma.

Eligible patients will receive pazopanib daily as an oral tablet (450 mg/m²/dose) or as a powder for suspension (460 **225** mg/m²/dose) in 28 day cycles. The maximum dose to be administered daily **for tablets** is 800 mg **and for suspension 400 mg**. Patients will be closely monitored with clinical and laboratory observations for adverse effects. Response will be evaluated using appropriate imaging studies after the 2nd cycle of pazopanib, after the 4th cycle, and then every 3rd cycle thereafter (baseline, prior to Cycle 3, prior to Cycle 5, prior to Cycle 8, prior to Cycle 11, etc). In the absence of severe toxicity or progressive disease, patients may continue receiving pazopanib ~~for up to 2 years~~.

This study will dose patients requiring suspension with a starting dose of 225 mg/m²/dose.. The previously-defined suspension MTD of 160 mg/m²/dose may result in suboptimal exposure to demonstrate efficacy. Two of 4 patients in the prior Phase I study demonstrated DLTs in the form of isolated and reversible Grade 3 elevations in ALT at 225 mg/m²/dose. Given that this toxicity was isolated and reversible, the first 6 patients receiving suspension will be dosed at 225 mg/m²/dose and assessed for first-cycle DLTs before continuing to enroll additional patients requiring suspension. If two or more of 6 patients demonstrate DLT, then the dose may be de-escalated to the previously- defined MTD of 160 mg/m²/dose.

~~The first ten 6 subjects enrolled on this trial will receive who require the suspension formulation during Cycle 1 with the option to change to the tablet formulation during Cycle 2 and subsequent cycles if they are able to swallow tablets and their BSA is ≥0.48 m². These subjects will have extended PK sampling with blood samples collected prior to dosing, 30 min, 1, 2, 4, 6, and 8 hours after the pazopanib dose on Days 1 and 15 of Cycle 1. Additional blood samples for analysis of steady state trough plasma pazopanib concentrations will be collected prior to every subsequent odd cycle (in conjunction with safety labs). All subsequent~~ **All** subjects (regardless of formulation) will have blood samples for analysis of plasma pazopanib concentration collected prior to dosing and 3 to 4 hours after dosing on Day 15 of Cycle 1. Additional blood samples for analysis of steady state trough plasma pazopanib concentrations will be collected prior to every subsequent odd cycle (in conjunction with safety labs).

[REDACTED] In addition, we will assess KDR polymorphism and pazopanib-induced change in VEGFR2; VEGFA **genotype**/haplotypes and changes in VEGF-A, response rate, and overall survival; and candidate SNPs and clinical endpoints as identified in ongoing large scale studies of pazopanib in the adult population. [REDACTED]

The study will be considered complete (analysis conducted and enrollment closed) when all subjects enrolled in the tumors of the primary interest strata have completed a minimum of 6 cycles of treatment, have disease progression, or have withdrawn from the study.

Section 3.1.1 Patient Registration, Previous Text:

PatientRegistration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with registration, please refer to the online help.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Upon completion of all the required baseline assessments, eligible subjects will be registered into the GSK interactive voice response system called RAMOS (Registration And Medication Ordering System), by the investigator or authorized site staff for stratification. Subject number and histology strata (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma, Ewing Sarcoma/Peripheral PNET, osteosarcoma, neuroblastoma (measureable), neuroblastoma (evaluatable) or hepatoblastoma) must be entered into the system in order to register the patient with GSK.

All calls to RAMOS are confirmed with a fax, which will be sent to the site upon completion of each call. Study-specific instructional worksheets will be provided for the use of RAMOS in the Study Procedures Manual.

Section 3.1.1 Patient Registration, Deleted and AddedText:

No study specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines).

Paragraph 2 (deleted text) ~~A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.~~

Paragraph 3, sentence 1, added text:

Upon completion of all the required baseline assessments, eligible subjects will be registered into the GSK interactive voice response system called RAMOS (Registration and Medication Ordering System) **and will be assigned a GSK study specific number and a randomization number**, by the investigator or authorized site staff for stratification.

[REDACTED]

[REDACTED]

Section 3.2.3 Body Surface Area, Previous Text:

Body Surface Area (for subjects taking tablet formulation only): Patients who will be receiving the tablet

formulation must have a BSA $\geq 0.48 \text{ m}^2$ at the time of study enrollment.

Section 3.2.3 Body Surface Area, Revised Text:

Body Surface Area (for subjects taking tablet formulation only): Patients who will be receiving the tablet formulation must have a BSA $\geq 0.48 \text{ m}^2$ at the time of study enrollment.

Section 3.2.6.3 Adequate Liver Function define as, Previous Text:

Adequate Liver Function defined as:

- a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) for age;
- b. SGPT (ALT) $\leq 2.5 \times$ ULN (for the purpose of this study, the ULN for SGPT is 45 U/L);
- c. Serum albumin $\geq 2 \text{ g/dL}$.

Section 3.2.6.3 Adequate Liver Function define as, Added Text:

- d. **Must not have active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).**
 - o **NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.**
- e. **No known positivity of hepatitis B surface antigen (HBsAg), or of positive hepatitis C antibody**

Section 3.2.6.4 Adequate Cardiac Function defined as, Revised and Added Text:

- c. ~~QTc~~ QTcB $< 450 \text{ msec}$ (See Section 5.4.5.2 to determine QTcB)

Section 3.3.2.7 CYP3A4 Substrates and drugs causing QTc prolongation, Previous Text:

Patients receiving drugs metabolized through several of the specific P450 cytochrome isoforms and those receiving drugs with a known risk of torsades de pointes are not eligible. See Appendices IIIA and IIIB for a list of enzyme inducing, enzyme inhibiting and other adversely interacting drugs and the appropriate washout periods required prior to study enrollment. Note: This list includes the prohibition of grapefruit juice for 14 days prior to enrollment.

Section 3.3.2.7 CYP3A4 Substrates and drugs causing QTc prolongation, Revised Text:

Patients receiving drugs ~~metabolized through several of the specific P450 cytochrome isoforms and those receiving drugs~~ with a known risk of torsades de pointes are not eligible. See Appendices IIIA and IIIB **and Section 4.8** for a list of enzyme inducing, enzyme inhibiting and other adversely interacting drugs and the appropriate washout periods required prior to study enrollment.

Note: This list includes the prohibition of grapefruit juice for 14 days prior to enrollment.

Section 4.1 Overview of Treatment Plan, Previous Text:

Pazopanib will be administered orally once daily on a continuous schedule. Patients will be treated with

pazopanib tablets at a dose of 450 mg/m²/dose or as a powder in suspension at a dose of 160 mg/m²/dose (the MTDs determined by Part 1 and Part 2A respectively of ADVL0815, the COG Phase I study). Note: The first 10 patients enrolled will receive the suspension formulation in Cycle 1 in order to obtain extended pharmacokinetic sampling. These patients may then switch to tablet formulation in Cycle 2 and subsequent cycles provided that they are able to swallow tablets and meet the required minimum BSA criteria for tablets (see Section 3.2.3). Please note the difference in dosing for the tablet and suspension formulations (see above).

A cycle will be defined as 28 days with no rest periods between cycles. Patients may receive a maximum of 24 cycles. Patients with benefit (stable disease or an objective response) may continue therapy for up to 2 years unless there is evidence of progressive disease or unacceptable treatment-related toxicity

Drug dosing for the tablet formulation should be determined using the dosing nomogram in Appendix II and rounded to the nearest 50 mg. For patients receiving powder for suspension (50 mg/mL), the dose will be rounded to the nearest 5 mg. Drug doses should be adjusted based on the BSA as determined by the height and weight obtained within 1 week prior to the beginning of each cycle.

Pazopanib should be taken on an empty stomach (at least 1 hour before a meal or 2 hours after a meal) at approximately the same time each day. Pazopanib tablets should be taken with clear liquids (approximately 2-4 ounces for children < 12 years of age and 4-8 ounces for children ≥ 12 years of age). Pazopanib suspension should be taken according to instructions in Appendix VII. The pazopanib suspension should be swirled for at least 30 seconds prior to removal of the dose from the bottle, which should be given immediately. If a patient vomits after a dose of pazopanib, the dose should not be repeated.

Section 4.1 Overview of Treatment Plan, Revised Text:

Pazopanib will be administered orally once daily ~~on a continuous schedule. Patients will be treated with pazopanib tablets as a tablet~~ at a dose of 450 mg/m²/dose or as a powder in suspension at a dose of ~~160~~ 225 mg/m²/dose. **450 mg/m²/dose was the MTD for tablet as determined by Part 1 and Part 2A, respectively ADVL0815, the COG Phase I study, while the dose for oral suspension of 225 mg/m²/dose exceeds the protocol-specified MTD of 160 mg/m²/dose established in that study. Two isolated and reversible laboratory-defined DLTs were observed at 225 mg/m²/dose. The maximum dose to be administered daily for tablets is 800 mg and for suspension 400 mg. Each cycle will be defined as 28 days.**

Note: The first ~~10~~ 6 patients enrolled ~~will who receive the suspension formulation in Cycle 1~~ **will be expected to complete extended PK sampling (Section 7.3.2) in order to obtain extended pharmacokinetic sampling PK and safety data. These data will be reviewed prior to further enrollment of patients may then switch to tablet formulation in Cycle 2 and subsequent cycles provided that they are able to swallow tablets and meet the required minimum BSA criteria for tablets (see Section 3.2.3). Please note requiring suspension to determine if 225 mg/m²/dose is tolerated and PK exposure is similar to exposure in adults associated with clinical efficacy. If 225 mg/m²/dose is not tolerated (≥ 2 DLTs in 6 evaluable patients), the difference in dosing dose for the tablet and patients who require suspension formulation (see above) may be reduced to 160 mg/m²/dose.**

A cycle will be defined as 28 days with no rest periods between cycles. Patients ~~may receive a maximum of 24 cycles. Patients~~ with benefit (stable disease or an objective response) may continue therapy ~~for up to 2 years~~ unless there is evidence of progressive disease or unacceptable treatment-related toxicity.

Patients must remain on the same formulation of pazopanib throughout the duration of their protocol therapy.

Drug dosing for the tablet formulation should be determined using the dosing nomogram in Appendix II ~~and rounded to the nearest 50 mg~~. For patients receiving powder for suspension (50 mg/mL), the dose will be rounded to the nearest 5 mg. Drug doses should be adjusted based on the BSA as determined by the height

and weight obtained within 1 week prior to the beginning of each cycle.

Pazopanib should be taken on an empty stomach (at least 1 hour before a meal or 2 hours after a meal) at approximately the same time each day. Pazopanib tablets should be taken with clear liquids (approximately 4 ounces for children < 12 years of age and 4-8 ounces for children ≥ 12 years of age). Pazopanib suspension should be taken according to instructions in Appendix VII. The pazopanib suspension should be swirled for at least 30 seconds prior to removal of the dose from the bottle, which should be given immediately. If a patient vomits after a dose of pazopanib, the dose should not be repeated.

A patient diary (see Appendices IA and IB) should be completed by the patient or their guardian and collected at the end of each cycle.

See Section 5.0 for Dose Modifications based on Toxicities

Section 4.1.1 Dose Reduction, Previous Text:

For patients who receive pazopanib tablets: A step-wise dose reduction will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 4.2 within 7 days following planned administration (see dosing nomogram for tablets in Appendix II). The first dose reduction will be to 350 mg/m²/dose and then to 250 mg/m²/dose if necessary. If toxicity has not resolved at 250 mg/m²/dose, a further dose reduction to 200 mg/m²/dose may be considered **after discussion with the Study Chair**.

For patients who receive pazopanib powder in suspension: A stepwise dose reduction will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 4.2 within 7 days following planned administration. The first dose reduction will be to 135 mg/m²/dose and then to 100 mg/m²/dose if necessary. If toxicity has not resolved at 100 mg/m²/dose, a further dose reduction to 75 mg/m²/dose may be considered **after discussion with the Study Chair**.

Section 4.1.1 Dose Reduction, Revised Text:

For patients who receive pazopanib tablets: ~~A step-wise dose~~ Dose reduction(s) will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 4.2 ~~within 7~~ **within 14** days following planned administration (see dosing nomogram for tablets in Appendix II). ~~The first dose~~ **Dose** reduction(s) will be ~~to 350 mg/m²/dose and then to 250 mg/m²/dose if necessary.~~ If toxicity has not resolved at 250 mg/m²/dose, a further dose reduction to 200 mg/m²/dose may be considered ~~after discussion with the Study Chair~~ **based on the Study Chair starting dose**.

Note: For patients receiving pazopanib tablets at a starting dose of 400 mg, there will only be one allowed dose reduction due to tablet size.

For patients who receive pazopanib powder in suspension: A stepwise dose reduction (**Tables 1 and 1a**) will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 4.2 ~~within 7 days following planned administration.~~ ~~The first dose reduction will be to~~ 135 mg/m²/dose and then to 100 mg/m²/dose if necessary. ~~If toxicity has not resolved at 100 mg/m²/dose, a further dose reduction to 75 mg/m²/dose may be considered after discussion with the Study Chair~~ **14 days following planned administration.**

Table 1: Stepwise Dose Reduction for Toxicity if suspension starting dose 225 mg/m²

Starting Dose	225 mg/m²/dose
First Dose Reduction	160 mg/m²/dose

Table 1a: Stepwise Dose Reduction for Toxicity if suspension starting dose reduced to 160 mg/m²

Starting Dose	160 mg/m²/dose
First Dose Reduction	135 mg/m²/dose

Section 4.1.2 Dose Escalation, Previous Text:

There will be no inter-patient dose escalation. However, following a dose modification for drug related toxicity and subsequent resolution of the toxicity the dose can then be increased step-wise back to initial starting dose using the same doses used to titrate down. The subject should be monitored for 10-14 days at each step to ensure that toxicity does not recur or worsen.

Section 4.1.2 Dose Escalation, Revised Text:

~~There will be no inter-patient dose escalation. However, following a dose modification for drug related toxicity and subsequent resolution of the toxicity the dose can then be increased step-wise back to initial starting dose using the same doses used to titrate down. The subject should be monitored for 10-14 days at each step to ensure that toxicity does not recur or worsen.~~

Dose escalations will not be allowed.

Section 4.1.3 Treatment Interruptions, Previous Text:

If a patient's treatment has been interrupted for more than 14 days due to toxicity or for reasons other than toxicity (unplanned travel or vacation, or lack of transportation to the site), the Study chair must be notified to review the patient's condition in order to resume treatment. In cases of toxicity, the re-challenge is possible if the patient's condition has been stable and has not deteriorated and the patient must have recovered from toxicity at the reduced dose level.

Section 4.1.3 Treatment Interruptions, Revised Text:

If a patient's treatment has been interrupted for more than 14 days due to toxicity or for reasons other than toxicity (unplanned travel or vacation, or lack of transportation to the site), the Study Chair must be notified to review the patient's condition in order to resume treatment. In cases of toxicity, **the re-challenge at a reduced dose** is possible if the patient's condition has been stable and has not deteriorated and the patient must have recovered from **the toxicity at the reduced dose level.**(Section 4.2)

Section 4.1.4.1 Management of Hypertension, Added Text (paragraph 2):

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted **(by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent)** according to the algorithm in Section 5.4.1.

Section 4.1.4.3 Treatment of Palmer-Plantar Erythrodysesthesia (Hand-foot Syndrome), Added Text:

Other supportive care measures for the treatment of hand-foot syndrome should be instituted as needed. If steroids are used, they must fall within the dosing parameters in Section 4.8.

Section 4.2 Criteria for Starting Subsequent Cycles, Previous Text:

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 3.2.7, does not have a dose limiting toxicity requiring permanent removal from protocol therapy (Section 5.1) or a toxicity requiring resolution prior to resuming study drug (eg: hypertension, hepatotoxicity, electrolyte abnormality, bleeding, wound healing, etc) as outlined in Section 5.0.

