SORAFENIB IN PATIENTS WITH HEPATOPULMONARY SYNDROME:

A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL

Test drug:	Sorafenib		
Clinical study phase:	II		
Version no.:	2.3	Date:	10 June 2016
Sponsor:	**NHLBI**		

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

Title	SORAFENIB IN PATIENTS WITH HEPATOPULMONARY SYNDROME: A DOUBLE-BLIND RANDOMIZED CLNICAL TRIAL
Clinical study phase	II
Study objectives	This study is being conducted to determine whether sorafenib may be effective at treating hepatopulmonary syndrome (HPS) compared to placebo. Primary Aim: 1. To determine whether sorafenib affects alveolar-arterial oxygen gradient ($AaPO_2$) at 12 weeks in patients with HPS Secondary Aims: 2. To determine whether sorafenib affects intrapulmonary shunting at 12 weeks 3. To determine whether sorafenib affects hematopoietic progenitor cell (HPC) and other biomarker levels at 8 and 12 weeks 4. To determine whether sorafenib affects SF-36 questionnaire scores and Mahler dyspnea index at 8 and 12 weeks 5. To determine whether sorafenib affects the distance walked in six minutes at 8 and 12 weeks 6. To determine whether sorafenib affects $AaPO_2$ and PaO_2 at 8 and 12 weeks in patients with HPS 7. To determine whether sorafenib affects oxygen saturation from pulse oximetry at 8 and 12 weeks in patients with HPS 8. To determine whether sorafenib affects functional class at 8 and 12 weeks 9. To determine the safety and side effects associated with sorafenib administration in patients with HPS
Indication	Hepatopulmonary syndrome
Diagnosis and main criteria for inclusion	*Inclusion Criteria* • Diagnosis of HPS: - $AaPO_2 \geq 15$ mm Hg (≥ 20 mm Hg for age > 64 yrs) - Intrapulmonary shunting - Absence of significant restriction (TLC < 70%) or obstruction (FEV1 < 80% & FEV1/FVC < 70%) - Presence of cirrhosis/hepatic fibrosis and/or portal hypertension • Child-Pugh class A or B liver disease • Platelet count $\geq 30\times10^9$ per liter • Hemoglobin ≥ 8.5 g per deciliter • International normalized ratio ≤ 2.3 • Albumin ≥ 2.8 g per deciliter • Total bilirubin ≤ 5 mg per deciliter • Alanine aminotransferase and aspartate aminotransferase ≤ 5 times the upper limit of the normal range • Serum creatinine ≤ 1.5 times the upper limit of the normal range and not

	receiving dialysis • Negative pregnancy test (for women of childbearing potential) at both screening and baseline visits. Post-menopausal women (defined as no menses for one year) and surgically sterilized women are not required to undergo a pregnancy test. • Subjects (men and women) of childbearing potential must agree to use medically acceptable contraception beginning at the signing of the ICF until at least 14 days after the last dose of study drug. • Age ≥ 21 years • Ability to provide informed consent *Exclusion Criteria* • Recent chronic heavy alcohol consumption • Enrollment in a clinical trial or concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 28 days of screening visit • Current hepatic encephalopathy • Active infection • Diagnosis of portopulmonary hypertension • WHO Class IV functional status • Congenital long-QT syndrome • Subjects who have used strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's Wort [Hypericum perforatum], dexamethasone at a dose of greater than 16 mg daily, or rifampin [rifampicin], and/or rifabutin) within 28 days before randomization • Subjects who are currently taking Coumadin®(warfarin) • Active or clinically significant cardiac disease, including: -Active coronary artery disease -Unstable angina (anginal symptoms at rest), new-onset angina within 12 weeks before randomization, or myocardial infarction within 24 weeks before randomization • Liver or other solid organ transplant recipients • Expectation of liver transplant within four months of randomization • Hepatocellular carcinoma that does not meet all of the following criteria: a. Single lesion ≤ 3 cm documented by LIRADS criteria b. Complete response to ablative therapy (TACE, RFA, alcohol ablation) using the modified RECIST criteria one month after therapy with no more than two treatments c. No other lesions develop after initiation of HCC therapy • Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg on repeated measurement) despite optimal medical management. • Any hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 3 or higher within 4 weeks before randomization • Presence of a non-healing wound, non-healing ulcer, or bone fracture • Women who are pregnant or breast-feeding • Major surgery 28 days prior to randomization • Subjects with any previously untreated or concurrent cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before randomization are allowed. All cancer treatments (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) must be completed at least 3 years prior to study entry (i.e., signature date of

