A Pilot Study of Pazopanib in Molecularly Selected Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

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Glossary of Abbreviations

ADL	Activities of daily living
AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATP	Adenosine triphosphate
CBC	Complete blood count
CFR	Code of Federal Regulations
CR	Complete response
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DBP	Diastolic blood pressure
DSM	Data and Safety Monitoring
DVT	Deep venous thrombosis
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
INR	International normalized ratio
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
LFT	Liver function tests
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PR	Partial response
QASMC	Quality Assurance and Safety Monitoring Committee

QD	Quaque die (every day)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
SAE	Serious adverse event
SBP	Systolic blood pressure
SCC	Siteman Cancer Center
SD	Stable disease
TCGA	The Cancer Genome Atlas
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
UPC	Urine protein creatinine
UPN	Unique patient number
VEGF	Vascular endothelial growth factor

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1.0 BACKGROUND AND RATIONALE

1.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer related death in both men and women in the United States.[19] Over 200,000 patients are diagnosed with lung cancer every year in the United States. More than 80% of these patients have non-small cell lung cancer (NSCLC) and over half of them present with advanced stage disease at the time of diagnosis. Platinum based chemotherapy remains the mainstay of first line treatment for patients with advanced stage NSCLC. In a prospective randomized study that compared four commonly used platinum-based chemotherapy regimens for patients with stage IIIB or stage IV disease: cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel, no regimen was found to have a significantly better response rate or survival time.[20] The response rate for all 1,158 of the eligible patients was 19%, and the median survival time was 7.9 months (95% CI, 7.3-8.5 months). The results from this study indicate that the combination of platinum with third generation chemotherapeutic agents (paclitaxel, docetaxel, vinorelbine, gemcitabine) has limited benefit in the treatment of patients with metastatic NSCLC. Unfortunately treatment benefit from 1st line cytotoxic chemotherapy is usually short lived with a median time to progression of 3 to 5 months. However, only a limited number of options are available for second line treatment. Therefore it is essential to develop effective second line treatment options for patients with relapsed/refractory NSCLC. Many patients with relapsed/refractory NSCLC also have marginal performance status and it is important to develop therapies that are tolerable.

1.2 Angiogenesis

Angiogenesis, an essential step for tumor growth and progression is defined as the growth of new blood vessels from existing vasculature.[1] Due to its critical role in several tumors including NSCLC, its inhibition represents a rational therapeutic strategy. VEGF is key ligand and regulator of both physiological and pathological angiogenesis, including from tumors, with the signaling occurring mostly through VEGFR2.[2] The two main mechanisms of VEGF inhibition are the use of monoclonal antibodies against circulating VEGF and small molecules that inhibit its tyrosine kinase activity. Bevacizumab, a humanized monoclonal antibody against circulating VEGF was the first antiangiogenic drug to be approved for NSCLC, with its use restricted to patient with non-squamous histology due to the increased risk of life-threatening bleeding in squamous cell carcinoma.[3] Two randomized clinical trials, Eastern Cooperative Oncology Group (ECOG) 4599 and Avastin in Lung (AVAiL), comparing chemotherapy alone or with bevacizumab, showed improved response rate and progression-free survival (PFS) for the combination therapy.[4,5] However, only the ECOG 4599 study showed a survival benefit. VEGFR tyrosine kinase inhibitors (TKIs) compete with adenosine triphosphate (ATP) for the active site of the kinase domain. Due to the well-conserved ATP binding site of the kinases, most VEGFR TKIs inhibit multiple receptors including PDGFR and KIT.[6,7] Several VEGFR TKIs have been tested in unselected patients with NSCLC. Although

well tolerated as single agents, the response rates have been disappointing.[8-10] Furthermore, the addition of VEGFR TKIs to chemotherapy was generally associated with increased toxicity without a survival benefit.[11-13] Additionally, recently published research shows that expression of VEGF-A correlated with mutations in TP53, suggesting that TP53 mutational status may also play a role in response to antiangiogenic therapies.[14,15]

PDGF promotes tumor cell proliferation, invasion, migration and angiogenesis.[16] The PDGF pathway plays a significant role in angiogenesis through its effects on pericytes and vascular smooth muscle cells, which in turn secrete VEGF.[17] This signaling cooperation could be explored with a dual inhibitor. One of the major obstacles for further development of anti-angiogenesis inhibitors is the lack of reliable predictors for response. We believe that with the use of a potent single agent TKI against VEGFR and PDGFR in a molecularly selected patient population may lead to a significant benefit in some patients and further evaluation of responders with a comprehensive molecular profile both at diagnosis and at progression, may provide valuable information predictors for response and mechanisms of resistance.