Section 4.2 Criteria for Starting Subsequent Cycles, Revised Text:

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 3.2.6 **and**, does not have a dose limiting toxicity requiring permanent removal from protocol therapy (Section 5.1) ~~or a toxicity requiring resolution prior to resuming study drug (eg: A patient may resume study drug at the same or a reduced dose if they have a toxicity that is adequately managed (eg: myelosuppression,~~ hypertension, hepatotoxicity, electrolyte abnormality, bleeding, wound healing, etc) as outlined in Section 5.0.

Section 4.4 Permitted Medications, Added Text (paragraph 4):

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT₃ antagonists) may be administered prophylactically in the event of nausea. **However, it is important to note that 5-HT₃ blockers that are given daily for a prolonged period of time may prolong QTc and should be used with caution. (Appendix IIIB).** Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Section 4.4 Permitted Medications – Use with Caution, Added Text:

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 **benefitting from treatment and require the initiation of** concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) **while on study. Note: Subjects are excluded from enrolling on the study if they are taking therapeutic doses of S-warfarin at the time of screening.** 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.

Section 4.5.4 Added Text:

Concomitant administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by 40% (AUC and C_{max}), and co-administration of pazopanib with medicines that increase gastric pH should be avoided. **Co-administration of pazopanib with medicines that increase gastric pH is PROHIBITED from 24 hours before the first dose of pazopanib until after the final PK blood sample is collected on Day 15 \pm 1 day of Cycle 1.** After this, if the concomitant use of a proton-pump inhibitor (PPI) is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI (**Section 4.8**). If the concomitant administration of an H₂-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H₂-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids.

Section 4.5.5 Deleted Text:

Concurrent Anti-Hypertensive Therapy: The algorithm in Section 5.4.1 will be used to grade and manage

pazopanib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, ~~which are permissible without notifying the study chair~~) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 5.4.1. ~~If patients are already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted according to the algorithm in Section 5.4.1.~~ **may be started without notifying the study chair.**

Section 4.5.6 Added Text:

Patients' medications should be reviewed at eligibility, before treatment initiation, and during treatment. Any concomitant medications that are "generally accepted" to cause a risk of Torsade de pointes are prohibited (see Appendix IIIB). Those "associated" with a risk of QTc prolongation and/or Torsades de pointes should be discontinued or replaced with drugs that do not carry these risks, if possible. Patients who must take these medications should be watched carefully for symptoms of QTc prolongation, such as syncope. Performing additional EKGs on patients who must take one or more of these medications is recommended but not required, at the investigator's discretion.

Section 4.8 Prohibited Medications, Added Text:

- Glucocorticoids for greater than 2 weeks duration: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)

Grapefruit or grapefruit juice is prohibited as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

As noted above, co-administration of pazopanib with medicines that increase gastric pH is prohibited from 24 hours before the first dose of pazopanib until after the final PK blood sample is collected on Day 15 ± 1 day of Cycle 1.

Section 4.9 and 4.10 Therapy Delivery Maps, Summary of Changes:


Dose for powder in suspension was changed from 160 to 225 mg/m² and max dose was changed to 400 mg

Minor formatting changes were made throughout in the tables included in these sections

Section 5.1.1 Non-hematological Dose-Limiting Toxicity, Deleted Text:

- ~~Grade 3 elevation of AST or ALT that returns to ≤5xULN within 7 days of treatment interruption and does not recur with the introduction of pazopanib. Note: for the purposes of this trial the ULN for ALT is defined as 45 U/L.~~

Section 5.1.2.4 Added Text:

Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption **may also be considered a DLT following discussion with the Study chair and a GSK medical monitor.**

Section 5.1.2 Hematological Dose Limiting Toxicity, Deleted Text:

~~Note: Grade 4 febrile neutropenia will not be considered a dose limiting toxicity~~

Section 5.2 Dose Modifications for Hematologic Toxicity, Previous Text (paragraphs 3 and 4):

Pazopanibtablets: For step-wise dose reductions (350 mg/m²/dose then 250 mg/m²/dose), see Appendix II for the dosing nomogram.

Pazopanibpowderinsuspension: For step-wise dose reductions (135 mg/m²/dose then 100 mg/m²/dose), see Appendix II for the dosing nomogram.

Section 5.2 Dose Modifications for Hematologic Toxicity, Revised Text (paragraphs 3 and 4):

Pazopanibtablets: For step-wise dose reductions (~~350mg/m²/dose then 250mg/m²/dose~~), see Appendix II for the dosing nomogram.

Pazopanibpowderinsuspension: For step-wise dose reductions (~~135mg/m²/dose then 100mg/m²/dose~~), see Appendix II for the dosing nomogram see **Tables I and Ia (Section 4.1.1)**

Section 5.2.2 Previous Text:

Patients who have a dose limiting hematological toxicity that does not resolve to baseline within 21 days of holding pazopanib, must be removed from protocol therapy.

Section 5.2.2 Revised Text:

Patients who have a dose limiting hematological toxicity that does not resolve to baseline **the parameters defined in Section 5.2.2** within ~~24~~ 28 days of holding pazopanib, **if re-challenge is to be considered the study chair** must be ~~removed from protocol therapy~~ **contacted and provide approval prior to re-challenge.**

Section 5.3 Dose Modifications for Non-Hematological Toxicity, Added Text:

Specific instructions for the management of potential pazopanib side effects are included in Section 5.4.

Section 5.4.2 Hepatotoxicity, Previous Text:

Adverse events & descriptions	Dose Modifications & Evaluations
Grade 1 ALT/AST elevation	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose. 2. Check liver function tests (LFTs)¹ as per protocol
Grade 2 ALT/AST elevation without bilirubin elevation (defined as total bilirubin ² < 1.5 x ULN or direct bilirubin ≤ 35% of total bilirubin) and without hypersensitivity symptoms (eg: fever, rash)	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Consider performing the following to exclude hypersensitivity and other contributing factors: <ol style="list-style-type: none"> a. Eosinophil count b. Viral serology⁴ for hepatitis A, B and C c. Liver imaging (Ultrasound) 3. Monitor patient closely for clinical signs and symptoms 4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until AST/ALT ≤ Grade 1

<p>Grade 3 ALT elevation without bilirubin elevation (defined as total bilirubin² < 1.5 x ULN or direct bilirubin ≤35% of total bilirubin) and without hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>1st occurrence–LiverEventInterruptionCriteria³:</u></p> <ol style="list-style-type: none"> 1. Hold pazopanib until ALT resolves to ≤ Grade 1 or baseline. 2. Re-check LFT's¹ within 72 hrs 3. Perform the following assessments to exclude hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Liver imaging (Ultrasound) 4. Monitor patient closely for clinical signs and symptoms
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	<p>5. Perform LFTs¹ weekly (or more frequently if clinically indicated) until ALT reduced to \leq Grade 1</p> <p>6. If the patient is benefitting from the study treatment, contact Study Chair for possible re-challenge. Re-treatment may be considered at the same dose if ALL of the following criteria are met:</p> <ul style="list-style-type: none"> • ALT/AST reduced to \leq Grade 1 • Total bilirubin $< 1.5 \times$ ULN or direct bilirubin $\leq 35\%$ of total bilirubin • No hypersensitivity signs or symptoms • Patient is benefitting from therapy <p>If approval for re-treatment is granted, the patient must be re-consented (with a separate informed consent specific to hepatotoxicity).</p> <p><u>Recurrence of toxicity – Liver Event Stopping Criteria³</u></p> <ol style="list-style-type: none"> 1. Discontinue pazopanib permanently 2. Monitor patient closely for clinical signs and symptoms 3. Perform LFTs¹ weekly (or more frequently if clinically indicated) until ALT/AST is \leq Grade 1
<p>\geq Grade 2 ALT <u>AND</u> elevation in bilirubin² (defined as total bilirubin $> 1.5 \times$ ULN and direct bilirubin $> 35\%$ of total bilirubin) or with hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>LiverEventStoppingCriteria³:</u></p> <ol style="list-style-type: none"> 1. Discontinue pazopanib permanently 2. Recheck LFT's¹, serum creatinine phosphokinase (CPK) and collect PK sample. Also check: <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein-Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Anti-nuclear antibody⁴, anti-smooth muscle antibody⁴, anti-mitochondrial antibody⁴ • Liver imaging (Ultrasound) 3. Recommend referral to (consult) a pediatric gastroenterologist/hepatologist. 4. Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs¹ weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
<p>For isolated total bilirubin² elevation without concurrent ALT increase (defined as ALT $< 3 \times$ ULN).</p>	<ol style="list-style-type: none"> 1. Isolated hyperbilirubinemia (in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Study treatment inhibits UGT1A1 and

	<p>OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.</p> <p>2. If bilirubin is $> 1.5 \times \text{ULN}$ in the absence of ALT elevation, fractionation of bilirubin should be performed. If the bilirubin is predominantly indirect (unconjugated), continue study treatment at the same dose. If bilirubin is $>35\%$ direct (conjugated), further evaluation should be undertaken for underlying cause of cholestasis</p>
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Section 5.4.2 Hepatotoxicity, Revised Text:

Adverse events & descriptions	Dose Modifications & Evaluations
Grade 1 ALT/AST elevation	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose. 2. Check liver function tests (LFTs)¹ as per protocol
Grade 2 ALT/AST elevation without bilirubin elevation (defined as total bilirubin ² $< 1.5 \times \text{ULN}$ or direct bilirubin $\leq 35\%$ of total bilirubin) and without hypersensitivity symptoms (eg: fever, rash)	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Consider performing the following to exclude hypersensitivity and other contributing factors: <ol style="list-style-type: none"> a. Eosinophil count b. Viral serology⁴ for hepatitis A, B and C c. Liver imaging (Ultrasound) 3. Monitor patient closely for clinical signs and symptoms 4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until AST/ALT \leq Grade 1
Grade 3 ALT elevation without bilirubin elevation (defined as total bilirubin ² $< 1.5 \times \text{ULN}$ or direct bilirubin $\leq 35\%$ of total bilirubin) and without hypersensitivity symptoms (e.g., fever, rash)	<p>1. ^{stn} occurrence – Liver Event Interruption/Stopping Criteria³:</p> <ol style="list-style-type: none"> 1. Hold pazopanib until ALT resolves to \leq Grade 1 or baseline. 2. Re-check LFTs¹ Repeat LFTs¹ within 72 hrs to confirm \geq Grade 3 ALT elevation, if confirmed 3. Perform the following assessments to exclude hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Liver imaging (Ultrasound) 4. Monitor patient closely for clinical signs and symptoms 5. Perform LFTs¹ weekly (or more frequently if clinically indicated) until ALT reduced to \leq Grade 1 6. If the Pazopanib may be held for up to 14

	<p>days, if ALT returns to \leq Grade 1 and patient is benefitting from the study treatment, contact Study Chair for possible re-challenge. Re-treatment may be considered if ALL of the following GSK governance approval (contact a GSK medical monitor via email or phone to start the approval process) criteria are met:</p> <ul style="list-style-type: none"> • ALT/AST reduced to \leq Grade 1 • Total bilirubin $< 1.5 \times$ ULN and direct bilirubin $< 35\%$ of total bilirubin • No hypersensitivity signs or symptoms • Patient is benefitting from therapy <p>If approval for re-treatment is granted, the patient must be re-consented (with a separate informed consent specific to hepatotoxicity).</p> <ul style="list-style-type: none"> • For patients on tablets dose reductions are as follows: <ul style="list-style-type: none"> ○ If on 800 mg, then reduce to 400 mg daily ○ If on 600 mg, then reduce to 400 mg daily ○ If on 400 mg, reduce to 200 mg daily • For patients on suspension: <ul style="list-style-type: none"> ○ Follow the sequential dose reduction (Section 4.1.1.), one dose level reduction is required (e.g. from 225 mg/m² to 160 mg/m²) <p>Following re-introduction of pazopanib, continue to monitor ALT weekly for 2 cycles, if ALT \geq Grade 2 recurs permanently discontinue pazopanib.</p> <p>1.</p>
<p>\geq Grade 2 ALT <u>AND</u> elevation in bilirubin² (defined as total bilirubin $> 1.5 \times$ ULN and or direct bilirubin $> 35\%$ of total bilirubin) or with hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>Liver Event Stopping Criteria</u>³:</p> <ol style="list-style-type: none"> 1. Discontinue pazopanib permanently 2. Recheck LFT's¹, serum creatinine phosphokinase (CPK) and collect PK sample. Also check: <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein-Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Anti-nuclear antibody⁴, anti-smooth

	<p>muscle antibody⁴, anti-mitochondrial antibody⁴</p> <ul style="list-style-type: none"> • Liver imaging (Ultrasound) <p>3. Recommend referral to (consult) a pediatric gastroenterologist/hepatologist.</p> <p>4. Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs¹ weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.</p>
For isolated total bilirubin ² elevation without concurrent ALT increase (defined as ALT < 3 x ULN).	<p>1. Isolated hyperbilirubinemia (in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Study treatment inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.</p> <p>2. If bilirubin is > 1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin should be performed. If the bilirubin is predominantly indirect (≥65% indirect (unconjugated), continue study treatment at the same dose. If bilirubin is >35% direct (conjugated), study treatment may also be continued however, further evaluation should be undertaken for underlying cause of cholestasis</p>

Section 5.4.5.2 QTcB Prolongation, Revised Text:

QTc was changed to QTcB throughout this section.

Section 5.3.1 was to Section 4.5.6

Section 5.4.6 Delays in Wound Healing, Added Text:

Patients treated with VEGF blocking agents appear to have an increased risk of wound healing complications. Therefore, if patients require **elective** major surgery on study, pazopanib should be held for 14 days prior to surgery and for 14 days after surgery. **Pazopanib should not be restarted if there is evidence of wound healing complications such as a wound infection.** Patients who require surgery less than 14 days from treatment with pazopanib should be monitored closely for wound complications. Patients who require major surgery during Cycle 1 of therapy must be removed from protocol therapy.

Section 5.4.7 Bleeding, Deleted Text, (4th Row of Table):

Grade 3 or higher <u>OR</u> Recurrent \geq Grade 2 event after dose interruption/reduction	Discontinue pazopanib permanently and remove from protocol therapy Note: If abnormality is not clearly associated with clinical consequences; may contact Study Chair to discuss restarting pazopanib at a reduced dose
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Section 6.1 Pazopanib (Formulation and Stability), Deleted Text:

- ~~50mg, round, white to off-white, packaged in bottles containing 17 tablets each~~

Section 7.0 Evaluations/Material and Data to be Accessioned, Deleted Text:

~~Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol). This policy does NOT apply to eligibility requirements; but to therapy and evaluations post consent and post the start of protocol directed care. GSK will not grant protocol waivers.~~

Section 7.1 Required [REDACTED] Clinical, Laboratory and Disease Evaluation, Revised Text:

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent cycles ¹	During Subsequent Cycles	End of Therapy ²
Serum AFP ¹²	X	End of cycle	Prior to Cycle 3, 5, 8, 11 and every 3 rd cycle thereafter ¹¹		X
Serum Pregnancy Test ¹⁴	X	-	X	-	

[REDACTED]

Change to footnotes:

6. If patient has LFT elevation repeat LFTs as described in Section 5.4.2.

11. Disease evaluation should be performed during Days 24 – 28 of the cycle for the first 2 assessments and Days 21 – 28 of subsequent indicated cycles. Patients who achieve a PR or CR should undergo the appropriate disease evaluation on the next consecutive cycle after initial documentation of either a PR or CR. Please note, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

A disease evaluation at Cycle 23 will not be required; however an end of study disease assessment should be completed

14. **Females** of childbearing potential require a negative **serum** pregnancy test prior to starting treatment.

[REDACTED]

Section 7.2.4 Pregnancy Testing and Reporting, Section Added:

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential. If a female subject is of childbearing potential, she must have a serum β -Human Chorionic Gonadotropin (β -HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below during the study until 30 days following the last dose of study treatment(s). Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. Study treatment should be immediately discontinued if pregnancy occurs during study participation. 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 study treatment(s), must be promptly reported to GSK.

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 GSK as described above.