	the informed consent form). • Inability to comply with the protocol and/or not willing or not available for follow-up assessments
Study design	Randomized, double-blind, placebo-controlled parallel trial of 30 subjects with HPS. Eligible subjects will be randomly assigned 1:1 to receive either sorafenib (400 mg QD) or placebo for 12 weeks.
Study observations	Subjects evaluated at screening, baseline, and every 2 weeks until the end of the study • Laboratory tests including a complete blood count with diff, routine chemistry tests, and coagulation studies at screening • Chemistries, complete blood count with diff, and coagulation studies monthly while subject is taking study drug • HPC levels at baseline and 8 and 12 weeks • Electrocardiogram, spirometry, and lung volumes at screening • Arterial blood gas at screening/baseline and 12 weeks (8 weeks optional) • Contrast echocardiogram at screening/baseline and 12 weeks • Six minute walk testing at baseline, 8, and 12 weeks • SF-36 and dyspnea index measures at baseline, 8 and 12 weeks
Type of control	Placebo
Number of subjects	30
Plan for statistical analysis	*Primary endpoint:* • Difference in changes in $AaPO_2$ between sorafenib and placebo groups at 12 weeks *Secondary endpoints:* • Difference in changes in intrapulmonary shunting between sorafenib and placebo groups at 12 weeks • Difference in changes in HPC and other biomarker levels between sorafenib and placebo groups at 8 and 12 weeks • Difference in changes in SF36 scores and Mahler dyspnea index scores between sorafenib and placebo groups at 8 and 12 weeks • Difference in changes in distance walked in six minutes between sorafenib and placebo groups at 8 and 12 weeks • Difference in changes in PaO_2 and oxygen saturation by pulse oximetry between sorafenib and placebo groups at 8 and 12 weeks • To assess the effect of sorafenib vs. placebo on $AaPO_2$ at 8 and 12 weeks (for those with available ABG at 8 weeks) • Differences in changes in functional class between sorafenib and placebo groups at 8 and 12 weeks • Safety and side effects associated with sorafenib administration in patients with HPS *Sample size and power:* A total of 30 patients will be enrolled (15 sorafenib, 15 placebo), which will provide 80% power to detect a 11.5 mm Hg difference in changes in $AaPO_2$ ($\alpha = 0.05$). *Data analysis:* The primary analysis will compare the absolute change from baseline to 12 weeks in $AaPO_2$ between the blinded treatment arms using a two-sample t-test. Incidence of adverse events and secondary endpoints will also be analyzed.

LIST OF ABBREVIATIONS

$AaPO_2$	Alveolar-arterial oxygen gradient
ABG	Arterial blood gas
AE	Adverse event
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CBDL	Common bile duct ligation
CCC	Clinical Coordinating Center
CTCAE	Common Terminology Criteria for Adverse Events
DTC	Differentiated thyroid carcinoma
ERK	Extracellular Signal-Regulated Kinases
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPC	Hematopoietic progenitor cell
HCC	Hepatocellular carcinoma
HFSR	Hand-foot-skin reaction
HPS	Hepatopulmonary syndrome
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
MEK	MAP Kinase / ERK Kinase 1
MOP	Manual of Procedures
NCI	National Cancer Institute
NM	Nano Molar number
PaO_2	Partial pressure of oxygen in arterial blood
PBMCs	Peripheral blood mononuclear cells
PDGFR	Platelet Derived Growth Factor Receptor
PI	Principal Investigator
PVCLD	Pulmonary Vascular Complications of Liver Disease
QD	quaque die (every day)
RCC	Renal cell carcinoma
SAE	Serious adverse event
6MWT	Six-minute walk test
TLC	Total lung capacity
TTE	Transthoracic echocardiography
UPHS	University of Pennsylvania Health System
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization

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ABSTRACT

Cirrhotic liver disease afflicts nearly 3 million Americans, and complications of cirrhosis are the fourth leading cause of death between ages 45 and 65. Hepatopulmonary syndrome (HPS) is one such complication which results when pulmonary microvascular dilations lead to an increased alveolar-arterial oxygen gradient ($AaPO_2$) determined by arterial blood gas (ABG) analysis and intra-pulmonary transit of microbubbles visualized by echocardiography after injection of agitated saline in a peripheral vein.

Recently, the tyrosine kinase-inhibitor sorafenib has been shown to reverse aberrant angiogenesis in the lungs, resolve gas exchange abnormalities, and reduce intrapulmonary shunting in the HPS animal model. Sorafenib has been studied extensively in patients with cirrhosis with hepatocellular carcinoma and is FDA-approved in this population.

The primary aim of this randomized, double-blind, parallel-arm, placebo-controlled, phase II trial of 30 patients is to determine whether sorafenib affects $AaPO_2$ at twelve weeks in patients with HPS. The study will also examine the effect of sorafenib on biomarkers of angiogenesis, including circulating hematopoietic progenitor cells, as well as its impact on six-minute walk distance and health-related quality-of-life. Ultimately, the feasibility and safety of the use of sorafenib as a novel therapeutic for the treatment of HPS will be determined.