1.3 Pazopanib

Pazopanib is a potent inhibitor of VEGFR1-3, PDGFRA, PDGFRB and KIT, with a broad *in vivo* antitumor activity.[18] In the phase I study, pazopanib was well tolerated in 63 patients with advanced cancer.[19] The maximum tolerated dose (MTD) was not determined, with hypertension as the most common grade 3 toxicity. The recommended phase 2 dose was 800 mg daily. Among the five patients with lung cancer, one patient achieved a prolonged disease stabilization lasting 13.6 months.

1.4 Next Generation Sequencing

It is a standard of care at Washington University School of Medicine to do next-generation sequencing in the tumor specimens from patients with metastatic NSCLC and at the time of disease progression when feasible following targeted therapies. Next generation sequencing involves targeted exon sequencing of 'clinically significant' cancer genes using next-generation sequencing technology.

1.5 Rationale

There has been a limited benefit from anti-angiogenesis drugs in patients with NSCLC. Bevacizumab provides a modest survival improvement when added to chemotherapy and VEGFR tyrosine kinase inhibitors have been associated with minimal efficacy as single agents and increased toxicity when combined with chemotherapy. We postulate that the response rates and survival may be improved with a better selection of patients based on abnormalities of the targets for the drugs. Since, despite the molecular selection prior to treatment, only a small percentage of patients will benefit from the treatment, we plan to further investigate those patients with whole exome sequencing in both the pre-treatment samples to identify the predictors for response and at the time of progression, with

repeated biopsy, in an attempt to identify the predictors for secondary resistance. By identifying more reliable predictors for response to pazopanib, our study may help to establish its role in the treatment of NSCLC.

1.6 Correlative Studies

Patients enrolled in this study will undergo optional next generation sequencing of tumor samples taken prior to treatment and at the time of disease progression. Archived formalin fixed paraffin embedded (FFPE) samples must have adequate viable cells for next generation sequencing to be performed. This routine sequencing involves targeted exon sequencing of "clinically significant" cancer genes, and allows for targeted "deep" sequencing to detect single nucleotide variants, copy number variants, and structural variations which are frequently associated with mutated solid and hematological genomes. The assay interrogates the exon sequences of a number of genes that have been selected based on current sequencing test order patterns by oncologists or literature-based knowledge of known clinical relevance to specific tumor types.

The genomic landscape of cancer is complex and evolves through the process of clonal evolution innately and in response to treatment. Unbiased whole exome and transcriptome sequencing performed on tumor samples at time of diagnosis in responders and non-responders will help us identify unique variations that confer susceptibility to pazopanib. Moreover, genomic analysis at time of progression after treatment with pazopanib (after response lasting for 6 months or longer) will provide some unique insights into mechanisms underlying acquired resistance.

2.0 OBJECTIVES

2.1 Primary Objectives

1. To evaluate the response rates by RECIST 1.1 for patients with advanced NSCLC with mutations in the target genes for pazopanib.
2. To evaluate progression-free survival for patients with advanced NSCLC with mutations in the target genes for pazopanib.

2.2 Secondary Objectives

1. To correlate outcomes with specific mutations.
2. To further evaluate extreme responders with whole genome and transcriptome sequencing.
3. To evaluate the mechanisms of secondary resistance.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed diagnosis of advanced (metastatic or unresectable) non-small cell lung cancer (NSCLC) with mutations, rearrangement and fusion involving RET oncogene, or abnormalities in the pazopanib target genes defined as VEGFR1-3, PDGFRA, PDGFRB, or TP53 with abnormalities including deletion, insertion, early stop codon, and/or nonsynonymous mutations with functional consequences. CLIA certified lab testing for pazopanib target genes using cell free DNA from peripheral blood and/or assays performed on tumor tissues are acceptable.