Section 7.3.2 Sampling Schedule, Previous Text (paragraph 2):

Extended pharmacokinetic sampling will be done in the first 10 patients enrolled (who will all receive the suspension formulation in Cycle 1). These patients will have a blood sample for analysis of the plasma pazopanib concentration collected at the following time points on Day 1 of Cycle 1: pre-dose, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. Samples will also be obtained on Day 15 \pm 1 day of Cycle 1: pre-dose, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. Additional blood samples for analysis of steady-state trough plasma pazopanib concentrations will be obtained prior to the start of every odd cycle. **The pre-dose sample on Day 15, Cycle 1 and trough plasma concentrations should be obtained between 22-26 hours after the previous dose of pazopanib.** Subjects should be instructed to hold their dose of pazopanib on the day that a pre-dose concentration is to be collected. These specimens should correspond to the timing of routine laboratory evaluations.

Section 7.3.2 Sampling Schedule, Revised Text (paragraph 2):

Extended pharmacokinetic sampling will be done in the first ~~10~~ 6 patients enrolled (who ~~will~~ receive the suspension formulation in Cycle 1). These patients will have a blood sample for analysis of the plasma pazopanib concentration collected at the following time points on Day 1 of Cycle 1: pre-dose, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. Samples will also be obtained on Day 15 \pm 1 day of Cycle 1: pre-dose, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. ~~Additional~~ **For all patients additional** blood samples for analysis of steady-state trough plasma pazopanib concentrations will be obtained prior to the start of every odd cycle. **The pre-dose sample on Day 15, Cycle 1 and trough plasma concentrations should be obtained between 22-26 hours after the previous dose of pazopanib.** Subjects should be instructed to hold their dose of pazopanib on the day that a pre-dose concentration is to be collected. These specimens should correspond to the timing of routine laboratory evaluations.

Section 7.4.1.2 Tumor Tissue, Deleted

~~Tumor tissue as well as a peripheral blood sample should be submitted if available for molecular (DNA, RNA and protein) studies including expression array analysis to determine molecular signatures associated with both relapse status as well as response to pazopanib.~~

Section 7.4.2.1.2, Revised Text:

~~Patients~~ **Sampling for circulating plasma levels of angiogenic cytokines for patients** who consent will have a specimen obtained ~~for~~ on Day 1, Cycle 1 prior to drug administration and during Week 4 or Week 8 (Section 7.1)

Section 7.4.2.1.2, Revised Text:

Patients who consent to VEGF haplotype on Day 1, Cycle 1 prior to drug administration and during Week 4 or Week 8.

Sections 7.4.2.2 Tumor Tissue and Section [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Section 8.0 Criteria for Removal from Protocol Therapy and Off Study Criteria, Revised Text:

- h) Repeat eligibility studies (if required) are outside the parameters required for ~~eligibility~~ **continued dosing as stated in Section 4.2.**
- k) Patient becomes pregnant

Section 9.3 Analysis Populations, Previous Text:

The Intent-to-Treat (ITT) population will comprise all subjects entered into the study. This population will be used for the analysis of efficacy.

Section 9.3 Analysis Populations, Revised Text:

The **Target** Intent-to-Treat (~~ITT~~tITT) population will comprise all subjects entered into the study **at the target dose. This population** **If after the first 6 subjects, the suspension dose is de-escalated to 160 mg/m²/dose then only the 160 mg/m²/dose subjects will be used for the analysis of efficacy data included in the tITT. All subjects taking the tablets will be included in the tITT.**

Section 9.8.2.5 Safety Measures, Added Text, (paragraph 1):

If there are multiple doses for the suspension then these will be presented in separate columns.

Section 9.12 Analysis of the Pharmacokinetic Parameters, Previous Text (paragraph 1, sentence 1):

Plasma pazopanib concentrations observed after administration of the suspension in the first 12 subjects enrolled in the study will be analyzed with standard noncompartmental methods using WinNonlin version 5.2 or higher.

Section 9.12 Analysis of the Pharmacokinetic Parameters, Revised Text (paragraph 1, sentence 1):

Plasma pazopanib concentrations observed after administration of the suspension in the first ~~12~~ 6 subjects enrolled in the study will be analyzed with standard noncompartmental methods using WinNonlin version 5.2 or higher.

Section 10.2 Response Criteria, Added Text (paragraph 1):

c) hepatoblastoma (Section 10.6)

Section 11.0 Adverse Event (AE) and Serious Adverse Events (SAE), Added Text:

Changes were made throughout this section to include that both GSK and COG will be notified of any serious adverse event within 24 hours as indicated in Section 11.7 of the protocol.

Section 11.1 Definition of Adverse Events (AEs), Added Text (paragraph 1):

CTCAE criteria version 4.0 will be used to grade severity of adverse events.

Section 11.2 Definition of Serious Adverse Events (SAEs), Deleted Text:

- ~~Protocol specific SAEs: squamous cell carcinoma, LVEF meeting stopping criteria, treatment emergent malignancies [basal cell carcinoma (BCC) is not required to be reported as a protocol specific SAE and it should be reported as an AE or SAE based on the discretion of the investigator]; fever accompanied by hypotension, dehydration requiring IV fluids, renal insufficiency and/or severe (\geq Grade 3) rigors/chills in the absence of an obvious infectious cause.~~

APPENDIX 1A: Patient Diary for Pazopanib Tablets, Deleted Text:

The column for 50 mg strength tablets was removed from the diary.

APPENDIX II: Pazopanib Dosing Nomogram for Tablets, Revised Table:

	Starting Dose	Dose Reduction #1	Dose Reduction #2
	450 mg/m ² /dose		
BSA*	Dose (mg) [†]		
0.84-0.94	400	200	0
0.95-1.05	400	200	0
1.06-1.16	400	200	0
1.17-1.27	600	400	200
1.28-1.38	600	400	200
1.39-1.50	600	400	200
1.51-1.61	600	400	200
1.62-1.72	800	600	400
≥ 1.73	800	600	400

Appendix III A: Title Changed From:

LIST OF KNOWN CYTOCHROME P450 P34A INHIBITORS AND INDUCERS

Appendix III A: Title Changed to:

LIST OF ANTICONVULSANT DRUGS THAT ARE ALLOWED

Appendix VI: Pharmacokinetic Study Form, Revised Text (footnote **)

These extended PK timepoints are to be collected in the 1st 106 patients **who require suspension enrolled on study
(~~and will receive suspension formulation~~)

13.13 APPENDIX XI AMENDMENT 03

Where the Amendment Applies

Amendment 03 applies to all sites who will conduct the study.

Minor administrative changes, including section number changes and minor changes to the text that do not impact the study conduct are not included in the summary below.

List of Abbreviations, Added Table

Experimental Design Schema Previous Text:

Pazopanib will be administered orally once daily as a tablet at 450 mg/m²/dose or as a powder in suspension at 225 mg/m²/dose. The maximum tolerated dose (MTD) for tablets was 450 mg/m²/dose as determined by ADVL0815, the COG Phase I study, while the dose for oral suspension of 225 mg/m²/dose exceeds the protocol-specified MTD of 160 mg/m²/dose established in that study. The 225 mg/m²/dose is where two isolated laboratory-defined dose-limiting toxicities (DLTs) were observed. The maximum dose to be administered daily for tablets is 800 mg. The maximum dose to be administered daily for suspension is 400 mg. Each cycle will be defined as 28 days.

The first 6 patients enrolled who receive suspension will be expected to complete extended pharmacokinetic (PK) sampling (Section 7.3.2) in order to obtain PK and safety data. These data will be reviewed prior to further enrollment of patients requiring suspension to determine if 225 mg/m²/dose is tolerated and PK exposure is similar to exposure in adults associated with clinical efficacy. If the 225 mg/m²/dose is not tolerated (≥ 2 dose limiting toxicities (DLTs) in 6 evaluable patients), the dose for patients who require suspension may be reduced to 160 mg/m²/dose.

Patients with benefit (stable disease or an objective response) may continue therapy (in the absence of unacceptable treatment related toxicity) unless there is evidence of progressive disease or unacceptable treatment-related toxicity.

Experimental Design Schema Revised Text:

This is an open label phase II trial designed to primarily assess the efficacy of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Patients will receive pazopanib monotherapy and the term “protocol therapy” will be used throughout this document to designate pazopanib monotherapy.

Pazopanib will be dosed daily as an oral tablet (450 mg/m²/dose, maximum 800 mg) or as an oral powder for suspension (225 mg/m²/dose, maximum 400 mg). Each cycle will be defined as 28 days, with no rest periods between cycles.

The first patients enrolled who receive powder suspension will be expected to complete extended pharmacokinetic (PK) sampling (Section 7.3.2) in order to obtain PK and safety data in 6 evaluable patients. If the 225 mg/m²/dose is not tolerated (≥ 2 patients with dose limiting toxicities (DLTs) in the first 6 evaluable patients), subsequent new patients will be enrolled at the 160 mg/m²/dose level until 6 evaluable patients are available for the safety review and the PK analysis.

Patients with benefit (stable disease or an objective response) may continue therapy unless there is evidence of progressive disease, unacceptable treatment-related toxicity, until death or until study closure [defined as 1 year after Last Patient First Visit (LPFV)], whichever occurs first.

Section 1.1 Primary Aims, Previous Text:

1.1.1. To determine the investigator assessed objective response rate of pazopanib in children, adolescents and young adults (subjects) with relapsed or refractory rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue

sarcomas, and Ewing sarcoma.

Section 1.1 Primary Aims, Revised Text:

1.1.1 To determine the investigator- assessed objective response rate of pazopanib in children, adolescents and young adults (patients) with relapsed or refractory solid tumors of the following types (each defining a cohort):

1. rhabdomyosarcoma,
2. non-rhabdomyosarcomatous soft tissue sarcoma, or
3. Ewing sarcoma/peripheral Primitive Neuro Ectodermal Tumor (PNET).

Section 1.2 Secondary Aims, Previous Text:

1.2.8 To further assess VEGF and KDR genotype/phenotype relationships in subjects with cancer treated with pazopanib.

Section 1.2 Secondary Aims, Revised Text:

1.2.8 To further assess VEGF-A and KDR genotype, their plasma concentration relationships in patients with cancer treated with pazopanib.

1.2.10 To assess overall survival (OS) in patients with relapsed or refractory solid tumors per cohort (described under Section 1.1.1 and 1.2.1).

Section 2.5 Overview of Proposed Pediatric Phase II Trial, Previous Text:

This is a two-stage open label phase II trial of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Tumors of primary interest are rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma (including synovial sarcoma, alveolar soft part sarcoma and desmoplastic small round cell tumor) and Ewing sarcoma. Tumors of secondary interest include hepatoblastoma, neuroblastoma (measurable and evaluable), and osteosarcoma.

Eligible patients will receive pazopanib daily as an oral tablet (450 mg/m²/dose) or as a powder for suspension (225 mg/m²/dose) in 28 day cycles. The maximum dose to be administered daily for tablets is 800 mg and for suspension 400 mg. Patients will be closely monitored with clinical and laboratory observations for adverse effects. Response will be evaluated using appropriate imaging studies after the 2nd cycle of pazopanib, after the 4th cycle, and then every 3rd cycle thereafter (baseline, prior to Cycle 3, prior to Cycle 5, prior to Cycle 8, prior to Cycle 11, etc). In the absence of severe toxicity or progressive disease, patients may continue receiving pazopanib.

This study will dose patients requiring suspension with a starting dose of 225 mg/m²/dose. The previously-defined suspension MTD of 160 mg/m²/dose may result in suboptimal exposure to demonstrate efficacy. Two of 4 patients in the prior Phase I study demonstrated DLTs in the form of isolated and reversible Grade 3 elevations in ALT at 225 mg/m²/dose. Given that this toxicity was isolated and reversible, the first 6 patients receiving suspension will be dosed at 225 mg/m²/dose and assessed for first-cycle DLTs before continuing to enroll additional patients requiring suspension. If two or more of 6 patients demonstrate DLT, then the dose may be de-escalated to the previously-defined MTD of 160 mg/m²/dose.

The first 6 subjects who require the suspension formulation will have extended PK sampling with blood samples collected prior to dosing, 30 min, 1, 2, 4, 6, and 8 hours after the pazopanib dose on Days 1 and 15 of Cycle 1. All subjects (regardless of formulation) will have blood samples for analysis of plasma pazopanib concentration collected prior to dosing and 3 to 4 hours after dosing on Day 15 of Cycle 1. Additional blood samples for analysis of steady state trough plasma pazopanib concentrations will be collected prior to every subsequent odd cycle (in conjunction with safety labs).

(PLGF), VEGFR2, and endoglin. In addition, we will assess KDR polymorphism and pazopanib-induced change in VEGFR2; VEGFA genotype/haplotypes and changes in VEGF-A, response rate, and overall survival; and candidate SNPs and clinical endpoints as identified in ongoing large scale studies of pazopanib in the adult population.

The study will be considered complete (analysis conducted and enrollment closed) when all subjects enrolled in the tumors of the primary interest strata have completed a minimum of 6 cycles of treatment, have disease progression, or have withdrawn from the study.

Section 2.5 Overview of Proposed Pediatric Phase II Trial, Revised Text:

This is a two-stage open label phase II trial of pazopanib in children, adolescents and young adults with recurrent or refractory solid tumors. Tumors of primary interest are rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma (including synovial sarcoma, alveolar soft part sarcoma and desmoplastic small round cell tumor) and Ewing sarcoma/peripheral PNET. Tumors of secondary interest include hepatoblastoma, neuroblastoma (measurable and evaluable), and osteosarcoma.

Each tumor type defines a cohort resulting in 7 total cohorts. The first stage of the study involves enrolling an initial 10 patients into each cohort. The response rate will be determined for each cohort after the target enrollment of 10 patients is reached for that cohort. If one or more confirmed responses are observed in the first 10 evaluable patients in a cohort, an additional 10 patients will be enrolled into that cohort in the second stage of study. Thus, for cohort(s) with one or more confirmed responses in the first stage of study, a total of 20 patients will be enrolled and evaluated to determine efficacy.

Eligible patients will receive pazopanib monotherapy. Pazopanib will be dosed daily as an oral tablet (450 mg/m²/dose, maximum 800 mg) or as a powder for oral suspension (225 mg/m²/dose, maximum 400 mg) in 28 day cycles.

The MTD for pazopanib tablets was 450 mg/m²/dose as determined by ADVL0815/PZP114411, the COG Phase I study in children with relapsed or refractory solid tumors. For the powder suspension formulation, the selected starting dose is higher than the protocol-defined MTD of 160 mg/m²/dose established in ADVL0815. This decision is driven by the considerations that the 160 mg/m²/dose may result in exposure that is suboptimal to demonstrate efficacy and that only two isolated and reversible laboratory-defined DLTs were observed at the 225 mg/m²/dose.

The first patients who are enrolled to receive pazopanib as powder suspension at 225 mg/m²/dose daily will be closely monitored for safety and for the occurrence of dose-limiting toxicity during the first cycle (28 days) of therapy. Patients who either receive 225 mg/m²/dose daily for at least 24 days (85% of the dose for a 28-day cycle with powder suspension at 225 mg/m²/dose) or are withdrawn from dosing due to one or more protocol-defined dose-limiting toxicities (Section 5.1) during the first cycle will be considered evaluable for the purpose of this safety review. Six evaluable patients are required.

The first patients enrolled to receive powder suspension at 225 mg/m²/dose will also be expected to complete extended PK sampling (Section 7.3.2) with blood samples collected prior to dosing, and 30 min, 1, 2, 4, 6, and 8 hours after the pazopanib dose on Day 1 and Day 15 ± 1 day of Cycle 1 (with no pazopanib dose modification or adjustment in the 10 days before Cycle 1 Day 15 sample collection). Patients who can provide adequate blood samples for the 2 scheduled extended PK collections will be considered to be evaluable patients for the purpose of this PK analysis, and PK data are required from 6 evaluable patients. If one or more of the first 6 patients fails to provide blood samples as specified in the protocol or if it is known that for some reason a patient's collected blood sample(s) cannot be analyzed, that patient will be determined to be non-evaluable for this analysis, and one or more additional patients will be enrolled for treatment with pazopanib as powder suspension for the purpose of obtaining the extended PK samples.