Chapter 1. Background and Significance

1.1 Background

Cirrhotic liver disease afflicts nearly 3 million Americans, and complications of cirrhosis are the fourth leading cause of death between ages 45 and 65.[1] Hepatopulmonary syndrome (HPS) is one such complication that results when pulmonary microvascular dilations lead to an increased alveolar-arterial oxygen gradient ($AaPO_2$) and intra-pulmonary transit of bubbles visualized by echocardiography after injection of agitated saline. HPS occurs in 33% of patients with cirrhosis and portal hypertension evaluated for liver transplantation (LT),[2] amounting to several hundreds of thousands of Americans with HPS. HPS (even without resting hypoxemia) has been shown to worsen quality of life and double the already significantly elevated risk of death of the cirrhotic patient. Although LT can resolve HPS, it is limited by donor availability and cost, and patients with HPS still have a worse survival rate after transplant compared to others with cirrhosis, in part due to delayed resolution in some. Unfortunately, the significant public health implications of HPS are magnified by the lack of any medical therapies for this lung disease.

Definition, assessment, and mechanisms of gas exchange abnormalities in HPS

The definition of HPS has been established by the Task Force on Pulmonary-Hepatic Disease.[3] A diagnosis of HPS requires documentation of shunting of the lungs and an increased $AaPO_2$ in the absence of parenchymal lung disease. Shunting (or more correctly, pulmonary capillary dilation) is assessed by contrast transthoracic echocardiography (TTE), in which agitated saline microbubbles are injected via a peripheral vein during imaging. Normally, these microbubbles appear in the right side of the heart and then are trapped in the pulmonary microvasculature without reappearing in the left atrium. With vascular dilations, bubbles transit through the lung microcirculation and appear in the left side of the heart three or more cardiac cycles after appearing in the right side ("delayed transit").

The mechanisms for increased $AaPO_2$ in HPS include: arteriovenous malformations (shunt), ventilation/perfusion mismatch, and capillary enlargement (diffusion impairment). Arteriovenous malformations and vascular engorgement are seen in post mortem lung samples from affected patients.[4]

Vascular alterations in portal hypertension: A paradigm for HPS?

Cirrhosis and portal hypertension trigger widespread cardiovascular alterations, and studies have shown a critical role for vascular remodeling. In the liver, angiogenesis, inflammation, and fibrosis create a "wound healing" response, worsening the disease, and vascular endothelial growth factor-A (VEGF-A) and platelet-derived growth factor are overexpressed. Tyrosine kinase inhibition in animal models not only decreases hepatic angiogenesis, liver fibrosis, and intrahepatic resistance but also directly inhibits variceal and collateral formation in the splanchnic vasculature, showing that angiogenesis is integral to vascular sequelae and outcomes in portal hypertension.[5-8]

Mechanisms of HPS

Early reports in HPS focused on decreased pulmonary vascular tone, increased cardiac output, and elevated pulmonary nitric oxide (NO), which normalized after NO inhibition or LT. More recently, it is recognized that reduction in NO does not treat HPS and HPS typically requires weeks to months to resolve after LT, indicating that structural vascular alterations are critical. Animal models have shown that HPS 1) occurs early in the course of induced cirrhosis via common bile duct ligation (CBDL), 2) is associated with increased pulmonary capillary density and growth, and 3) may be prevented by overexpression of the anti-angiogenic molecules endostatin and angiostatin or administration of sorafenib.[9-10] Macrophages have been linked to angiogenesis in a variety of diseases.

Single nucleotide polymorphisms in angiogenic genes are associated with HPS in humans[11] and there are increased circulating hematopoietic progenitor cells (HPCs) in HPS [unpublished data]. While alternative mechanistic pathways have been investigated, the most consistent "signals" in human and animal models point to pulmonary angiogenesis as key to the pathogenesis of HPS.

Physiologic and mechanistic endpoints

The diagnosis of HPS is predicated on measures of gas exchange and intrapulmonary vascular dilation, and these are both improved (and in fact normalized) within 3-6 months after LT, justifying them as end points in this Phase II trial. While there are controversies surrounding HPCs, it is clear that HPCs 1) indicate and contribute to ongoing angiogenesis, 2) are identifiable by their cell surface expression profile, 3) can be reliably measured in multicenter human studies, and 4) may be increased in patients with HPS. HPCs also respond to therapeutic interventions which affect angiogenic potential, making them attractive biomarkers.

Definition and epidemiology of HPS

HPS patients are defined by:

1. $AaPO_2 \geq 15$ mmHg (≥ 20 mmHg for age > 64 yrs)
2. Intrapulmonary shunting by contrast TTE
3. Absence of significant restriction (TLC < 70%) or obstruction (FEV1 < 80% and FEV1/FVC < 70%) on spirometry
4. Presence of cirrhosis/hepatic fibrosis and/or portal hypertension

Sorafenib improves $AaPO_2$ and decreases intrapulmonary shunting in CBDL animal model

We administered sorafenib 5mg/kg daily for two weeks to 3-week CBDL animals to assess effects on the onset of HPS (which develops < 2 weeks after CBDL). Treatment resulted in a significant decrease in lung angiogenesis, and improvement in $AaPO_2$ relative to controls. These findings demonstrate that sorafenib has direct anti-angiogenic effects in the lung which result in improvement in HPS.