2. Evaluable disease by imaging or physical exam OR measurable disease defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam.

3. Failed at least one standard chemotherapeutic treatment for NSCLC.

4. At least 18 years of age.

5. ECOG performance status ≤ 2 (see Appendix A)

6. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500/mcl
   b. Platelets ≥ 100,000/mcl
   c. Hemoglobin ≥ 9.0 g/dL

d. PT or INR ≤ 1.2 x IULN
e. aPTT ≤ 1.2 x IULN
f. Total bilirubin ≤ 1.5 x IULN
g. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN
h. Creatinine ≤ 1.5 mg/dL OR creatinine clearance ≥ 30 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 mg/dL
i. UPC < 1 or, if UPC ≥ 1, 24-hour urine protein < 1 g; use of urine dipstick for renal function assessment is not acceptable.

7. Patients receiving anticoagulation therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.

8. Ability to swallow and retain oral tablets.

9. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

10. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Treatment with any of the following anti-cancer therapies:
   a. Radiation therapy, surgery, or tumor embolization within 14 days prior to the first dose of pazopanib OR
   b. Chemotherapy, immunotherapy, investigational therapy or hormonal therapy within 14 days prior to the first dose of pazopanib.

2. Prior treatment with any VEGFR tyrosine kinase inhibitor.

3. Administration of any <u>non-oncologic</u> investigational drug within 30 days or 5 half-lives (whichever is longer) prior to the first dose of pazopanib.

4. Use of a strong CYP3A4 inhibitor less than 14 days prior to initiation of study treatment (please refer to Section 5.2.5).

5. A history of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.

6. Symptomatic brain metastases. Patients with known brain metastases are allowed if they are asymptomatic.

7. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib or other agents used in the study.

8. Any ongoing toxicity from prior anti-cancer therapy that is > grade 1 and/or that is progressing in severity (except alopecia). Any IO related adverse events must be ≤ grade 1 to be eligible.

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled seizure disorder, chronic underlying liver disease unrelated to cancer, or psychiatric illness/social situations that would limit compliance with study requirements.

10. Corrected QT interval (QTc) > 480 msecs.

11. History of any one or more of the following cardiovascular conditions within the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina pectoris, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure as defined by the New York Heart Association (see Appendix B).

12. Poorly controlled hypertension (defined as systolic blood pressure of ≥ 160 mmHg or diastolic blood pressure of ≥ 90 mmHg). Note: initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure must be reassessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between antihypertensive medication initiation or adjustment and blood pressure measurement. These three values should be averaged to obtain the mean diastolic and systolic blood pressures, which must be < 140/90 mmHg in order for a patient to be eligible for the study.

13. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding, including (but not limited to) active peptic ulcer disease, known intraluminal metastatic lesions with risk of bleeding, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other GI conditions with increased risk of perforation, history of abdominal fistula or intra-abdominal abscess within 28 days prior to beginning study treatment.

14. Clinically significant gastrointestinal abnormalities that may affect absorption of pazopanib, including (but not limited to) malabsorption syndrome or major resection of the stomach or small bowel.

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

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

17. Evidence of active bleeding or bleeding diathesis.

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

19. Recent hemoptysis (≥ ½ teaspoon of red blood within 8 weeks before first dose of pazopanib).

20. Pregnant and/or breastfeeding. Patient must have a negative serum pregnancy test within 14 days of study entry.

21. Known HIV-positivity. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Agent Administration

Pazopanib at a dose of 800 mg QD should be taken orally without food at least one hour before or two hours after a meal. One cycle of pazopanib is 28 days. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant.

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

If vomiting occurs after taking pazopanib, the subject should not take a replacement dose on that day. The subject should resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists, the subject should be instructed to notify the investigator.