Because patients receiving the powder suspension enrolled in the safety review group may be different from those in the PK analysis group, enrollment onto powder suspension may follow several different paths:

- If ≥ 2 out of 6 evaluable patients have dose-limiting toxicities (DLT and as defined in Section 5.1) within the first cycle, then enrollment onto 225 mg/m²/dose pazopanib will be halted. Subsequent new patients will be enrolled at the 160 mg/m²/dose level until 6 evaluable patients from this dose group are available for the safety review and 6 patients are available

for PK analysis at 160 mg/m²/dose.

- If 6 PK evaluable patients are enrolled prior to enrollment of 6 patients who are evaluable for the safety review, the extended PK sample collection may be suspended.
- If < 2 DLTs are observed during the first cycle in 6 patients evaluable for safety at 225 mg/m²/dose and these 6 patients are not all evaluable for the PK analysis, then enrollment will continue until 6 PK evaluable patients are available.

All patients will be closely monitored with clinical and laboratory observations for adverse effects.

Tumor response will be evaluated using appropriate imaging assessments at baseline, prior to Cycle 3, Cycle 5, Cycle 8, Cycle 11 and then every 3rd cycle thereafter.

[REDACTED] In addition, we will assess KDR polymorphism and pazopanib-induced change in soluble VEGFR2; VEGF-A genotype and changes in VEGF-A concentration; KDR and VEGF-A genotypes and response rate, and progression-free survival; and candidate SNPs and clinical endpoints as identified in the adult population.

The primary analysis will be performed 20 weeks after the last patient's first visit in the three cohorts of primary interest (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma and Ewing sarcoma/peripheral PNET).

The study will be completed one year from the date of the last patient's first visit and the end of study analysis will be performed at the time of study completion.

For patients who are still on treatment and continue to derive benefit from it at the time of study completion, and for whom no other treatment options are available, Novartis will discuss individual patient cases with investigators to identify possible access to study treatment after termination of the VEG116731/ADVL1322/PZP034X2203 trial.

A patient will be considered to have completed the study if the patient:

- Dies while on study and prior to study completion
- Stays on study in follow-up until the time of study completion

Section 3.1.1 Patient Registration, Previous Text (Paragraphs 1, 3, 4):

No study specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines).

Upon completion of all the required baseline assessments, eligible subjects will be registered into the GSK interactive voice response system called RAMOS (Registration and Medication Ordering System) and will be assigned a GSK study specific number and a randomization number, by the investigator or authorized site staff for stratification. Subject number and histology strata (rhabdomyosarcoma, non- rhabdomyosarcomatous soft tissue sarcoma, Ewing Sarcoma/Peripheral PNET, osteosarcoma, neuroblastoma (measureable), neuroblastoma (evaluable) or hepatoblastoma) must be entered into the system in order to register the patient with GSK.

All calls to RAMOS are confirmed with a fax, which will be sent to the site upon completion of each call. **Study-specific instructional worksheets will be provided for the use of RAMOS in the Study Procedures Manual.**

Section 3.1.1 Patient Registration, Revised Text (Paragraphs 1, 3, 4):

No study-specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines), defining the study entry.

Upon completion of all required baseline assessments, the investigator or authorized site staff will assign each eligible patient a Sponsor study-specific patient identification number. Each site will be assigned a range of patient numbers, and this information is provided in the Study Procedure Manual (SPM). The patient ID number

consists of 6 digits including leading zeros. Using this patient ID number and patient's histology cohort (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma, Ewing sarcoma/peripheral PNET, osteosarcoma, neuroblastoma (measureable), neuroblastoma (evaluable) or hepatoblastoma), each patient will then be registered into the interactive voice response system RAMOS (Registration and Medication Ordering System). RAMOS will then provide an identification number consistent with the patient's tumor type.

All calls to RAMOS are confirmed (with a fax or e-mail), which will be sent to the site upon completion of each call. Study-specific instructional worksheets will be provided for the use of RAMOS in the Study Procedures Manual.

Section 3.1.2 Patient Rescreening, Added Text:

Patients may be rescreened if the reasons for the initial screen failure were non-medical or if the medical issues leading to screen failure have resolved. Approval by the Study Chair is required prior to rescreening. A new informed consent form must be signed. Please refer to detailed instructions in the Study Procedure Manual for rescreening.

Section 3.1.4 Study Enrollment Status, Added Text:

While the study remains open for enrollment, enrollment into each cohort will proceed independently from the other cohorts (see Section 9.2 for details). The enrollment in the cohorts of secondary interest may remain open if after review of the data, an efficacy signal is seen.

Section 3.1.6 Requirements to Initiate Protocol Therapy, Previous Text:

Imaging Studies: Imaging studies must be performed within 14 calendar days of initiating protocol therapy. If more than 14 calendar days have elapsed between the date imaging studies to determine eligibility were obtained (Section 3.2) and the enrollment date, then repeat imaging studies must be obtained prior to initiating protocol therapy.

Cardiac studies: Cardiac ECHO and electrocardiogram (ECG) must be performed within 14 calendar days of initiating protocol therapy. If more than 14 days have elapsed between the date imaging studies to determine eligibility were obtained (Section 3.2.6.4) and the enrollment date, then repeat imaging studies must be obtained prior to initiating protocol therapy.

Bone Marrow Evaluations (Solid Tumors with known Marrow Involvement): BM aspirate and/or biopsy must be performed within 14 calendar days of initiating protocol therapy. If more than 14 calendar days have elapsed between the date bone marrow evaluation to determine eligibility was obtained (Section 3.2.6.1) and the enrollment date, then repeat BM aspirate and/or biopsy must be obtained prior to initiating protocol therapy.

Section 3.1.7 Requirements to Initiate Protocol Therapy, Revised Text:

Imaging Studies: Imaging studies must be performed within 14 calendar days prior to initiating protocol therapy. If more than 14 calendar days have elapsed between the date imaging studies to determine eligibility were obtained (Section 3.2) and the enrollment date, then repeat imaging assessments must be obtained prior to initiating protocol therapy.

Cardiac studies: Cardiac ECHO and electrocardiogram (ECG) must be performed within 14 calendar days prior to initiating protocol therapy. If more than 14 days have elapsed between the date cardiac studies to determine eligibility were obtained (Section 3.2.8.4) and the enrollment date, then repeat cardiac studies must be obtained prior to initiating protocol therapy.

Bone Marrow (BM) Evaluations (Solid Tumors with known Marrow Involvement): Bone Marrow aspirate and/or biopsy must be performed within 14 calendar days prior to initiating protocol therapy. If the Bone Marrow evaluation was performed more than 14 days prior to enrollment date and if it was negative, then BM aspirate and/or biopsy must be repeated prior to initiating protocol therapy. If the Bone Marrow evaluation was obtained more than 14 calendar days prior to enrollment and it was positive, and there was no intervening treatment provided to the patients, then there is no need to repeat the Bone Marrow evaluation.

Section 3.2 Eligibility: Inclusion Criteria, Added Text

3.2.3 Patient must have disease that has either relapsed or is refractory to prior therapy

Section 3.2.3 Body Surface Area, Previous Text Body Surface Area (for subjects taking tablet formulation only): Patients who will be receiving the tablet formulation must have a BSA $\geq 0.84 \text{ m}^2$ at the time of study enrollment.

Section 3.2.4 Body Surface Area, Revised Text

Body Surface Area (BSA) (for subjects taking tablet formulation only): Patients who will be receiving the tablet formulation must have a BSA $\geq 0.84 \text{ m}^2$ at baseline. The same method should be used to calculate a given patient's BSA throughout their study participation.

Section 3.2.8.2 Adequate Renal and Metabolic Function, Previous Text

No more than Grade 1 abnormalities of potassium, calcium (confirmed by ionized calcium), magnesium and phosphorous (supplementation allowed).

Section 3.2.8.2 Adequate Renal and Metabolic Function, Revised Text

Adequate thyroid function: either normal TSH or on a stable dose of thyroid replacement for at least than 4 weeks (see Section 3.3.2.8)

No more than Grade 1 abnormalities of:

- a. Potassium
- b. Calcium (confirmed by ionized calcium)
- c. Magnesium d. Phosphorous

Oral supplementation is allowed.

Section 3.3 Exclusion Criteria, Previous Text

3.3.1 Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method beginning at the signing of the informed consent until at least 30 days after the last dose of the study drug.

3.3.2.7 Note: This list includes the prohibition of grapefruit juice for 14 days prior to enrollment.

3.3.3 Patients who are unable to swallow tablets or liquid are not eligible.

3.3.5.4 History of hemoptysis within 6 weeks prior to study enrollment.

Section 3.3 Exclusion Criteria, Revised Text

3.3.1 Females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method beginning at the signing of the informed consent until at least 30 days after the last dose of the study drug.

3.3.2.7 Note: This list includes the prohibition of grapefruit juice for 14 days prior to enrollment and while receiving pazopanib.

3.3.3 Patients who are unable to swallow tablets or liquid are not eligible. Pazopanib cannot be administered via NG tube or G-tube.

3.3.5.4 History of clinically significant bleeding (grade 3 hemorrhage) within 6 weeks prior to study enrollment, including CNS, pulmonary, or GI hemorrhage.

Section 3.4 Regulatory, Previous Text

All patients and/or their parents or legal guardians must sign a written informed consent.

Section 3.4 Regulatory, Revised Text

All patients and/or their parents or legal guardians must sign a written informed consent (and assent, if indicated, according to institutional guidelines).

Section 4.1 Overview of Treatment Plan, Previous Text

Pazopanib will be administered orally once daily as a tablet at a dose of 450 mg/m²/dose or as a powder in suspension at a dose of 225 mg/m²/dose. 450 mg/m²/dose was the MTD for tablet as determined by ADVL0815, the COG Phase I study, while the dose for oral suspension of 225 mg/m²/dose exceeds the protocol-specified MTD of 160 mg/m²/dose established in that study. Two isolated and reversible laboratory-defined DLTs were observed at 225 mg/m²/dose. The maximum dose to be administered daily for tablets is 800 mg and for suspension 400 mg. Each cycle will be defined as 28 days.

Note: The first 6 patients enrolled who receive suspension will be expected to complete extended PK sampling (Section 7.3.2) in order to obtain PK and safety data. These data will be reviewed prior to further enrollment of patients requiring suspension to determine if 225 mg/m²/dose is tolerated and PK exposure is similar to exposure in adults associated with clinical efficacy. If 225 mg/m²/dose is not tolerated (≥ 2 DLTs in 6 evaluable patients), the dose for patients who require suspension may be reduced to 160 mg/m²/dose.

A cycle will be defined as 28 days with no rest periods between cycles. Patients with benefit (stable disease or an objective response) may continue therapy unless there is evidence of progressive disease or unacceptable treatment-related toxicity.

Patients must remain on the same formulation of pazopanib throughout the duration of their protocol therapy.

Drug dosing for the tablet formulation should be determined using the dosing nomogram in Appendix II. For patients receiving powder for suspension (50 mg/mL), the dose will be rounded to the nearest 5 mg. Drug doses should be adjusted based on the BSA as determined by the height and weight obtained within 1 week prior to the beginning of each cycle.

Pazopanib should be taken on an empty stomach (at least 1 hour before a meal or 2 hours after a meal) at approximately the same time each day. Pazopanib tablets should be taken with clear liquids (approximately 4 ounces for children < 12 years of age and 4-8 ounces for children ≥ 12 years of age). Pazopanib suspension should be taken according to instructions in Appendix VII. The pazopanib suspension should be swirled for at least 30 seconds prior to removal of the dose from the bottle, which should be given immediately. If a patient vomits after a dose of pazopanib, the dose should not be repeated.

A patient diary (see Appendices IA and IB) should be completed by the patient or their guardian and collected at the end of each cycle.

Section 4.1 Overview of Treatment Plan, Revised Text

Pazopanib will be dosed daily as an oral tablet at 450 mg/m²/dose or as a powder for oral suspension at 225 mg/m²/dose.

For the tablet formulation, the maximum tolerated dose (MTD) was 450 mg/m²/dose as determined by ADVL0815/PZP114411, the COG Phase I study. The maximum dose to be administered daily for tablets is 800 mg.

For the powder suspension formulation, the selected starting dose is 225 mg/m²/dose, higher than the protocol-specified MTD of 160 mg/m²/dose established in study ADVL0815. This decision is driven by the considerations that the 160 mg/m²/dose may result in exposure that is suboptimal to demonstrate efficacy and that only two isolated and reversible laboratory-defined dose-limiting toxicities (DLTs) were observed at the 225 mg/m²/dose. The maximum dose to be administered daily for oral suspension is 400 mg.

Note: The first patients enrolled who receive powder suspension will be reviewed for safety and will be expected to complete extended PK sampling (Section 7.3.2). A minimum of 6 evaluable patients for safety and 6 evaluable patients for PK are required as described in section 2.5. Safety and PK data from these patients will be reviewed prior to further enrollment of patients requiring powder suspension to determine if the 225 mg/m²/dose is tolerated and if the PK exposure is similar to exposure in adults associated with clinical efficacy. If 225 mg/m²/dose is not tolerated (≥ 2 patients with DLTs in the first 6 evaluable patients during their first cycle), all subsequently enrolled patients will receive 160 mg/m²/dose, and an additional 6 subjects will be assessed for safety and PK.

Patients will take pazopanib continuously, once daily. A cycle will be defined as 28 days with no rest periods between cycles. Patients with benefit (stable disease or an objective response) may continue therapy unless there is evidence of progressive disease or unacceptable treatment-related toxicity, death or until study closure defined as 1 year after Last Patient First Visit.

Patients must remain on the same formulation of pazopanib throughout the duration of their protocol therapy.

Drug dosing for the tablet formulation should be determined using the dosing nomogram in Appendix II. For patients receiving powder for suspension (50 mg/mL), the dose will be rounded to the nearest 5 mg. Drug doses should be adjusted based on the BSA as determined by the height and weight obtained within 1 week prior to the beginning of each cycle.

Pazopanib should be taken on an empty stomach (at least 1 hour before a meal or 2 hours after a meal) at approximately the same time each day. Pazopanib tablets should be taken with clear liquids (approximately 4 ounces for children < 12 years of age and 4-8 ounces for children ≥ 12 years of age). Pazopanib suspension should be taken according to instructions in Appendix VII. The pazopanib suspension should be swirled for at least 30 seconds prior to removal of the dose from the bottle, which should be given immediately. If a patient vomits after a dose of pazopanib, the dose should not be repeated.

A patient diary (see Appendices IA and IB) should be completed by the patient or their guardian and collected at the end of each cycle.

Section 4.1.1 Dose Reduction, Previous Text

For patients who receive pazopanib tablets: Dose reduction(s) will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 4.2 within 14 days following planned administration (see dosing nomogram for tablets in Appendix II). Dose reduction(s) will be based on the starting dose.

Note: For patients receiving pazopanib tablets at a starting dose of 400 mg, there will only be one allowed dose reduction due to tablet size.

For patients who receive pazopanib powder in suspension: A stepwise dose reduction (Tables 1 and 1a) will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 4.2 within 14 days following planned administration.

Table 1: Stepwise Dose Reduction for Toxicity if suspension starting dose 225 mg/m²

Starting Dose	225 mg/m ² /dose
First Dose Reduction	160 mg/m ² /dose

Table 1a: Stepwise Dose Reduction for Toxicity if suspension starting dose reduced to 160 mg/m²

Starting Dose	160 mg/m ² /dose
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First Dose Reduction	135 mg/m ² /dose
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Section 4.1.1 Dose Reduction, Revised Text

For patients who receive pazopanib tablets: Dose reduction(s) in response to toxicity may be implemented according to guidance in Sections 5.2, 5.3, and 5.4 of the protocol. Outside the specific management guidance described in these sections, patients who recover from an adverse event to starting criteria as outlined in Section 4.2 within 14 days following planned administration will also be permitted to receive protocol therapy at a reduced dose. Dose reduction(s) will be based on the starting dose and should follow the Dosing Nomogram in Appendix II.

Note: For patients receiving pazopanib tablets at a starting dose of 400 mg, there will only be one allowed dose reduction due to tablet size.