1.2 Rationale of the Study

This trial targets a clinically significant pulmonary complication of cirrhosis that affects almost 1 million Americans and dramatically shortens survival, yet has no available medical therapy. HPS is treatable only with LT, but LT is a demanding surgical procedure limited by donor availability with complicated post-operative management and inferior outcomes in patients with HPS. Many patients do not have another indication for LT beyond HPS, so it is not an appropriate therapeutic option for the vast majority of HPS patients. Thus there is an urgent need to study effective medical therapies.

Sorafenib has potent anti-angiogenic effects and treats HPS in the animal model of the disease. The goal of this study is to determine if sorafenib is beneficial and safe in patients with HPS.

1.3 Sorafenib

1.3.1 Preclinical

Sorafenib is a multikinase inhibitor which affects specific targets that are imperative for tumor cell proliferation, including the serine/threonine kinases C and B isoforms of Rapidly Accelerated Fibrosarcoma protein (C-RAF and B-RAF) (IC_{50} 6 and 25 nM respectively) and the receptor tyrosine kinase RET, Flt-3 and stem cell factor receptor tyrosine kinase (c-KIT) (IC_{50} 47, 33 and 68 nM respectively). Sorafenib has potent activity against receptor tyrosine kinases important in tumor angiogenesis, including the vascular endothelial growth factor receptor family (VEGFR1, -2, -3; IC_{50} 26, 90 and 20 nM respectively) and platelet derived growth factor-beta (PDGFR-í; IC_{50} 57 nM). In cellular mechanistic (on target) assays, sorafenib was found to be a potent inhibitor of VEGFR-2, VEGFR-3, and PDGFR and Flt-3 receptor phosphorylation. The anti-tumor activity of sorafenib in vivo is driven by its direct effects on tumor growth through its inhibition of the Raf/MEK/ERK pathway and on the anti-angiogenic activity of the compound. Sorafenib demonstrates broad anti-tumor activity in human tumor xenograft models of liver, kidney, lung, prostate, breast and leukemia. In human hepatocellular tumor cell lines, sorafenib potently inhibited cellular proliferations and Raf/MEK/ERK signaling and induced apoptosis. Sorafenib has potent activity against the human tumor xenograft model of hepatocellular carcinoma with tumor stabilization seen at moderate doses and partial tumor regressions observed at higher doses.

1.3.2 Clinical Experience

Sorafenib as a single agent has been evaluated globally in multiple Phase I and II trials in various malignancies. Three pivotal Phase III, international, multi-institutional, single-agent, randomized, placebo-controlled trials led to sorafenib's approval for renal cell carcinoma (RCC) (US 2005, EU 2006) worldwide,hepatocellular carcinoma (HCC) (2007) worldwide, and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) (US 2013).

TARGET (**T**reatment **A**pproaches in **R**enal Cancer **G**lobal **E**valuation **T**rial) used a randomized, double-blind, placebo-controlled design to assess the efficacy of sorafenib in 903 subjects with advanced RCC who received one prior systemic regimen.[12] The formal analysis of progression

free survival using data available as of January 28, 2005, demonstrated a statistically significant doubling of progression free survival in subjects treated with sorafenib as well as a favorable safety profile of sorafenib in advanced RCC subjects. This trial supported the US and European Union approvals of sorafenib in RCC, followed by regulatory approvals around the world, the first approved agent for this disease in over a decade.

Clinical results in Phase I studies of sorafenib as a single agent were suggestive of a therapeutic effect in HCC and led to the design of a single-arm Phase II study (10874), in which 137 subjects with advanced, inoperable HCC Child-Pugh classes A and B were treated. The results of this study provided the basis for the randomized, placebo-controlled Phase III study in subjects with advanced HCC (SHARP, **S**orafenib **H**CC **A**ssessment **R**andomized **P**rotocol).[13] This large (602 subjects) study was the first international, randomized, double-blind, placebo-controlled study to demonstrate a statistically significant and clinically meaningful improvement in overall survival in advanced HCC subjects treated with sorafenib over placebo. The median overall survival was 10.7 months in the 299-patient sorafenib group and 7.9 months in the 303-subject placebo group (hazard ratio, 0.69; 95% confidence interval, 0.55 to 0.87; $p<0.001$). Thus sorafenib had a statistically significant effect on prolonging overall survival versus placebo, representing a 31% relative reduction in risk of death.

The DECISION (stu**D**y of soraf**E**nib in lo**C**ally advanced or metastat**I**c patient**S** with radioactive **I**odine refractory thyr**O**id ca**N**cer) trial was an international, multicenter, placebo-controlled study. A total of 417 patients with locally advanced or metastatic, RAI-refractory, differentiated thyroid cancer who had received no prior chemotherapy, tyrosine kinase inhibitors, monoclonal antibodies that target VEGF or VEGF receptor, or other targeted agents for thyroid cancer were randomized to receive 400 mg of oral sorafenib twice daily (207 patients) or matching placebo (210 patients).[14] Ninety-six percent of randomized patients had metastatic disease. Sorafenib significantly extended progression-free survival (PFS), the primary endpoint of the study, compared to placebo. The median PFS was 10.8 months among patients treated with sorafenib, compared to 5.8 months among patients receiving placebo (HR=0.587 [95% CI, 0.454-0.758]; $p<0.0001$). Safety and tolerability in the study were generally consistent with the known profile of sorafenib.