5.2 General Concomitant Medication and Supportive Care Guidelines

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

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT3 antagonists) may be administered prophylactically in the event of nausea. Anti-

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

5.2.1 Anticoagulants

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

5.2.2 Hypoglycemic Therapy

Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib[20]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

5.2.3 Use of Statins

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib dose modification and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

5.2.4 Medications that Raise Gastric pH

In a drug interaction trial in patients with solid tumors, concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor, decreased the exposure of pazopanib by approximately 40% (AUC and Cmax). Therefore, concomitant use of pazopanib with drugs that raise gastric pH should be avoided. IF such drugs are needed, short-acting antacids should be considered in place of proton pump inhibitors and H2 receptor antagonists. Separate antacid

and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure.

5.2.5 Medications to Use with Caution

In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9, or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, 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.

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

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (see

Section 5.2.5); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

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 include (but are not limited to):

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

5.2.6 Prohibited Medications

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 study drug until discontinuation from the study. **Strong CYP3A4 inhibitors include (but are not limited to):**

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

5.3 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum pregnancy test within 14 days prior to the first dose of pazopanib.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 28 days following the last dose of pazopanib.

If a patient is suspected to be pregnant, pazopanib should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy

or within 28 days after the last dose of pazopanib, the investigator must be notified in order to facilitate outcome follow-up.

5.4 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue indefinitely until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason other than withdrawal of consent will be followed as indicated in the study calendar.

5.5 Duration of Follow-up

Patients will be followed every 2 months until death. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

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

If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the pazopanib dose can then be increased step-wise back to the pre-event dose

(in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).

Dose-level	0	-1	-2	-3	-4
Dose	800 mg QD	600 mg QD	400 mg QD	200 mg QD	Discontinue

For patients at dose-level -3, 200 mg QD, a maximum dose delay of 14 days is allowed for management of toxicities. If toxicity does not resolve in 14 days, the patient should be discontinued from study.

Dose Modification Algorithms for Potential Treatment-Related Adverse Events

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

AE Terms & Descriptions	Dose Modification Algorithms
Hemorrhage/Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	For hemoptysis, interrupt pazopanib and consider whether further treatment with pazopanib is appropriate. For other grade 1 hemorrhage/bleeding event, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolved to ≤ grade 1. Step 2. Restart pazopanib; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or recurrent ≥ grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue pazopanib at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt pazopanib. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume pazopanib at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No grade 3 or 4 or clinically significant grade 2 hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib dosing (e.g., re initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue pazopanib and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any grade	Discontinue pazopanib and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue pazopanib with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt pazopanib until toxicity resolves to ≤ grade 2. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ grade 2 or recurrent grade 3 or 4 thrombocytopenia, discontinue pazopanib and follow-up per protocol
Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, edema,	Continue pazopanib with current dose.

AE Terms & Descriptions	Dose Modification Algorithms
hyperkeratosis)	
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (peeling, blisters, edema, bleed, hyperkeratosis)	Step 1. Hold pazopanib. Step 2. Treat as clinically appropriate. Step 3. Upon resolution to grade 1 or better, restart pazopanib with a dose reduction to 400 mg. Step 4. If recurrent, consider a further dose reduction to 200 mg or discontinuation.
Grade 3 Severe skin changes with pain and limiting self-care activities of daily living	Discontinue pazopanib
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue pazopanib; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 1. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue pazopanib and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.	
QTc ≥ 480-500 msec	Continue pazopanib; monitor as clinically indicated.
QTc ≥ 500 msec	Discontinue pazopanib and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.

b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4)

Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	Step 1. Continue pazopanib at current dose levels. Step 2. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT is reduced to grade 1.
(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria:** Step 1. Interrupt pazopanib until toxicity resolves to ≤ grade 1 or baseline. Report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. Step 2. Liver imaging and other laboratory investigations should be considered as clinically appropriate. Step 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT is reduced to grade 1. Step 4. If the subject is benefiting from the study treatment, re-treatment may be considered if ALL following criteria are met: - ALT reduced to Grade 1

Event	Dose Modification Algorithms
	- Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. **<u>Recurrence – Liver Event Stopping Criteria:</u>** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT is reduced to grade 1.
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**<u>Liver Event Stopping Criteria:</u>** Step 1. Discontinue pazopanib immediately, report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. Step 2. Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging - Consider toxicological blood screen for possible contributing chemical/medical entities Step 3. Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs[a] weekly or more frequently if clinically indicated until LFTs are reduced to grade 1.
For isolated total bilirubin[b] elevation without concurrent ALT increases (defined as ALT < 3 X ULN).	Step 1. Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. Step 2. If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

Event	Dose Modification Algorithms

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.