For patients who receive pazopanib oral powder for suspension:

Dose reduction(s) in response to toxicity may be implemented according to guidance in Sections 5.2, 5.3 and 5.4 of the protocol. Outside the specific management guidance described in these sections, patients who recover from an adverse event to starting criteria as outlined in Section 4.2 within 14 days following planned administration will also be permitted to receive protocol therapy at a reduced dose. Dose reduction(s) will be based on the starting dose and should follow the guidance in Table 1 and Table 1a.

Table 1: = Dose Reduction for Toxicity if powder suspension starting dose is 225 mg/m²

Starting Dose	225 mg/m ² /dose
First Dose Reduction	160 mg/m ² /dose
Second Dose Reduction	135 mg/m ² /dose

Table 1a: Dose Reduction for Toxicity if powder suspension starting dose has been reduced to 160 mg/m²

Starting Dose	160 mg/m ² /dose
First Dose Reduction	135 mg/m ² /dose

Any subsequent dose reduction would need to be discussed and agreed by the Study Chair.

Section 4.1.3 Treatment Interruptions, Added Text

If the protocol therapy has been interrupted for more than 28 days, the patient should be permanently discontinued from protocol therapy and will continue to be followed for survival.

Section 4.1.4 Missed Doses, Added Text

Missed doses should be documented in the electronic case report form (eCRF).

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

Section 4.1.3.2 Management of Hypothyroidism, Previous Text

Patients with Grade 2 hypothyroidism should be evaluated by an endocrinologist for further management. Patients with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol therapy. Patients with Grade 3 or greater hypothyroidism will be considered to have had a dose-limiting toxicity. These patients should be managed according to Section 5.3 and should also be evaluated by an endocrinologist for further management.

Section 4.1.5.2 Management of Hypothyroidism, Revised Text

Patients with Grade 2 hypothyroidism should be evaluated by an endocrinologist for further management. Patients with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol

therapy. Patients with Grade 3 or greater hypothyroidism attributable to pazopanib will be considered to have had a dose-limiting toxicity. These patients should be managed according to Section 5.3 and should also be evaluated by an endocrinologist for further management. If Grade 3 or greater hypothyroidism is adequately managed with thyroid hormone replacement and improves to grade 2 or less, pazopanib may be restarted.

Section 4.1.5.4 Blood-product Support, Added Text

Patients should be supported with transfusion of blood and blood products (including platelet transfusion) per institutional standards.

Section 4.3 Concomitant Therapy, Previous Text

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

Section 4.3 Concomitant Therapy, Revised Text

If new data become available showing an interaction between a concomitant medication and pazopanib that is considered significant enough to impact the risk/benefit balance of pazopanib, the list of permitted/prohibited medications in the Investigator Brochure will be updated either during the annual update or within an IB supplement. Any such changes will be communicated to the site via a letter which should be stored in the site's study file.

Section 4.5.1 Specific recommendations regarding anticoagulants, Previous Text

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 benefitting from treatment and require the initiation of concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) while on study.

Section 4.5.1 Specific recommendations regarding anticoagulants, Revised Text

Hemorrhagic events, however, have been reported in clinical studies with pazopanib. Therefore, if the investigator decides to continue pazopanib and anticoagulants use concomitantly, it should be used with caution in patients with increased risk of severe bleeding or who are benefitting from treatment and require the initiation of concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) while on study.

Section 4.7 The Effects of Other Drugs on Pazopanib, Previous Text

Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein.

Section 4.7 The Effects of Other Drugs on Pazopanib, Revised Text

Furthermore, *in vitro* data suggest that pazopanib is a substrate for P-glycoprotein and for breast cancer resistance protein.

Section 4.8 Prohibited Medications, Previous Text

Glucocorticoids for greater than 2 weeks duration: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)

As noted above, co-administration of pazopanib with medicines that increase gastric pH is prohibited from 24 hours before the first dose of pazopanib until after the final PK blood sample is collected on Day 15 ± 1 day of Cycle 1.

Section 4.8 Prohibited Medications, Revised Text

Glucocorticoids for greater than 2 weeks duration: cortisone (>50 mg/day), hydrocortisone (>40 mg/day), prednisone (>10 mg/day), methylprednisolone (>8 mg/day), dexamethasone (>1.5 mg/day)

As noted above, co-administration of pazopanib with medicines that increase gastric pH should be avoided and is prohibited from 24 hours before the first dose of pazopanib until after the final PK blood sample is collected on

Day 15 ± 1 day of Cycle 1.

Section 4.9 Therapy Delivery Map (TDM) – Cycle 1, Revised Table

- Removed Screening assessments from Cycle 1 Day 1
- Added PD assessments

Section 4.9 Therapy Delivery Map - Subsequent Cycles of Therapy, Revised Table

- Added PD assessments

Section 5 Definitions and Dose Modification for Toxicity, Added Text

The cycle duration remains 28 consecutive days in patients who have dose interruption.

Section 5.1.2 Hematological Dose Limiting Toxicity, Previous Text

- a. For patients who are evaluable for hematologic toxicity (patients **without** bone marrow involvement)
 - Grade 4 Neutropenia not due to malignant infiltration.
 - Grade 4 Thrombocytopenia (platelet count < 25,000/ μ L)
 - Myelosuppression that causes a treatment interruption of \geq 14 days

Section 5.1.1 Hematological Dose Limiting Toxicity, Revised Text

- a. For patients who are evaluable for hematologic toxicity assessment (patients **without** bone marrow involvement)
 - Grade 4 Thrombocytopenia (platelet count < 25,000/mm³) or Grade 4 neutropenia
 - Any hematologic toxicity requiring dose reduction or treatment interruption for >14 days

Section 5.1.1 Non-Hematological Dose Limiting Toxicity, Previous Text

Any Grade 3 non-hematological toxicity that is attributable to pazopanib, with the specific exclusion of the following:

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 fever or infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation (see Section 5.4.3 for dose modifications)

Hypertension will be graded according to the NCI CTCAE, however, dose limiting hypertension will be considered as the following:

- Grade 4 hypertension
- A blood pressure >25 mmHg above the 95th percentile for age, height, and gender (see Appendix V) confirmed by repeated measurement (See Sections 5.4.1 and 4.1.3.1 for management)
- In patients already on anti-hypertensive therapy due to previous hypertension (see Section 3.2.6.5), any blood pressure 1-25 mmHg above the 95th percentile for age, height, and gender (Appendix V) for > 14 days (See Sections 5.4.1 and 4.1.3.1 for management)

Section 5.1.2 Non-Hematological Dose Limiting Toxicity, Revised Text

Any Grade 3 non-hematological toxicity, with the specific exclusion of the following:

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 fever or infection,
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation within 7 days of start of supplement (see Section 5.4.4 for dose modifications)

Hypertension will be graded according to the NCI CTCAE, however, dose limiting hypertension will be considered as the following:

- Grade 4 hypertension
- A blood pressure >25 mmHg above the 95th percentile for age, height, and gender (see Appendix V) confirmed by repeated measurement on the same day (See Sections 5.4.1 and 4.1.4.1 for management)
- In patients already on anti-hypertensive therapy due to previous hypertension (see Section 3.2.8.5), any blood pressure 1-25 mmHg above the 95th percentile for age, height, and gender (Appendix V) for > 14 days (See Sections 5.4.1 and 4.1.4.1 for management)

Section 5.2 Dose Modifications for Hematologic Toxicity, Previous Text

Note: The cycle duration remains 28 consecutive days in patients who have dose interruption of an ongoing cycle. Cycle initiation may be delayed for toxicity as outlined below. All

dose modifications should be based on the worst preceding toxicity.

Pazopanib tablets: For step-wise dose reductions, see Appendix II for the dosing nomogram. Pazopanib

powderin suspension: For step-wise dose reductions see Tables 1 and 1a (Section 4.1.1).

5.2.1 For all patients:

5.2.1.1 If Grade 4 neutropenia occurs, a)

Pazopanib should be held.

b) Subsequent doses of pazopanib should be given at a reduced dose, when $ANC \geq 750$.

5.2.1.2 If Grade 4 thrombocytopenia occurs, a)

Pazopanib should be held.

b) Subsequent doses of pazopanib should be given at a reduced dose, when platelet count $\geq 75,000/\mu L$.

5.2.1.3 If dose-limiting myelosuppression occurs as noted in Section 5.1.2,

a) The dose of pazopanib should be resumed at a reduced dose, once $ANC \geq 750$ and platelet count $\geq 75,000/\mu L$.

5.2.2 Patients who have a dose limiting hematological toxicity that does not resolve to the parameters defined in Section 5.2.2 within 28 days of holding pazopanib, if re-challenge is to be considered the study chair must be contacted and provide approval prior to re-challenge.

Section 5.2 Dose Modifications for Hematologic Toxicity, Revised Text

All dose modifications should be based on the worst preceding toxicity.

Pazopanib tablets: For step-wise dose reductions, see Appendix II for the dosing nomogram.

Pazopanib powderin suspension: For step-wise dose reductions see Tables 1 and 1a (Section 4.1.1).

5.2.1 For all patients:

5.2.1.1 If Grade 4 neutropenia occurs,

a) Pazopanib should be held.

b) CBCs should be checked at least twice a week (every 3 to 4 days) until

ANC \geq 750/ μ L.

c) Subsequent doses of pazopanib should be given at a reduced dose, when ANC \geq 750/ μ L.

5.2.1.2 If Grade 4 thrombocytopenia occurs,

a) Pazopanib should be held.

b) CBCs should be checked at least twice a week (every 3 to 4 days) until platelet count \geq 75,000/ μ L without need for platelet transfusion in the preceding 7 days.

c) Subsequent doses of pazopanib should be given at a reduced dose, when platelet count \geq 75,000/ μ L without need for platelet transfusion in the preceding 7 days.

5.2.1.3 If dose-limiting myelosuppression occurs as noted in Section 4.1.1,

a) The dose of pazopanib should be resumed at a reduced dose, once ANC \geq 750/ μ L and platelet count \geq 75,000/ μ L without need for platelet transfusion in the preceding 7 days.

5.2.1 For patients who have a dose limiting hematological toxicity that does not resolve to the parameters defined in Section 5.2.1 within 14 days of holding pazopanib: if re-challenge is to be considered, the Study Chair must be contacted and provide approval prior to re-challenge.

Section 5.3 Dose Modifications for Non-Hematological Toxicity, Previous Text

If dose-limiting toxicity recurs in a patient who has resumed treatment after 2 dose reductions, the patient must be removed from protocol therapy, unless the patient has been approved for a further dose reduction following discussion with the Study Chair.

Section 5.3 Dose Modifications for Non-Hematological Toxicity, Revised Text

If DLT recurs in a patient who has resumed treatment after the maximum allowed dose reductions, the patient must be removed from protocol therapy, unless the patient has been approved for a further dose reduction following discussion with the Study Chair.

Section 5.4.1 Hypertension, Previous Text

Arm 5 of algorithm:

If the participant develops Grade 4 hypertension, **discontinue** pazopanib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 8.1).

Section 5.4.1 Hypertension, Revised Text

Arm 5 of algorithm:

If the participant develops Grade 4 hypertension, **discontinue** pazopanib, monitor BP and administer anti-hypertensive therapy as clinically indicated. A nephrology and/or cardiology consult is recommended. The patient must be removed from Protocol Therapy (Section 8.1).

Section 5.4.9 Abdominal Pain, Previous Text

Abdominal pain is not an uncommon symptom with vascular endothelial growth factor (VEGF) receptor antagonists, of which pazopanib is one. Bowel perforations have been reported in clinical trials of pazopanib and with other agents in this class. Bowel perforations have been associated in some patients with tumor in the bowel wall, or diverticulitis, while in others there has been no clear explanation. Although bowel perforation is a rare event, investigators and study staff at the site are advised to be vigilant of this potential complication in patients receiving pazopanib. Please contact the Study chair if you need further guidance or would like to discuss an event involving abdominal pain or bowel perforations.

Section 5.4.2 Abdominal Pain, Revised Text

Abdominal pain is not an uncommon symptom with vascular endothelial growth factor (VEGF) receptor antagonists such as pazopanib. Bowel perforations have been reported in clinical trials of pazopanib and with

other agents in this class. Bowel perforations have been associated in some patients with tumor in the bowel wall, or diverticulitis, while in others there has been no clear explanation.

Although bowel perforation is a rare event, investigators and study staff at the site are advised to be vigilant of this potential complication in patients receiving pazopanib. Abdominal complaints should be assessed during AE review at every visit. In addition, every physical exam should include a complete abdominal exam. For patients with abdominal complaints and/or abnormal findings on clinical exam, follow the dose modifications and evaluations described below.

Adverse events & descriptions	Dose Modifications & Evaluations
Mild to Moderate abdominal pain or other abdominal complaints with no associated abnormal findings on physical exam	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Implement supportive care as indicated and per institutional standards; consider imaging studies 3. Advise the patient to seek medical attention should their complaints worsen 4. Appropriate follow-up until complaints resolve or origin of the pain is identified. Imaging studies to confirm the absence of abdominal pathology should be performed based on the investigator judgment.
Severe abdominal pain or a concerning abdominal exam	<ol style="list-style-type: none"> 1. Hold pazopanib 2. Recommend to obtain appropriate imaging studies to evaluate the patient's specific complaints or exam findings 3. Resume pazopanib at previous dose if imaging studies confirm the absence of abdominal pathology
Confirmed or any suspicion of abdominal perforation	<ol style="list-style-type: none"> 1. Remove from protocol therapy

Contact the Study chair if you need further guidance or would like to discuss an event involving abdominal pain or bowel perforations.

Section 5.4.2 Hepatotoxicity, Previous Text

Adverse events & descriptions	Dose Modifications & Evaluations
Grade 1 ALT/AST elevation	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose. 2. Check liver function tests (LFTs)¹ as per protocol
Grade 2 ALT/AST elevation without bilirubin elevation (defined as total bilirubin ² < 1.5 x ULN or direct bilirubin ≤ 35% of total bilirubin) and without hypersensitivity symptoms (eg: fever, rash)	<ol style="list-style-type: none"> 1. Continue pazopanib at current dose 2. Consider performing the following to exclude hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • Eosinophil count

	<ul style="list-style-type: none"> • Viral serology⁴ for hepatitis A, B and C • Liver imaging (Ultrasound) <p>3. Monitor patient closely for clinical signs and symptoms</p> <p>4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until AST/ALT \leq Grade 1</p>
<p>\geqGrade 3 ALT elevation without bilirubin elevation (defined as total bilirubin² $< 1.5 \times$ ULN or direct bilirubin $\leq 35\%$ of total bilirubin) and without hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>LiverEventInterruption/StoppingCriteria³:</u></p> <p>1. Hold pazopanib. Repeat LFTs¹ within 72 hrs to confirm \geqGrade 3 ALT elevation; if confirmed:</p> <p>2. Perform the following assessments to exclude hypersensitivity and other contributing factors:</p> <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Liver imaging (Ultrasound) <p>3. Monitor patient closely for clinical signs and symptoms</p> <p>4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until ALT reduced to \leq Grade 1</p> <p>5. Pazopanib may be held for up to 14 days, if ALT returns to \leq Grade 1 and patient is benefitting from treatment, pazopanib may be resumed at a reduced dose following GSK governance approval (contact the Sponsor medical monitor via email or phone to start the approval process). If approval for re-treatment is granted, the patient must be re-consented (with a separate informed consent) specific to hepatotoxicity.</p> <ul style="list-style-type: none"> • For patients on tablets dose reductions are as follows: <ul style="list-style-type: none"> ○ If on 800 mg, then reduce to 400 mg daily ○ If on 600 mg, then reduce to 400 mg daily ○ If on 400 mg, reduce to 200 mg daily • For patients on suspension: <ul style="list-style-type: none"> ○ Follow the sequential dose reduction (Section 4.1.1.), one dose level reduction is required (e.g. from 225 mg/m² to 160 mg/m²) <p>6. Following re-introduction of pazopanib, continue to monitor ALT weekly for 2 cycles, if ALT \geq Grade 2 recurs permanently discontinue pazopanib</p>