As of December 31, 2013, over 10,000 cancer patients with various malignancies have been exposed to sorafenib either as single agent or in combination with other chemotherapeutic agents in Phase I/II/III studies. Sorafenib has been generally well tolerated at doses up to 400 mg p.o. twice daily (BID). The most common drug-related adverse events have included hand-foot skin reaction (HFSR), diarrhea, fatigue, hypertension, pain and rash. Grade 3 and 4 drug-related adverse events are uncommon. There was no evidence of cumulative toxicity and the majority of the adverse events were reversible.

Chapter 2. Objectives and Specific Aims

2.1 Objectives

This study is being conducted to determine whether sorafenib may be effective at treating HPS. The hypothesis is that sorafenib will effectively reverse the physiologic abnormalities which characterize HPS, decreasing $AaPO_2$ and reducing intrapulmonary shunting. A variety of biomarkers will be included to confirm the mechanism of activity, as well as a number of quality-of-life, functional, and clinical outcome endpoints to support the primary analyses. The goals of this study are 1) to provide evidence of a significant effect of sorafenib on HPS physiology, 2) to determine whether there are positive "signals" for sorafenib in terms of how these patients feel or function, 3) to demonstrate the feasibility of performing an NIH-funded clinical trial in HPS, and 4) to find treatment effect sizes for clinical endpoints in order to plan a Phase III trial. This randomized, placebo-controlled trial of 30 patients addresses the following specific aims.

2.2 Specific Aims

Primary Aim:

1. To determine whether sorafenib affects $AaPO_2$ at 12 weeks in patients with HPS

Secondary Aims:

2. To determine whether sorafenib affects intrapulmonary shunting at 12 weeks
3. To determine whether sorafenib affects HPC and other biomarker levels at 8 and 12 weeks
4. To determine whether sorafenib affects SF-36 questionnaire scores and Mahler dyspnea index at 8 and 12 weeks
5. To determine whether sorafenib affects the distance walked in six minutes at 8 and 12 weeks
6. To determine whether sorafenib affects $AaPO_2$ and PaO_2 at 8 and 12 weeks in patients with HPS
7. To determine whether sorafenib affects oxygen saturation from pulse oximetry at 8 and 12 weeks in patients with HPS
8. To determine whether sorafenib affects functional class at 8 and 12 weeks
9. To determine the safety and side effects associated with sorafenib administration in patients with HPS

Other aims include demonstrating the feasibility of studying a novel therapeutic in HPS and determining the sample size necessary to conduct a Phase III study.

Chapter 3. Screening, Subject Selection and Randomization

3.1 Recruitment: Identification and Screening Process

Thirty subjects with HPS will be recruited at the University of Texas - Houston, the Mayo Clinic-Rochester, MN, Mayo Clinic - Phoenix, AZ), Columbia University Medical Center, the Medical University of South Carolina, Northwestern University, and the University of Pennsylvania Health System (UPHS) and randomized to either sorafenib or placebo in a double blind fashion. Patients will be identified by the medical staff in the liver and pulmonary clinics and liver transplant programs. Recruitment efforts will also expand to additional clinics and health systems in the surrounding areas of the previously mentioned sites. Phone calls to local pulmonologists and hepatologists seeking referrals and/or letters describing the study and seeking referrals for this study will be sent to pulmonologists and hepatologists in these surrounding clinics.

For screening, we will perform computerized searches at the sites for patients with an ICD-9 or ICD-10 code for HPS (573.5 or K76.81) or with late shunting by contrast echo with an abnormal arterial blood gas (ABG). In addition, an active recruitment effort will be mounted by sending emails to pulmonologists and hepatologists at the recruiting centers and surrounding centers.

We expect to screen approximately 3,000 patients (including both "new evals" for LT and prevalent cirrhotic patients at each center) providing ~900 patients with HPS over approximately 3 years between the seven centers. Of these, we expect approximately 20% (180) to meet inclusion/exclusion criteria. Using our current study numbers as a guide, we expect approximately 80-90 patients to consent and approximately 32%-35% to meet inclusion and randomize, leaving 30 in the final study sample.