Please see Section 7.8 for adverse event reporting instructions for hepatotoxicity.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

Novartis requires that all events be reported as outlined in Section 7.4.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death

- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

7.1.4 Life-Threatening Adverse Experience

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

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the

IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to Novartis

All events must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form by fax to (fax: 877-778-9739) within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets**. (See Appendices E and F). This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

From the time a subject consents to participate in and completes the study all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to Novartis concomitant medication, will be reported promptly to Novartis.

Any SAE brought to the investigator's attention within 30 days following completion of the study considered by the investigator as possibly related to investigational product must be reported to Novartis. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Pazopanib Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has

been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Please note that all events meeting liver stopping criteria must be recorded as an SAE.

Pregnancy

Any pregnancy that occurs during study participation must be reported to Novartis. To ensure subject safety, each pregnancy must be reported to Novartis within 24 hours of learning of its occurrence using the pregnancy reporting form. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis.
In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

All serious adverse events must be reported by facsimile within 24 hours to Novartis.
FAX: 1-877-778-9739
Email: ct.suspected@novartis.com
Phone: Sheila Bell, 862-778-6763 (if you experience difficulty faxing the form)
Please use the attached fax cover sheet, located in Appendices E and F.

	Initial Reports	Follow-up Information on a Previous Report
Type of Event	**Time Frame**	**Documents**
All SAEs	24 hours	For follow-up report, please submit findings from the previous report, if appropriate
Pregnancy	24 hours	
Liver Chemistry Abnormalities (the below are not always considered an SAE unless they fulfill the definition of an SAE in Section 7.7)		
ALT: >3.0 x ULN **with** concomitant elevation in bilirubin[a] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) **or with** hypersensitivity symptoms (e.g., fever, rash).	24 hours	For follow-up report, please submit findings from the previous report, if appropriate
ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[a] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	24 hours	For follow-up report, please submit findings from the previous report, if appropriate

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

7.5 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

8.1 Pazopanib

8.1.1 Pazopanib Description

GW786034 (pazopanib) is a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI) being developed by Novartis for oncology indications (as an oral formulation) and for ophthalmology indications (eye drops and low dose oral). Pazopanib has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma (RCC) (New Drug Application [NDA] #022465).

Chemical Name: 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride

Molecular Formula: $C_{21}H_{23}N_7O_2S \bullet HCl$

Molecular Weight: 473.99 g/mol (monohydrochloride salt); 437.53 g/mol (free base)

8.1.2 Pharmacokinetics and Drug Metabolism

Pazopanib is absorbed orally with median time to achieve peak concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean AUC and Cmax of 1,037 mcg·hr/mL and 58.1 mcg/mL (equivalent to 132 µM), respectively.

8.1.3 Supplier(s)

Pazopanib will be provided to the sites by Novartis. Please use the ISS Drug Supply Request form (Appendix D) to order drug. Contact Marybeth Nyhuis (mary.nyhuis@novartis.com) and Desiree Hiraman (desiree.hiraman@novartis.com) and cc Lixian Jin (lixian.jin@novartis.com) on ALL requests.

8.1.4 Dosage Form and Preparation

Pazopanib is supplied as 200 mg tablets. Tablets are packaged in a sealed bottle with an affixed content label identifying the product.

8.1.5 Storage and Stability

Store at room temperature between 20°C and 25°C; excursions permitted to 15°C to 30°C.

8.1.6 Administration

Pazopanib at a dose of 800 mg QD (four 200 mg tablets) should be taken orally without food at least one hour before or two hours after a meal.

9.0 CORRELATIVE STUDIES

9.1 Tumor Tissue For Research Purposes

With patient consent, archived formalin fixed paraffin embedded specimens from the time of diagnosis may be sequenced as part of the patient's routine care. If archival tissue samples are available and/or biopsy is obtained for clinical purposes at the time of disease progression, WUSM may request a tumor sample, with patient consent, for research purposes, including whole exome and transcriptome sequencing. The specimens will be collected in accordance with standard of care practice and will be taken to the Washington University Tissue Procurement Core for processing and storage per institutional practice.