\geq Grade 2 ALT <u>AND</u> elevation in bilirubin ² (defined as total bilirubin > 1.5 x ULN and direct bilirubin > 35% of total bilirubin) or with hypersensitivity symptoms (e.g., fever, rash)	<u>LiverEventStoppingCriteria</u> ³ : 1. Discontinue pazopanib permanently 2. Recheck LFT's ¹ , serum creatinine phosphokinase (CPK) and collect PK sample.
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	<p>Also check:</p> <ul style="list-style-type: none"> Eosinophil count Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein-Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) Anti-nuclear antibody⁴, anti-smooth muscle antibody⁴, anti-mitochondrial antibody⁴ Liver imaging (Ultrasound) <p>3. Recommend referral to (consult) a pediatric gastroenterologist/hepatologist.</p> <p>4. Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs¹ weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.</p>
For isolated total bilirubin ² elevation without concurrent ALT increase (defined as ALT < 3 x ULN).	<p>1. Isolated hyperbilirubinemia (in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Study treatment inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.</p> <p>2. If bilirubin is > 1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin should be performed. If the bilirubin is predominantly indirect (≥65%) indirect (unconjugated), continue study treatment at the same dose. If bilirubin is >35% direct (conjugated), study treatment may also be continued however, further evaluation should be undertaken for underlying cause of cholestasis.</p>

Section 5.4.3 Hepatotoxicity, Revised Text

Adverse events & descriptions	Dose Modifications & Evaluations
Grade 1 ALT/AST elevation	<p>1. Continue pazopanib at current dose</p> <p>2. Check liver function tests (LFTs)¹ as per Evaluations table in Section 7.1</p>
Grade 2 ALT/AST elevation without bilirubin elevation (defined as total bilirubin ² ≤ 1.5 x ULN or direct bilirubin ≤ 35% of total bilirubin) and without hypersensitivity symptoms (eg: fever, rash)	<p>1. Continue pazopanib at current dose</p> <p>2. Consider performing the following to exclude hypersensitivity and other contributing factors:</p> <ul style="list-style-type: none"> Eosinophil count Viral serology⁴ for hepatitis A, B and C Liver imaging (Ultrasound) <p>3. Monitor patient closely for clinical signs and symptoms</p> <p>4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until AST/ALT ≤ Grade 1</p>

<p>≥Grade 3 ALT elevation without bilirubin elevation (defined as total bilirubin² ≤ 1.5 x ULN or direct bilirubin ≤35% of total bilirubin) and without hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>LiverEventInterruption/StoppingCriteria³</u>: 1. Hold pazopanib. Repeat LFTs¹ within 72 hrs to confirm ≥Grade 3 ALT elevation; if confirmed:</p>
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	<p>2. Perform the following assessments to exclude hypersensitivity and other contributing factors:</p> <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Liver imaging (Ultrasound) <p>3. Monitor patient closely for clinical signs and symptoms</p> <p>4. Perform LFTs¹ weekly (or more frequently if clinically indicated) until ALT reduced to \leq Grade 1</p> <p>5. Pazopanib may be held for up to 14 days, if ALT returns to \leq Grade 1 and patient is benefitting from treatment, pazopanib may be resumed at a reduced dose following GSK governance approval (contact the Sponsor medical monitor via email or phone to start the approval process). If approval for re-treatment is granted, the patient must be re-consented (with a separate informed consent) specific to hepatotoxicity.</p> <ul style="list-style-type: none"> • For patients on tablets dose reductions are as follows: <ul style="list-style-type: none"> ○ If on 800 mg, then reduce to 400 mg daily ○ If on 600 mg, then reduce to 400 mg daily ○ If on 400 mg, reduce to 200 mg daily • For patients on powder suspension: <ul style="list-style-type: none"> ○ Follow the sequential dose reduction (Section 4.1.1.), one dose level reduction is required (e.g. from 225 mg/m² to 160 mg/m²) <p>6. Following re-introduction of pazopanib, continue to monitor ALT weekly for 2 cycles, if ALT \geq Grade 2 recurs permanently discontinue pazopanib</p>
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<p>≥ Grade 2 ALT <u>AND</u> elevation in bilirubin² (defined as total bilirubin > 1.5 x ULN and direct bilirubin > 35% of total bilirubin) or with hypersensitivity symptoms (e.g., fever, rash)</p>	<p><u>LiverEventStoppingCriteria</u>³:</p> <ol style="list-style-type: none"> 1. Discontinue pazopanib permanently 2. Recheck LFT's¹, serum creatinine phosphokinase (CPK) and collect PK sample. <p>Also check:</p> <ul style="list-style-type: none"> • Eosinophil count • Optional viral serology⁴ for hepatitis A, B, C and E, cytomegalovirus⁴, Epstein-Barr virus⁴ (IgM antibody, heterophile antibody, or monospot testing) • Anti-nuclear antibody⁴, anti-smooth muscle antibody⁴, anti-mitochondrial antibody⁴ • Liver imaging (Ultrasound)
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	<ol style="list-style-type: none"> 3. Recommend referral to (consult) a pediatric gastroenterologist/hepatologist. 4. Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs¹ weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin ² elevation without concurrent ALT increase (defined as Grade 1 ALT $\leq 3 \times$ ULN).	<ol style="list-style-type: none"> 1. Isolated hyperbilirubinemia (in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Study treatment inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. 2. If total bilirubin is $> 1.5 \times$ ULN in the absence of ALT elevation, fractionation of bilirubin should be performed. <ul style="list-style-type: none"> • If the bilirubin is predominantly indirect ($\geq 65\%$) indirect (unconjugated), continue study treatment at the same dose. • If bilirubin is $> 35\%$ direct (conjugated), study treatment may also be continued however, further evaluation should be undertaken for underlying cause of cholestasis.

Section 5.4.4 Proteinuria, Previous Text

- If urinalysis shows \geq trace protein then obtain a urine protein:creatinine ratio (UPC).
- If the UPC is ≥ 1 , then obtain a 24-hour urine collection for protein estimation.
- If the urine protein is ≥ 3.5 g/24-hours then hold pazopanib and re-assess urine protein weekly.
- If the urine protein decreases to < 3.5 g/24 hours in < 21 days then resume pazopanib at a reduced dose.
- If pazopanib is held for ≥ 21 days then the patient must be removed from protocol therapy.
- Monitor the 24 hour urine protein weekly for 2 consecutive weeks once pazopanib is resumed.

Section 5.4.5 Proteinuria, Revised Text

- If urinalysis shows \geq trace protein then obtain a urine protein: creatinine ratio(UPC).
- If the UPC is ≥ 1 , then obtain a 24-hour urine collection for protein estimation.
- If the urine protein is ≥ 3.5 g/24-hours then hold pazopanib and re-assess urine protein weekly.
- If the urine protein decreases to < 3.5 g/24 hours in < 21 days then resume pazopanib at a reduced dose.
- Monitor the 24 hour urine protein or UPC weekly for 2 consecutive weeks once pazopanib is resumed.
- If pazopanib is held for ≥ 21 days then the patient must be removed from protocol therapy.

Section 5.4.5.1 Left Ventricular Systolic Dysfunction, Previous Text

Adverse events & descriptions	Dose Modifications & Evaluations
LV EF $< \text{LLN}$ but $\geq 50\%$ OR LV SF $< \text{LLN}$ but $\geq 24\%$ without symptoms of cardiac dysfunction	Continue drug and repeat Echo on Day 28 of subsequent cycle
LV EF 40 – 50% OR LV SF 15 – 24% OR Absolute decrease in SF of 8 percentage points from baseline	Hold pazopanib and obtain repeat Echo in 7 days. If toxicity confirmed, then remove from protocol therapy. If not confirmed, then resume drug at reduced dose and repeat Echo 14 and 28 days after resuming pazopanib. If any 2 Echos demonstrate LV EF 50-40% OR LV SF 24- 15% OR > 8 percentage point decrease in SF then remove from protocol therapy and refer to pediatric cardiologist
Grade 3 LV EF decreased OR Grade 3 LV SF decreased	Discontinue pazopanib permanently and remove from protocol therapy – refer to pediatric cardiologist

Section 5.4.6.1 Left Ventricular Systolic Dysfunction, Revised Text

Adverse events & descriptions	Dose Modifications & Evaluations
LV EF $< \text{LLN}$ but $\geq 50\%$ OR LV SF $< \text{LLN}$ but $\geq 24\%$ without symptoms of cardiac dysfunction	Continue drug and repeat Echo on Day 28 of subsequent cycle
LV EF 40 – 49% OR	Hold pazopanib and obtain repeat Echo in 7

LV SF 15 – 23% OR Absolute decrease in SF \geq 8 percentage points from baseline	days. If toxicity confirmed, then remove from protocol therapy. If not confirmed, then resume drug at reduced dose and repeat Echo 14 and 28 days after resuming pazopanib. If any 2 Echos demonstrate LV EF 49-40% OR LV SF 23-15% OR \geq 8 percentage point decrease in SF then remove from protocol therapy and refer to pediatric cardiologist
Grade 3 LV EF decreased OR Grade 3 LV SF decreased	Remove from protocol therapy – refer to pediatric cardiologist

- Cardiac evaluation by Echo but MUGA (Multiple-Gated Acquisition) may be used if clinically indicated

Section 5.4.6.2 QT Prolongation, Added Text

Only the Bazett's formula should be used to calculate the corrected QT interval.

Section 5.4.8 Vascular Thrombosis, Previous Text

	Dose Modifications & Evaluations
Grade 2	Continue pazopanib at the current dose and monitor as clinically indicated.
Grade 3 (CVL associated only)	1. Hold pazopanib 2. Initiate treatment with Low Molecular Weight Heparin (LMWH) [Warfarin is allowed but INR has to be monitored] 3. Resume pazopanib at the current dose during the period of full- dose anticoagulation if all of the following criteria are met: <ul style="list-style-type: none"> • The patient must have received anti-coagulation for at least 1 week • No Grade 3 or 4 hemorrhagic events have occurred while on
	anticoagulation treatment 4. Patient should be monitored as clinically indicated during anticoagulation treatment and after resuming pazopanib
All non-CVL associated Grade 3 AND all Grade 4	Discontinue pazopanib permanently and remove from protocol therapy

Section 5.4.9 Vascular Thrombosis, Revised Text

	Dose Modifications & Evaluations
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Grade 2	Continue pazopanib at the current
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	dose and monitor as clinically indicated.
Grade 3 (CVL associated only)	<ol style="list-style-type: none"> 1. Treat thrombosis according to institutional standards; would consider removal of the CVL. 2. Resume pazopanib when all symptoms have resolved. If anticoagulation is required, use with caution.
All non-CVL associated Grade 3 AND all Grade 4	Discontinue pazopanib permanently and remove from protocol therapy

Section 6.1 Pazopanib, Previous Text

Pregnancy Category D

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.

Agent Accountability

A record of the number of doses of pazopanib suspension taken by the subject at each visit must be maintained and reconciled with the study medication and compliance records in the eCRF. At each site visit, the cause of any missed doses should be discussed and documented.

Section 6.1 Pazopanib, Revised Text

Pregnancy Category D

There are no adequate and well-controlled studies of pazopanib in pregnant women. Protocol therapy should be immediately discontinued if pregnancy occurs while the patient is on therapy. Women of childbearing potential should be advised to avoid becoming pregnant while taking pazopanib and for up to 30 days after stopping pazopanib.

Agent Accountability

A record of the number of milligrams (determined by weight) of pazopanib in oral powder suspension dispensed to and returned by each patient at each visit must be maintained and reconciled with the study medication and compliance records in the eCRF. At each site visit, the cause of any missed doses should be discussed and documented.

After completion of the study, a final review of accountability records and inventory of unused study medications will be performed by the study monitor and site personnel. If the site has received documented approval from Sponsor, unused study medication may be destroyed, prior to inventory by the study monitor. In this case, the study monitor would review only study medication accountability records at the end of study visit. Additional information on the drug accountability process is provided in the Study Procedure Manual.

Section 7.1 Required [REDACTED] Clinical, Laboratory and Disease Evaluations, Revised Table

- Added Survival Follow-up visit
- Added Performance Status to be done on Cycle 1 Day 1
- Clarified frequency of the following assessments: CBC, differentials, platelets, electrolytes, creatinine,

ALT, bilirubin, amylase, lipase, total protein, albumin, PT, PTT, INR

■ [REDACTED]

Section 7.2.1 Growth Plate Toxicity, Previous Text

- Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physal pathology and undergo more frequent x-ray follow up. MRI should be performed without contrast.
- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of pazopanib should take into account the presence of any symptoms referable to the knee as well as the patient's response to pazopanib. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue pazopanib or not.

Section 7.2.1 Growth Plate Toxicity, Revised Text

- Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physal pathology and undergo more frequent x-ray follow up. MRI should be performed without contrast. If no MRI changes are seen, x-rays may be performed approximately every 2 months.
- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of pazopanib should take into account the presence of any symptoms referable to the knee as well as the patient's response to pazopanib. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue pazopanib or not. Consultation with orthopedics and with the Study Chair is advised.

Section 7.2.4 Pregnancy Testing and Reporting, Added Text

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to the Sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Section 7.3.2 Sampling schedule, Previous Text

All patients will have a blood sample for analysis of the plasma pazopanib concentration collected: prior to the first dose in Cycle 1; and on Day 15 ± 1 day of Cycle 1, both prior to dosing and 3-4 hours after dosing.

Additional blood samples for analysis of steady-state trough plasma pazopanib concentrations will be obtained prior to the start of every odd cycle. The pre-dose sample on Day 15, Cycle 1 and trough plasma concentrations should be obtained between 22-26 hours after the previous dose of pazopanib. Subjects should be instructed to hold their dose of pazopanib on the day that a pre-dose concentration is to be collected. These specimens should correspond to the timing of routine laboratory evaluations.

Extended pharmacokinetic sampling will be done in the first 6 patients enrolled (who receive the suspension formulation). These patients will have a blood sample for analysis of the plasma pazopanib concentration collected at the following time points on Day 1 of Cycle 1: pre-dose, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. Samples will also be obtained on Day 15 ± 1 day of Cycle 1: pre-dose, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. For all patients additional blood samples for analysis of steady-state trough plasma pazopanib concentrations will be obtained prior to the start of every odd cycle. The pre-dose sample on Day 15, Cycle 1 and trough plasma concentrations should be obtained between 22-26 hours after the previous dose of pazopanib. Subjects should be instructed to hold their dose of pazopanib on the day that a pre-dose concentration is to be collected. These specimens should correspond to the timing of routine laboratory evaluations.

Section 7.3.2 Sampling schedule, Revised Text

All patients (whether receiving pazopanib as tablet or as oral powder suspension) will have a blood sample for analysis of the plasma pazopanib concentration collected prior to the first dose on Day 1 of Cycle 1. In addition, all patients will have 2 blood samples collected on Day 15 \pm 1 day of Cycle 1: one sample prior to the dose and one sample 3-4 hours after dosing.

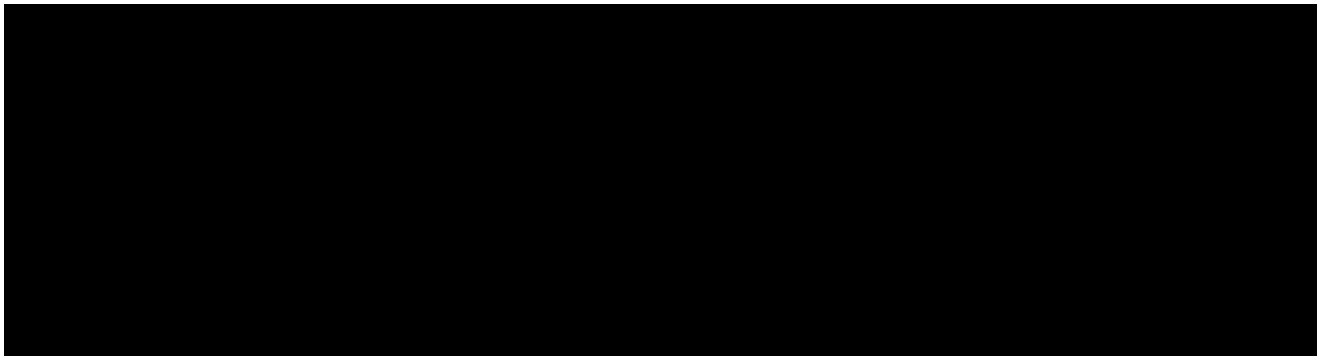
Blood samples for analysis of steady-state trough plasma pazopanib concentrations will also be obtained prior to the start of every subsequent odd-numbered cycle (that is, pre-dose prior to Cycle 3, pre-dose prior to Cycle 5, etc). These steady-state trough plasma concentration samples can be collected between Day 22 of the previous cycle to Day 1 of the odd-numbered cycle, and the actual date and time of sample collection recorded on the PK sample collection form.