3.2 Subject Selection Criteria

3.2.1 Inclusion Criteria

- Diagnosis of HPS:
  - $AaPO_2 \geq 15$ mm Hg (≥ 20 mm Hg for age > 64 yrs)
  - Intrapulmonary shunting determined by echo core (bubbles appear ≥ 3 beats after appearance of bubbles in the right atrium on contrast TTE)
  - Absence of significant restriction (TLC < 70%) or obstruction (FEV1 < 80% & FEV1/FVC < 70%) (If TLC is not measurable, then FVC may be used to meet this criterion)
  - Presence of cirrhosis/hepatic fibrosis and/or portal hypertension
- Child's class A and B liver disease
- Platelet count $\geq 30\times10^9$ per liter
- Hemoglobin ≥ 8.5 g per deciliter
- International normalized ratio ≤ 2.3
- Albumin ≥ 2.8 g per deciliter
- Total bilirubin ≤ 5 mg per deciliter

- Alanine aminotransferase and aspartate aminotransferase ≤ 5 times the upper limit of the normal range
- Serum creatinine ≤ 1.5 times the upper limit of the normal range and not receiving dialysis
- Negative pregnancy test (for women of childbearing potential) at both screening and baseline visits. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
- Subjects (men and women) of childbearing potential must agree to use medically acceptable contraception beginning at the signing of the ICF until at least 14 days after the last dose of study drug.
- Age ≥ 21 years
- Ability to provide informed consent

3.2.2 Exclusion Criteria

- Recent chronic heavy alcohol consumption
- Enrollment in a clinical trial or concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) within 28 days of screening visit
- Current hepatic encephalopathy
- Active infection
- Diagnosis of portopulmonary hypertension
- WHO Class IV functional status
- Congenital long-QT syndrome
- Subjects who have used strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's Wort [Hypericum perforatum], dexamethasone at a dose of greater than 16 mg daily, or rifampin [rifampicin], and/or rifabutin) within 28 days before randomization
- Subject who are currently taking Coumadin®(warfarin)
- Active or clinically significant cardiac disease, including:
  - Active coronary artery disease
  - Unstable angina (anginal symptoms at rest), new-onset angina within 12 weeks before randomization, or myocardial infarction within 24 weeks before randomization
- Liver or other solid organ transplant recipients
- Expectation of liver transplant within four months of randomization
- Hepatocellular carcinoma that does not meet all of the following criteria:
  a. Single lesion ≤ 3 cm documented by LIRADS criteria
  b. Complete response to ablative therapy (TACE, RFA, alcohol ablation) using the modified RECIST criteria one month after therapy with no more than two treatments
  c. No other lesions develop after initiation of HCC therapy
- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg on repeated measurement) despite optimal medical management
- Any hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 3 or higher within 4 weeks before randomization
- Presence of a non-healing wound, non-healing ulcer, or bone fracture
- Women who are pregnant or breast-feeding
- Major surgery within 28 days of randomization.

- Subjects with any previously untreated or concurrent cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before randomization are allowed. All cancer treatments (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) must be completed at least 3 years prior to study entry (i.e., signature date of the informed consent form)
- Inability to comply with the protocol and/or not willing or not available for follow-up assessments

3.3 Randomization

Randomization will incorporate Field Center as a stratification variable, and will be blocked to ensure balance over time. The Research Pharmacy at the University of Pennsylvania will prepare numbered drug kits which will be shipped and stored at each Field Center. At the baseline visit, when the research coordinator registers the patient as meeting all inclusion/exclusion criteria, the number of the kit for use by that patient will be provided by the web-based database.

3.4 Maintenance of Treatment Randomization Code and Procedures for Breaking the Code

Unblinding may only occur for emergency purposes which would affect clinical care. Investigators should note that the occurrence of a serious adverse event or progressive disease should not routinely precipitate the immediate unblinding of the label. If unblinding is necessary for the treatment of a subject for a serious adverse event, every attempt should be made to contact the Principal Investigator (PI) prior to unblinding. If this is not feasible, then the Principal Investigator must be contacted within 24 hours of unblinding.

Chapter 4. Treatments

4.1 Sorafenib

Sorafenib tablets are purchased from Bayer HealthCare. The 200-mg tablet formulation contains sorafenib tosylate and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, and magnesium stearate. The tablets have a film coating comprised of hypromellose, polyethylene glycol, titanium dioxide, and red ferric oxide, which has no effect on the release rate of the active ingredient, sorafenib tosylate. The tablets are un-debossed, salmon colored, weigh approximately 350 mg each, and are 10 mm (millimeter) round in shape.

The chemical name for sorafenib tosylate is 4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido] -phenoxy}-pyridine-2-carboxylic acid methylamide-4-methylbenzene-sulfonate, and its molecular weight is 637 daltons. The structure of sorafenib is depicted in Figure 0-1.

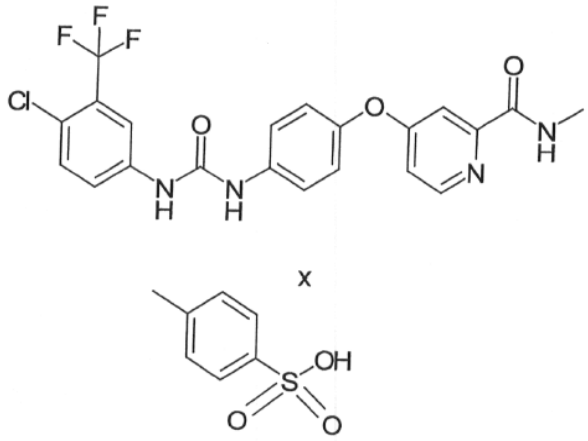


Figure 0-1: Structure of Sorafenib (BAY 43-9006)

Sorafenib tablets do not need to be protected from light. They are sufficiently stable with regard to light, oxidation, thermal stress, and hydrolytic degradation. The formulation is presented as an immediate release dosage form, i.e., the active ingredient is completely dissolved under in vitro test conditions within a short period of time.