For the purpose of eligibility, patients expressing pazopanib targeted genes in either tissue assays or peripheral blood should be considered for study.

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted no more than 14 days prior to start of protocol therapy. Scans and x-rays must be done no more than 4 weeks prior to the start of the protocol therapy. All visits have a window of +/- 3 days.

	Screening	**D1 of each cycle**	**C1D8**	**C1D15 and C2D15**	**End of every even-numbered cycle**	**EOT**	**F/U[9]**
Informed consent	X						
PE, H&P, PS	X	X				X	
VS	X	X[1]	X			X	
CBC	X	X	X			X	
CMP	X	X	X			X	
LFTs[2]	X	X[2]	X[2]	X[2]		X	
Pregnancy test[3]	X					X	
UPC	X	X[10]				X	
TSH, T4	X	X[4]					
PT/PTT, INR	X					X	
ECG	X	X[5]					
CT scan	X				X	X	
Pazopanib		X ---------- X[6]					
Collect/review medication diary		X					
Toxicity assessment	X	X				X[11]	
Tissue for Research Purposes	X[7]					X[7]	

1. Monitoring of BP only at Day 7 +/- 3 days. Can be assessed by any method as long as the study physician is informed of the measurement, verifies any measurement that is not normal, and takes appropriate action.

2. Monitor serum liver tests before initiation of treatment with pazopanib and C1D15, C2D1, C2D15, C3D1, C4D1, C5D1, and as clinically indicated. Periodic monitoring should continue after C5.

3. Women of childbearing potential only.

4. Monitor between every 8 to every 16 weeks.

5. C2D1, C4D1, C7D1 and then every 16 weeks (Day 1 of every fourth cycle) until EOT.

6. To be taken PO QD. Each cycle is 4 weeks long.

7. Optional tissue for research purposes per section 9.1.9. Patients will be followed every 2 months for recurrence and survival until death.

10. Day 1 of each cycle through Cycle 6, then Day 1 of every even-numbered cycle thereafter.

11. Last assessment to take place 30 days following end of treatment.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Tumor Biopsy Form	Prior to starting treatment
Treatment Form Pill Diary	Every cycle
Toxicity Form	Continuous
Treatment Summary Form Tumor Biopsy Form	Completion of treatment
Follow Up Form	Every 2 months until death
Tumor Measurement Form	Baseline, end of every even numbered cycle, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 8 weeks after initiation of pazopanib and then every 8 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

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

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

12.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize

each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

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

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

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

exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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

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

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

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

biopsy resolution/sensitivity.

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

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

12.4.2 Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the

progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

12.4.4 Duration of Response

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.4.5 Progression-Free Survival

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

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual

suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Objectives and Endpoints

The primary objective of this study is to investigate the response rate and progression-free survival of single agent pazopanib in a molecularly selected population of patients with advanced NSCLC. Patients with advanced NSCLC and abnormalities in VEGFR or PDGFR will receive single agent pazopanib at 800 mg daily. Patients may elect at study entry to provide tissue, from either archival or freshly obtained tissue, for research purposes. Optional tumor tissue testing will include whole exome and transcriptome sequencing performed in 10 patients. This willinclude 4 to 6 responders and 4 to 6 non-responders in order to identify the predictors for benefit; initial predictors are the mutations in VEGFR or PDGFR, but sequencing will be used to evaluate for other predictors as well. Patients mayalso elect to submit tissue from any standard of care biopsy performed at the time of progression in an attempt to identify the mechanisms for secondary resistanc.

14.2 Study Design and Analyses

This is an open label, single-arm pilot study to obtain preliminary information of the efficacy of single agent pazopanib. A total of N=20 patients will be enrolled for this study. The sample size is determined primarily based on clinical feasibility rather than statistical power. According to the general guidelines regarding sample size for pilot and translational study[18], however, the proposed sample size will provide us a reasonable precision to estimate the preliminary information. If 4 responders are observed out of 20

patients, for example, we would have 80% confidence that the "true" rate would fall between 9% and 36%. If the "true" response rate is 20% or higher, there would be 80% chance of observing at least 3 responders out of 20 patients. Conversely, there would be <10% chance to observe 3 or more responders if the true rate is less than 5%.