The pre-dose sample on Day 15 \pm 1 day of Cycle 1 and the trough plasma concentration samples taken prior to dosing for every odd-numbered cycle should be obtained between 22-26 hours after the previous dose of pazopanib. Patients should be instructed to hold their dose of pazopanib on the day that a pre-dose PK sample is to be collected. Collection of these PK samples should correspond to the timing of routine laboratory evaluations.

Extended PK sampling will be done during Cycle 1 in the first patients who receive the powder suspension formulation, until 6 patients are considered evaluable for the PK analysis. These patients will have a blood sample for analysis of the plasma pazopanib concentration collected at the following time points on Day 1 of Cycle 1: pre-dose and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. Samples will also be obtained on Day 15 \pm 1 day of Cycle 1: pre-dose and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose. If one or more of these 6 patients fail to provide blood samples as specified in the protocol or if it is known that for some reason a patient's collected blood sample(s) cannot be analyzed, that patient(s) will be determined to be non-evaluable for this analysis and one or more additional patients will be enrolled for treatment with pazopanib as powder for oral suspension and provision of the extended PK samples. These patients will also provide blood samples for analysis of steady-state trough plasma pazopanib concentrations prior to the start of every subsequent odd-numbered cycle as described in the preceding paragraph.

Pazopanib dosing of either tablet or powder suspension must have continued uninterrupted and at the same dose level for at least 10 days prior to acquisition of the Cycle 1 Day 15 PK samples. If pazopanib dosing has been interrupted or modified <10 days prior to Cycle 1 Day 15, then the PK samples should be taken between Cycle 1 Day 15 and Cycle 1 Day 22 on a study day that meets the condition of at least 10 consecutive days of dosing at the same dose level. The Cycle 1 Day 15 PK kit should be used and the actual date and time of sample collections should be recorded in the eCRF.

If ≥ 2 out of 6 evaluable patients have dose-limiting toxicities as defined in Section 5.1) during the first cycle, then enrollment at the 225 mg/m²/dose dose level of pazopanib oral suspension will be halted. Subsequent new patients will be enrolled at the 160mg/m²/dose level until 6 evaluable patients from this dose group are available for the safety review and 6 patients are available for PK analysis.



Section 8.1 Criteria for Removal From Protocol Therapy, Previous Text

- a) Progressive disease.
- b) Adverse Events requiring removal from protocol therapy, as stated in Section 5.
- c) Patients who receive concurrent anticancer or investigational therapy, as stated in Section 3.3.2.
- d) Patients who require major surgery during Cycle 1, as stated in Section 5.4.6 e)
- Refusal of further protocol therapy by patient/parent/guardian.
- f) Completion of two years of therapy.
- g) Physician determines it is in patient's best interest.
- h) Repeat eligibility studies (if required) are outside the parameters required for continued dosing as stated in Section 4.2.
- i) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
- j) Patients who develop a second malignant neoplasm.
- k) Patient becomes pregnant

Patients who are removed from protocol therapy (except for 8.1.h) are to be followed for a maximum of five years or until they meet at least one of the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

Section 8.1 Criteria for Removal From Protocol Therapy, Revised Text

Patients will be permanently discontinued of protocol therapy if any of the following occur:

- a) Progressive disease

- b) Adverse Events requiring removal from protocol therapy, as stated in Section 5.
- c) Concurrent use of other anticancer or investigational therapy, as stated in Section 3.3.2. d) Requirement for major surgery during Cycle 1, as stated in Section 5.4.7
- e) Refusal of further therapy by patient/parent/guardian
- f) Physician determines it is in patient's best interest
- g) Major protocol deviations including non-compliance h)
- Development of a second neoplasm
- i) Pregnancy

Section 8.2 Follow-up assessments after Removal From Protocol Therapy, Added Text

Patients who are removed from protocol therapy are to be followed until they meet at least one of the criteria for withdrawal from study (see Section 8.3). Survival Follow-up data will be required unless consent was withdrawn.

Safety follow-up:

All patients will be followed for adverse events and serious adverse events for 28 days after last dose.

Survival follow-up:

The following information will be collected and reported every 3 months:

- Survival status
- Antineoplastic therapies taken since discontinuation of protocol therapy

The primary reason protocol therapy was permanently discontinued must be documented in the patient's medical records and eCRF. If the patient discontinues from protocol therapy due to toxicity, AE will be recorded as the primary reason for permanent discontinuation on the eCRF. Once a patient has permanently discontinued protocol therapy, the patient will not be allowed to be retreated.

Section 8.2 Off Study Criteria, Previous Text

- a) Death.
- b) Lost to follow-up.
- c) Entry into another study with tumor therapeutic intent (e.g., at recurrence).
- d) Withdrawal of consent for any further data submission. e)

The study is closed for any reason.

Section 8.3 Criteria for Withdrawal from Study, Revised Text

Patients will be withdrawn from the study if any of the following occur:

- a) Death
- b) Lost to follow-up
- c) Withdrawal of consent for follow-up
- d) The study is closed/ terminated e)
- Investigator discretion

Section 9.1 Sample Size and Study Duration, Deleted Text

If activity is detected in any category, further trials in subcategories of the category may be conducted at the discretion of the Developmental Therapeutics Steering and study committees.

Section 9.3 Analysis Populations, Previous Text

The Target Intent-to-Treat (tITT) population will comprise all subjects entered into the study at the target dose. If after the first 6 subjects, the suspension dose is de-escalated to 160 mg/m²/dose then only the 160 mg/m²/dose subjects will be included in the tITT. All subjects taking the tablets will be included in the tITT.

The Per Protocol (PP) population will be a subset of the ITT population which will exclude subjects with major protocol violations. What constitutes a major protocol violation will be fully described in the Reporting and Analysis Plan (RAP).

The Safety population will comprise all subjects in the ITT population who receive at least one dose of investigational product. The safety population will be used for the analysis of safety data.

Section 9.3 Analysis Populations, Revised Text

The modified Intent-to-Treat (mITT) population is the primary analysis population. The mITT will consist of all patients who have received at least one dose of protocol therapy.

The Safety population will comprise all patients in the mITT population. The safety population will be used for the analysis of safety data.

The Pharmacokinetic population will comprise all patients in the mITT population for whom a pharmacokinetic sample is obtained and analyzed. The Pharmacokinetic Extended Sampling population will comprise all subjects in the Pharmacokinetic population who received powder suspension and have at least one non-predose sample collected and analyzed using the extended sampling schedule in Section 7.3.2.

Section 9.4 Analysis Data Sets, Previous Text

The primary data set for assessing efficacy will comprise the target intent-to-treat population.

Section 9.4 Analysis Data Sets, Revised Text

The primary data set for assessing efficacy will comprise the modified intent-to-treat population.

Section 9.6 Interim Analysis, Previous Text

No formal interim analysis is planned outside of the study design. The study team will review safety data periodically over the course of the study.

Expansion of tumor specific cohorts will be done when there is at least one investigator determined confirmed response in that cohort/strata within the first 10 enrolled patients. The time point for the decision to expand will be the earliest of the following: an investigator determined confirmed response within the first 10 pts, the time when the first 10 patients are no longer eligible for obtaining a response (i.e., 18 weeks have elapsed and a response is unlikely, has progressed, has discontinued therapy, has withdrawn consent).

Therefore, the clinical cut off for analysis purposes per cohort/strata, will be the earliest of 18 weeks from last subject first visit, all subjects have documented radiological progression or withdrawn consent from the study.

Section 9.6 Primary Analysis and End of Study Analysis, Revised Text

No formal interim analysis is planned outside of the study design. The study team will review safety data periodically over the course of the study.

Expansion of tumor specific cohorts will be done when there is at least one investigator determined confirmed response in that cohort within the first 10 enrolled patients. A given tumor specific cohort will not be expanded if all the patients in the cohort have:

- Progressed
- Discontinued therapy
- Withdrawn consent
- Been determined to be lost-to-follow-up
- Or have been treated for at least 20 weeks, making it unlikely that a response

will occur.

The primary analysis will be performed 20 weeks after the last patient's first visit in the three cohorts of primary interest (rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma and Ewing sarcoma/peripheral PNET).

The study will be completed one year from the date of the last patient's first visit and the end of study analysis will be performed at the time of study completion.

Any additional data collected after the primary analysis will be included in a supplementary analysis and reported in a final Clinical Study Report.

Section 9.7.2 Missing Data, Deleted Text

If a progression event occurs after an extensive lost-to-follow-up time (greater than 8 weeks) the primary analysis will censor those subjects at the date of their last adequate disease assessment.

Section 9.8.1 Primary Endpoint: Objective Response Rate, Previous Text

Confirmation will be based on the next scheduled disease assessment after the initial response.

Section 9.8.1 Primary Endpoint: Objective Response Rate, Revised Text

Confirmation will be based on the disease assessment performed 1 cycle after the initial response. The objective response rate will be computed for the 3 tumor types of primary interest.

Section 9.8.2.3 Progression-free survival (PFS) and overall survival (OS), Added Text

Overall survival is defined as the time from the first dose of the study medication until death due to any cause. The OS analysis will be performed on the mITT population and summarized using a Kaplan-Meier survival curve. The Kaplan-Meier estimate for the median OS time and the first and third quartiles will be presented, along with a naive approximate 90% confidence interval if there are a sufficient number of deaths.

Section 9.8.2.4 Clinical Benefit, Previous Text

This is defined as the percentage of subjects achieving either a complete or partial tumor response or stable disease for at least 16 weeks as per RECIST criteria.

Section 9.8.2.4 Clinical Benefit, Revised Text

This is defined as the percentage of patients achieving either a complete or partial tumor response or stable disease for at least two protocol scheduled disease assessments as per RECIST criteria.

Section 9.8.2.5 Other Safety Measures, Previous Text

Vital signs (blood pressure, heart rate, temperature) and weight will be listed for each subject and change from baseline will be included for blood pressure and heart rate.

Section 9.8.2.5 Other Safety Measures, Revised Text

Vital signs (blood pressure, heart rate, temperature), height and weight will be listed for each patient and change from baseline will be included for blood pressure and heart rate.

Section 9.9 Evaluability for Response, Previous Text

Response will be determined on the target intent to treat (tITT) population consisting of all patients enrolled into the study at the target dose.

In addition, response will be determined using a modified ITT (mITT) consisting of patients who are eligible and received at least one dose of study drug.

Section 9.9 Evaluability for Response, Revised Text

Response will be determined on the modified intent to treat (mITT) population consisting of all patients who are eligible and received at least one dose of protocol therapy.

Section 9.10 Evaluability for Toxicity, Deleted Text

All patients who receive at least one dose of pazopanib will be considered in the evaluation of toxicity.

Monitoring for Excessive Toxicity

A patient will be considered for toxicity monitoring if one of the following occurs: (1) complete one cycle of pazopanib; (2) die on protocol therapy for a reason considered possibly, probably or likely related to pazopanib; or (3) are removed from protocol therapy because of an adverse experience possibly, probably or likely related to pazopanib. A toxicity-evaluable patient will be considered in the analysis during the interval from study enrollment until protocol therapy is terminated or a dose-limiting toxicity is observed. A toxicity-evaluable patient will be considered to have experienced an excessive toxicity event if: (1) the patient dies on protocol therapy for a reason considered possibly, probably or likely related to pazopanib; or (2) experiences a dose-limiting toxicity.

The analytic unit for monitoring for excessive toxicity will be the patient-cycle: Each cycle where the patient receives at least 24 doses of pazopanib (approximately 85% of planned therapy) or where an excessive toxicity event is observed will be considered in the analysis. Onar-Thomas and Xiong demonstrate that, over typical dose-toxicity relationships the Rolling-6 methodology identifies, with probability approximately 95%, an MTD with a first-cycle-DLT probability less than or equal to 30%.⁴⁴ If there is overwhelming evidence that the dose selected for this trial has a per-cycle- DLT probability of more than 30%, we will identify the regimen to the COG Phase I and II DSMC, DVL leadership and CTEP as associated with a toxicity profile that may require modification of the regimen.

We will use a Bayesian rule to monitor for excessive toxicity.^{45,46} We will assume a beta prior distribution with $\alpha=0.6$ and $\beta=1.4$. At least once per month, we will calculate:

$$P(p_{\text{Excessive Toxicity}} > 0.30 | \text{Data}) = \frac{\int_{0.30}^1 \binom{n}{x} p^x (1-p)^{n-x} \frac{\Gamma(2)}{\Gamma(0.6)\Gamma(1.4)} p^{-0.4} (1-p)^{0.4} dp}{\int_0^1 \binom{n}{x} q^x (1-q)^{n-x} \frac{\Gamma(2)}{\Gamma(0.6)\Gamma(1.4)} q^{-0.4} (1-q)^{0.4} dq}$$

Where n is the number of excessive-toxicity-evaluable cycles and x is the number of such cycles on which an excessive toxicity event is observed. If this posterior probability exceeds 80%, we will identify the regimen to the COG Phase I and II DSMC, DVL leadership and CTEP as associated with a toxicity profile that may require modification of the regimen. Examples of situations in which this rule will indicate excessive toxicity have been noted and are presented below:

Number of Toxicity-Evaluable Cycles	Number of Cycles with Excessive Toxicity Observed	P ($p_{\text{Excessive Toxicity}} > 0.30 \text{Data}$)
5	3	0.92
10	5	0.87
15	7	0.89
20	8	0.81
25	10	0.80
30	12	0.80

35	13	0.80
40	15	0.83

Section 9.12 Analysis of the Pharmacokinetic Parameters, Previous Text

Plasma pazopanib concentrations observed after administration of the suspension in the first 6 subjects enrolled in the study will be analyzed with standard noncompartmental methods using WinNonlin version 5.2 or higher. The parameters maximum plasma pazopanib concentration (C_{max}), the time to C_{max} (t_{max}), and the area under the curve (AUC) from zero to the time of the last quantifiable concentration (AUC(0-t)) will be calculated. The AUC from zero to 24 hours after administration (AUC(0-24)) on Day 15 will be calculated by using the predose plasma pazopanib concentration for the concentration 24 hours after dosing.

A mixed-effects model generated with data from adult subjects with solid tumors will be fit to the plasma pazopanib concentration-time data to generate post-hoc estimates of pharmacokinetic parameters using NONMEM VII. The post-hoc estimates of pharmacokinetic parameters will be compared to the parameters generated from data in adult subjects with cancer.

The change in plasma trough pazopanib concentrations will be characterized at the first cycle and each odd cycle after the first. The effect of cycle on change in plasma trough concentrations will be assessed by fitting the parametric model:

Section 9.11 Analysis of the Pharmacokinetic Parameters, Revised Text

Plasma pazopanib concentrations observed in the first 6 patients who receive pazopanib as powder for oral suspension and are evaluable for pharmacokinetics will be analyzed with standard noncompartmental methods using WinNonlin version 5.2 or higher. Parameter values for maximum plasma pazopanib concentration (C_{max}), the time to C_{max} (t_{max}), and the area under the curve (AUC) from zero to the time of the last quantifiable concentration (AUC(0-t)) will be calculated. The AUC from zero to 24 hours after administration (AUC (0-24)) on Day 15 will be calculated by using the predose plasma pazopanib concentration as the concentration 24 hours after dosing. The analysis to assess pazopanib pharmacokinetics after administration of the suspension prior to continuing enrollment on suspension may be performed using scheduled time. Calculations of noncompartmental parameter values for the final analysis will be based on actual sampling times.