Sorafenib 400 mg QD by mouth or an identically encapsulated placebo will be administered daily as the starting dose. This dosage is significantly above the effective weight-based dose in the HPS animal experiments and is a commonly attainable dose in clinical practice.

Subjects will be instructed on the proper administration of sorafenib. Sorafenib tablets should be taken at approximately the same time each day preferably in the morning. Sorafenib tablets should be taken without food, at least 1 hour before and at least 2 hours after a meal, and with up to 240 mL (approximately 1 cup or 8 oz) of water.

4.2 Placebos and Packaging of Study Medication

Sorafenib and placebo tablets will be over-encapsulated by the Research Pharmacy at the University of Pennsylvania. At the Research Pharmacy, capsules will be packaged into HDPE bottles with a liner, cotton, and childproof cap. Bottles will be fully labeled to meet state and FDA requirements, and packaged into labeled kits. There will be one bottle of drug product dispensed to study subjects at the Baseline Visit, Visit# 3 (Week 4), and Visit # 4 (Week 8) during the treatment phase. Study drug must be stored at room temperature and protected from moisture. Subjects will be asked to bring bottles to each study visit to allow for tracking of compliance and medication control. At the end of the study, after accountability has been completed and notification by the Clinical Coordinating Center (CCC) has been sent, study product can be destroyed at each Field Center's Research Pharmacy.

4.3 Administration of Study Medication

The occurrence of planned or unplanned procedures may warrant holding study medication from a patient safety standpoint (surgery, etc.). As holding such therapy when these procedures are planned or occur is part of normal usage (and required to maximize patient safety in the trial), the patient's physician will be allowed to temporarily stop the sorafenib/placebo and restart therapy when considered safe from standard clinical practice. The timing and duration of such events will be recorded. Temporary interruption of sorafenib prior to major surgical procedures is recommended. The decision to resume sorafenib should be based on clinical judgment of adequate wound healing, which will be the recommended strategy in this study. Patients will be instructed to inform all treating physicians of their participation in the trial and the possibility of sorafenib use, and we will alert the patient's primary medical doctor and HPS clinician of participation in this trial.

4.4 Management of Other Medical Therapies during the Trial

All concomitant medications (including start/stop dates and indication) must be recorded in the subject's source documentation.

Permitted prior and concomitant therapy

- Treatment with non-conventional therapies (e.g., herbs [with the exception of St. John's Wart], acupuncture) and vitamin/mineral supplements is acceptable.
- Subjects may receive standard of care for any underlying illness.
- In the event of neutropenia, anemia, or thrombocytopenia, subjects may receive appropriate supportive care (e.g., transfusion, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). This supportive care should not substitute a recommended dose modification.
- Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with sorafenib. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when these are co-administered with sorafenib.

Excluded concomitant therapy

- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids.
  - However, prophylactic anticoagulation as described below is allowed:
    - Low dose aspirin (≤ 100 mg daily).
    - Prophylactic doses of heparin.

4.5 Treatment Masking

All study personnel and subjects will be masked for the duration of the study until the last subject completes follow-up assessments. The University of Pennsylvania Research Pharmacist will be unmasked, the statistical analyst, and the DSMB will be unmasked; the Research Pharmacist will supply the DSMB and analyst with the drug/placebo identifier.

4.6 Drug Logistics and Accountability

Each Field Center will have limited supply of study drug kits available on study, which will be replenished by the University of Pennsylvania Research Pharmacy as they are dispensed to study subjects. All study drugs dispensed to the Field Centers will be stored in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

4.6.1 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational agent using the drug accountability form.

4.6.2 Destruction and Return

At the end of the study, unused supplies of sorafenib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

Chapter 5. Data Collection

5.1 Study Visits

5.1.1 Informed Consent

Potentially eligible subjects will be referred if there is interest in enrolling. The following procedures will be performed during the screening process:

- Sign and date the ICF and HIPAA release
- Review of inclusion/exclusion criteria
- Schedule Screening Visit

After the subject has consented, the subject will be scheduled for a screening visit within 56 days if the subject meets inclusion/exclusion criteria thus far. The research coordinator will call the subject 1-2 days prior to the screening visit and send a reminder letter as well if the screening visit is not conducted within the 2 weeks following consent. The coordinator will instruct the subject to not eat or drink (except water) and to avoid heavy exercise for 12 hours prior to the study visit. The coordinator will also request that the subject refrain from smoking for 12 hours prior to the study visit. Subjects will be instructed to hold their routine medications on the morning of the visit and to bring their medications and a snack with them to the visit to take at the center after blood draw.