As a pilot study for proof of principal, the data analysis will be descriptive in nature. Demographic and clinical characteristics of the sample, as well as response, toxicity by grade and loss to follow up will be summarized using descriptive statistics. Kaplan-Meier product limit estimator will be used to describe the distribution of progression free survival. The 95% confidence interval (CI) for RR and 6-month PFS will also be calculated. The association between response and specific mutation status will be assessed by permutation analysis. Taking the relationship between VEGFR1 expression and RR as an example, for instance, we first compute the observed test statistics, e.g., the sample mean difference between responders versus non-responders. Then to simulate the null distribution of the test statistics, or the distribution of the observed mean differences if there were truly no difference, we repeat the following 10,000 times: we randomly shuffle the response status, and then calculate the sample difference between the newly designated groups. The permutation p-value equals the proportion of simulations from the null distribution that exceed the observed test statistics.

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APPENDIX A: ECOG Performance Status Scale

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

APPENDIX B: New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

The Criteria Committee of the NYHA, Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX C: Medication Diary

Today's Date: _____ Agent: Pazopanib

Cycle: _____

Patient Name: _____ Study ID#: _____

1. Complete one form for each month. Take 800 mg of pazopanib once daily under fasting conditions (at least one hour before a meal or two hours after a meal). Take pazopanib with a glass of water and drink the glass of water in as little time as possible.
2. Record the date, the amount taken, and when you took it.
3. If you forgot to take your dose, you may make it up if there are more than 12 hours remaining before your next scheduled dose. Otherwise, restart pazopanib at the next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment.

Day	Date	# of tablets taken	Dose time	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
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19				
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24				
25				
26				
27				
28				

APPENDIX D: Investigator Sponsored Study (ISS) Drug Supply Request Form

Principal Investigator: Daniel Morgensztern, MD

GSK Study Number: 201566

In order to facilitate your shipment for drug supply, please fill in the applicable information and send by way of email to Marybeth Nyhuis (mary.nyhuis@novartis.com) and Desiree Hiraman (desiree.hiraman@novartis.com) and cc Lixian Jin (Lixian.jin@novartis.com) on ALL requests.

PLEASE NOTE: UPON RECEIPT OF THIS FORM, IT MAY TAKE UP TO THREE WEEKS TO RECEIVE YOUR DRUG SHIPMENT.

Enter the full shipping address for drug supply:
Institution Name:
Pharmacist:
Street and Room number:
City, State, Zip:
Phone (required):

200 mg Pazopanib (34 tablets per bottle)	GSK1120212 (0.5g)	GSK1120212 (2mg)	Placebo	Powder suspension
#	#	#	#	#

# patients currently receiving Investigational Product	Estimated Monthly Accrual Rate	Total Patient enrollment to date	Estimated monthly supply quantities (Ex- # 200mg bottles, etc)
#	#	#	#

Pazopanib tablets are packaged in a sealed bottle. A content label will be affixed to each bottle identifying the product. Where possible please request a minimum of one month's supply for all ongoing patients. Quarterly supplies would be preferable if your site has capacity.

For Investigator Sponsored Studies, the Investigator/Institution is responsible for following CFR and GCP for labeling and dispensing (21 CFR 312.6).

You are required to label the drug supply provided to you for use in this study to indicate that the drug is being used for investigational purposes in this trial. Per FDA regulation, "the package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use." The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated."

APPENDIX E: SAE Fax Cover Sheet-Suspected/Unknown

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk
Fax Number: 877-778-9739
(If you experience difficulty faxing this form, please contact Sheila Bell at 862-778-6763.

Investigator contact details:
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

This document contains important safety information.
If fax is received in error, please forward to +44 1403 323500

Version 3.0 Dec 2013

APPENDIX F: SAE Fax Cover Sheet-Not Suspected

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk
Fax Number: 877-778-9739
(If you experience difficulty faxing this form, please contact Sheila Bell at 862-778-6763.

Investigator contact details:
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

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