Plasma pazopanib concentration values at each sampling occasion will be summarized by cohort as well as after combining the data from all cohorts, separately for each formulation and each dose level, if needed. In addition, plasma pazopanib concentration values at each sampling occasion will be summarized by age subgroups (2 to <12 years old, 12 to 18 years old) for each formulation and dose level, if needed. This analysis will combine data across all disease cohorts unless pharmacokinetic differences between the cohorts are observed.

The pharmacokinetic parameter values in the patients with extended sampling will be summarized for Cycle 1 Day 1 and Cycle 1 Day 15, combining data from all patients, separately by dose level, if needed.

Section 9.12 Analysis of Biological and Correlative Endpoints, Deleted Text

Objective 1.2.3 will be assessed by examining the change in biological parameter between the samples taken on Days 1 and 15. Initially, such analyses will not be segregated by tumor type. The null hypothesis H₀: No change in median value of the biological parameter between Day 1 and 15 will be assessed by the Wilcoxon signed rank test. The power associated with this test as a function of the variability of the biological parameter and patients contributing to the analysis is summarized in the following table:

Number of Paired Specimens Available	True Difference in Pre- vs. Post Median Measurement (Multiples of the Standard Deviation of the Measurement)	Power Using a Two-Sided Test of Size 0.05
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40	2σ	0.85
50	2σ	0.92
60	2σ	0.96

No adjustment will be made for multiple comparisons for this exploratory analysis. The changes in biological measures may be examined within particular disease types, but such results will not have sufficient precision to make definitive conclusions if the null hypothesis is not rejected.

The effect of genotype on change in biological parameter will be assessed by fitting the parametric model:

$$y_{i2} = \beta_0 + \beta_1 y_{i1} + \beta_2 \underline{x}_i + \varepsilon_i ; \varepsilon_i \sim N(0, \sigma^2)$$

where y_{2i} is the post-treatment value for the biological measure

y_{i1} is the pre-treatment value for the biological measure

\underline{x}_i is the (categorized) SNP observed

$\underline{\beta}$ are the true effect of initial biological measure level and SNP

The sensitivity for detection of a particular true treatment effect will depend on departures from normality in the distribution of the characteristic and the number of pairs that will contribute to the analysis.

Section 10.8 Survival Follow-up, Added Text

Patients who have discontinued protocol therapy will be followed for Survival status. The investigator site will collect and report Survival follow-up in the eCRF every 3 months, which would include the patient's survival status and any antineoplastic therapies taken since discontinuation of protocol therapy, until death, lost to follow-up, or withdrawal of consent from survival follow-up occurs or final cut-off for survival analysis.

The date and cause of death should be recorded in the eCRF.

Section 11 Adverse Event (AE) and Serious Adverse Event (SAE), Previous Text

AEs will be collected from the start of Study Treatment and until completion of the final 30 day study visit.

Section 11 Adverse Event (AE) and Serious Adverse Event (SAE), Revised Text

AEs will be collected from the start of protocol therapy and until 28 days following last dose of protocol therapy.

Medical occurrences that begin prior to the start of protocol therapy but after obtaining informed consent should be recorded on the Medical History/Current Medical Conditions section of the eCRF.

Any new primary cancer must be recorded as an SAE and will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.

Section 11.2 Definition of Serious Adverse Events (SAEs), Previous Text

All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT \geq 3xULN and bilirubin \geq 1.5x ULN (>35% of total bilirubin is direct) or ALT \geq 3xULN and INR>1.5, if INR measured termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

Section 11.2 Definition of Serious Adverse Events (SAEs), Revised Text

All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT > 3xULN and bilirubin > 1.5x ULN (>35% of total bilirubin is direct) or ALT > 3xULN and INR>1.5, if INR measured termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

Section 11.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs, Added Text

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Section 11.5 Recording of AEs and SAEs, Deleted Text

Subject-completed health outcomes questionnaires and the collection of AE data are independent components of the study. Responses to each question in the health outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.

The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

Section 12.1 Data and Safety Monitoring, Previous Text

- The study team, which includes the GSK Medical Monitor, representatives from the Clinical Pharmacology/Modelling and Simulations Group, the safety review team (SRT), and the COG protocol chair will review and discuss safety data at periodic intervals throughout the duration of the study
- The entire pazopanib development program utilizes an internal SRT that is independent from study teams. The remit of the SRT is to periodically review the safety data across clinical trials in order to protect and enhance patient safety. The SRT provides a central and dedicated forum for review of emerging data that could impact patient safety. All safety-related issues and safety outputs from this study will be sent to the SRT for review and discussion. If safety issues are identified within the SRT forum these will be escalated as required.

Section 12.1 Data and Safety Monitoring, Revised Text

- The study team, which includes the Medical Monitor, representatives from the Clinical Pharmacology Group, and the COG protocol chair will review and discuss safety data at periodic intervals throughout the duration of the study

Appendix IA: Patient Diary for Pazopanib Tablets, Previous Text

Please write the date, time and dose of pazopanib given. Please make note of all prescription medications, nonprescription medications, and herbal remedies you take. Return the completed diary to your institution after each treatment cycle.

Appendix IA: Patient Diary for Pazopanib Tablets, Revised Text

Please write the date, time and dose of pazopanib given. Please make note of all prescription medications, nonprescription medications, and herbal remedies you take. Also, please remember to take the tablets at least 1 hour before or 2 hours after a meal. Return the completed diary to your institution after each treatment cycle along with any unused study medication or empty study medication bottles.

Appendix IB: Patient Diary for Pazopanib Powder in Suspension, Previous Text

Return the completed diary to your institution after each treatment cycle.

Appendix IB: Patient Diary for Pazopanib Powder in Suspension, Revised Text

Return the completed diary to your institution after each treatment cycle along with all the bottles of study medication, even empty.

Appendix II: Pazopanib Dosing Nomogram for Tablets, Previous Text

Dosing Nomogram for Starting Dose of 450 mg/m²/dose and for Dose Reductions if required

	Starting Dose	Dose Reduction #1	Dose Reduction #2
	450 mg/m ² /dose		
BSA*	Dose (mg) [†]		
0.84 -0.94	400	200	0
0.95-1.05	400	200	0
1.06-1.16	400	200	0
1.17-1.27	600	400	200
1.28-1.38	600	400	200
1.39-1.50	600	400	200

1.51-1.61	600	400	200
1.62-1.72	800	600	400
≥ 1.73	800	600	400

Appendix II: Pazopanib Dosing Nomogram for Tablets, Revised Table
Dosing Nomogram for Target Starting Dose of 450 mg/m²/dose and for Dose Reductions if required

	Starting Dose	Dose Reduction #1	Dose Reduction #2
	Target : 450 mg/m ² /dose		
BSA*	Dose (mg) [†]		
0.84-1.16	400	200	0
1.17 -1.61	600	400	200
≥ 1.62	800	600	400

Appendix VI: Pharmacokinetic Study Form, Revised Form

PK form revised to capture date/time of dose given on PK sampling days and date/time of PK sample collection

Appendix VII: Instructions to Patient/Caregiver for Administering Pazopanib Suspension, Previous Text

1. Insert the provided adapter (Baxa 28 mm Press-In-Bottle Adapter - PIBA®) into the neck of the bottle.
2. **Immediately** prior to removal of dose for administration, mix the contents of the bottle by **swirling** for 30 seconds to one minute in order to ensure homogeneity of suspension.
3. Insert the tip of a suitable graduated syringe (recommended: Exacta-Med® Baxa) into the Adapter after ensuring that the syringe plunger is pushed fully into the barrel.
4. Invert the bottle and dispense at least 5 mL of suspension into the syringe. Then push it back into the bottle in order to purge the syringe of any air bubbles. Repeat this step until syringe is free of air bubbles.
5. Withdraw the prescribed dose. Investigator/study staff will fill in the dose below for each patient.

The dose is ____mg = mL each day.

Appendix VII: Instructions to Patient/Caregiver for Administering Pazopanib Oral Suspension, Revised Text

1. The pharmacist should insert the provided adapter (Baxa 28 mm Press-In-Bottle Adapter - PIBA®) into the neck of the bottle. Once the adapter has been placed into the bottle neck, DO NOT REMOVE.
2. **Immediately** before planned dose administration, mix the contents of the bottle by **swirling** for 30 seconds to one minute in order to ensure homogeneity of suspension.
Note#1: Women who are pregnant or nursing should put on a suitable size of gloves to avoid contact between the liquid and skin (Latex gloves can be used; however, for people who are sensitive to latex, it is recommended to use Nitrile gloves). Take care not to spread material to unprotected skin (such as your face) or other body surfaces by touching them with a wet glove.
Note#2: In case of spillage, see section C for Clean-up instructions.
3. Insert the tip of an appropriate syringe (recommended: Exacta-Med® Baxa) into the Adapter after ensuring that the syringe plunger is pushed fully into the barrel.
4. Tip the bottle upside down and dispense at least 3-5 mL of suspension into the syringe. Then push the suspension back into the bottle in order to purge the syringe of any air bubbles. Repeat this step until syringe is free of air bubbles.
5. Withdraw the prescribed dose. Investigator/study staff will fill in the dose below for each patient.

The dose is mg, corresponding to mL each day.

Please note that the number of milligrams of pazopanib and, therefore, the number of milliliters of pazopanib oral suspension may change as the body surface area of the patient changes during study participation.

Appendix VIII: Youth Information Sheets, Previous Text

This 28 day regimen may be repeated for up to 2 years (you would receive pazopanib continuously).

Appendix VIII: Youth Information Sheets, Revised Text

This 28 day regimen may be repeated until you benefit from treatment or until study closure.

13.14 APPENDIX XII AMENDMENT 04

Amendment Summary of Main Changes:

Section(s)	Change	Rationale
Title page	Title page replaced as per Novartis requirements	Change in study sponsorship from GSK to Novartis
Sponsor Information Page	GSK contact information has been replaced with Novartis details	Change in study sponsorship from GSK to Novartis
Sponsor signatory	Change of sponsor signatory	Change in study sponsorship from GSK to Novartis
Multiple	The term 'GSK medical monitor' has been replaced by Novartis Medical Lead	To align with the change of sponsorship from GSK to Novartis.
Multiple	Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents	To align with the change of sponsorship from GSK to Novartis.
Multiple	Make administrative changes	To align with the change of sponsorship from GSK to Novartis.

Section: 3.1.1, Patient Registration

Original Text:

No study-specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines), defining the study entry.

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with registration, please refer to the online help.

Upon completion of all required baseline assessments, the investigator or authorized site staff will assign each eligible patient a Sponsor study-specific patient identification number. Each site will be assigned a range of patient numbers, and this information is provided in the Study Procedure Manual (SPM). The patient ID number consists of 6 digits including leading zeros. Using this patient ID number and patient's histology cohort (rhabdomyosarcoma, non- rhabdomyosarcomatous soft tissue sarcoma, Ewing sarcoma/peripheral PNET, osteosarcoma, neuroblastoma (measureable), neuroblastoma (evaluable) or hepatoblastoma), each patient will then be registered into the interactive voice response system RAMOS (Registration and Medication Ordering System). RAMOS will then provide an identification number consistent with the patient's tumor type.

All calls to RAMOS are confirmed (with a fax or e-mail), which will be sent to the site upon completion of each call. **Study-specific instructional worksheets will be provided for the use of RAMOS in the Study Procedures Manual.**

Revised Text:

No study-specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines), defining the study entry.

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with registration, please refer to the online help.

Upon completion of all required baseline assessments, the investigator or authorized site staff will assign each eligible patient a Sponsor study-specific patient identification number. Each site will be assigned a range of patient numbers, and this information is provided in the Study Procedure Manual (SPM). The patient ID number consists of 6 digits including leading zeros. Using this patient ID number and patient's histology cohort (rhabdomyosarcoma, non- rhabdomyosarcomatous soft tissue sarcoma, Ewing sarcoma/peripheral PNET, osteosarcoma, neuroblastoma (measureable), neuroblastoma (evaluatable) or hepatoblastoma), each patient will then be registered into the interactive ~~webvoice~~ response system **(IWRs) RAMOS** (~~Registration and Medication Ordering System~~). ~~The IWRs RAMOS~~ will then provide ~~an~~ a **randomization** identification number consistent with the patient's tumor type.

All ~~sessions~~ ~~calls~~ to IWRsRAMOS are confirmed with an on screen confirmation (~~with a fax or e-mail~~), which will **also** be sent **via email** to the site upon completion of each call. **Study-specific instructionsal worksheets will be provided for the use of IWRsRAMOS in the Study Procedures Manual and in the user manual.**

Section: 3.1.5, Study Enrollment

Original Text:

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Specific procedures related to the requirements for patient enrollment are described in protocol Section 3 and in the Study Procedures Manual. Sites will be required to complete a call into RAMOS (IVRS) to record patient information as described in Section 3.1.1.

Revised Text:

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Specific procedures related to the requirements for patient enrollment are described in protocol Section 3 and in the Study Procedures Manual. Sites will be required to complete a ~~session~~call into **the (IWRs)RAMOS (IVRS)** to record patient information as described in Section 3.1.1.

Section: 7.2.4, Pregnancy Testing and Reporting

Original Text:

The need for a screening pregnancy test depends on whether a female patient is of childbearing potential or non-childbearing potential. If a female patient is of childbearing potential, she must have a serum -Human Chorionic Gonadotropin (β -HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). Patients with a positive pregnancy test result must be excluded from the study. Patients with a negative pregnancy test result must agree to use an adequate contraception method as described below during the study until 30 days following the last dose of study treatment(s). Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure patient safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. Study treatment should be immediately discontinued if pregnancy occurs during study participation. 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 (Section 11.8). Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study treatment(s) must be promptly reported to GSK.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to the Sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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 GSK as described above.

Revised Text:

The need for a screening pregnancy test depends on whether a female patient is of childbearing potential or non-childbearing potential. If a female patient is of childbearing potential, she must have a serum -Human Chorionic Gonadotropin (β -HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). Patients with a positive pregnancy test result must be excluded from the study. Patients with a negative pregnancy test result must agree to use an adequate contraception method as described below during the study until 30 days following the last dose of study treatment(s). Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure patient safety, each pregnancy must be reported to ~~NovartisGSK~~ within **24 hours** ~~2-weeks~~ of learning of its occurrence. Study treatment should be immediately discontinued if pregnancy occurs during study participation. 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 (Section 11.8). Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study treatment(s) must be promptly reported to ~~NovartisGSK~~.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to the Sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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 ~~NovartisGSK~~ as described above.

Section: 11, Adverse Events (AE) and Serious Adverse Events (SAE)

Original Text:

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

- AEs will be collected from the start of protocol therapy and until 28 days following last dose of protocol therapy.
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed

as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.

- Medical occurrences that begin prior to the start of protocol therapy but after obtaining informed consent should be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any new primary cancer must be recorded as an SAE and will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK and COG within 24 hours, as indicated in Section 11.8.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants.
- However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator should promptly notify GSK and COG.

Revised Text:

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

- AEs will be collected from the start of protocol therapy and until 28 days following last dose of protocol therapy.
- SAEs will be collected over the same time period as stated above for AEs. **From the time a patient consents to participate in and completes the study, However, any all SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be reported promptly to Novartis as indicated in Section 11.8.** ~~recorded from the time a patient consents to participate in the study up to and including any follow-up contact.~~
- Medical occurrences that begin prior to the start of protocol therapy but after obtaining informed consent should be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any new primary cancer must be recorded as an SAE and will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to **Novartis**GSK and COG within 24 hours, as indicated in Section 11.8.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants.
- However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator should promptly notify **Novartis**GSK and COG.

Section: 12, Study Reporting and Monitoring

Original Text:

For this study, patient data will be entered into electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Patient initials will not be collected or transmitted to GSK according to GSK policy.

Revised Text:

For this study, patient data will be entered into electronic case report forms (eCRFs), transmitted electronically to **NovartisGSK** or designee and **be** combined with data provided from other sources in a validated data system.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures with the objective of resolving errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report.. All AEs and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom dictionary. ~~Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug. eCRFs (including queries and audit trails) will be retained by NovartisGSK, and copies will be sent to the investigator to maintain as the investigator copy. Patient initials will not be collected or transmitted to GSK according to GSK policy.~~

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