5.1.2 Visit 0: *(Screening)*

The following procedures will be performed during the screening process:

- Review medical history
- Vital signs
- Physical exam
- WHO functional capacity assessment
- Review current medications
- Labs/Phlebotomy: complete blood count with differential, including hemoglobin, hematocrit, and platelet count, clinical chemistries, and coagulation studies
- Serum HCG pregnancy test (for women of childbearing potential)
- Electrocardiogram (ECG)
- Spirometry and lung volumes
- ABG (seated while breathing room air)
- Contrast echocardiogram
- Provide instructions on recording of new medications and dose changes
- Instruct subjects to bring routine medications to baseline visit and to avoid heavy exercise and smoking for 12 hours before the baseline visit

After the consent and screening visits, the subject will be scheduled for a baseline study visit within 28 days at the study center if all inclusion/exclusion criteria are met. The research

coordinator will call the subject and send a follow-up letter more than two weeks before the baseline visit as a reminder.

5.1.3 Visit 1: *(Baseline)*

The research coordinator will call the subject 1-2 days before the visit as a reminder. The coordinator will instruct the subject to not eat or drink (except water) and to avoid heavy exercise for 12 hours before the study day assessment. The coordinator will also request that the subject refrain from smoking for 12 hours prior to the study visit. Lastly, subjects will be instructed to hold their routine medications on the morning of the visit and to bring their medications and a snack with them to the visit to take at the center after blood draw.

Baseline information will be used to characterize the participants and to compare the experimental groups with regards to demographics and other variables. Safety laboratories, ABG, and contrast TTE obtained at the screening visit will be used as baseline measurements. Eligibility criteria will be reviewed prior to randomization to treatment group.

The subject will arrive at the study site outpatient clinic. The following procedures will be performed:

- Review of inclusion/exclusion criteria
- Phlebotomy (HPC levels, angiogenesis biomarkers, etc.)
- Urine collection for pregnancy test (for women of childbearing potential)
- Eat a small snack
- Interim medical history
- Vital signs
- Physical exam
- WHO functional class assessment
- Review current medications
- Complete SF36
- Complete Mahler Baseline Dyspnea Index (BDI)
- Six minute walk testing with Borg scores
- Randomization to treatment group
- Dispense supply of study drug
- Dispense study supply of moisturizing cream
- Reinforce instructions on recording of new medications and dose changes
- Reinforce instructions on bringing the subject's routine and study medications to all visits

Blood samples for study assays will be processed and banked or shipped, and urine pregnancy test will be performed (for women of child-bearing potential).

After the labs have been drawn, the subject will eat a snack. The investigator or research nurse will take an interim medical history and perform a physical examination including vitals, review current medications, and complete the BDI. The subject will complete the SF36.

The subject will then perform the six-minute walk test (6MWT).

After confirming a negative pregnancy test (for subjects of child-bearing potential) and other inclusion criteria, the subject will be randomized to a treatment group using the Web-based database. A pre-packaged 4 week supply of study medication (encapsulated sorafenib 200 mg or placebo capsules) will be given to the subject. Subjects will be instructed on the proper administration of the study medication. Study medication capsules should be taken at approximately the same time each day preferably in the morning. Study medication capsules should be taken without food, at least 1 hour before or at least 2 hours after a meal and with up to 240 mL (approximately 1 cup or 8 oz) of water.

After study drug dispensing and instruction, the study coordinator should supply the subject with study moisturizing cream and instruct the subject to apply twice daily to hands and feet upon starting study drug.

Because diarrhea and fatigue are also common side effects, preventive/management strategies for diarrhea and fatigue should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status for diarrhea).

Once instruction has been given to the subject and the subject expresses understanding, the research coordinator will thank the subject for their attendance and reinforce compliance with the study medication and protocol. The subject's medical doctors will be alerted to the subject's participation in the clinical trial.

5.1.4 Visit 2: *(Week 2 ± 3 days)*

The research coordinator will call the subject 1-2 days before the visit as a reminder. Subjects will be encouraged to take their routine medication and study medication as they usually would prior to the visit, but subjects will still be instructed to bring their routine and study medications with them to each visit.

The subject will arrive at the study site outpatient clinic. The following procedures will be performed:

- Interim medical history
- Vital signs
- Physical exam
- Review current medications
- Study drug accountability
- Reinforce instructions on recording of new medications
- Reinforce instructions on bringing the subject's routine and study medications to all visits

The research coordinator will reinforce instructions on bringing the subject's routine and study medications to each visit and will also perform a pill count. The investigator or research nurse will take an interim medical history and perform a physical examination, and assess side effects.

The research coordinator will thank the subject for their attendance and reinforce compliance with the study medication and protocol.

5.1.5 Visit 3: *(Week 4 ± 3 days)*

The research coordinator will call the subject 1-2 days before the visit as a reminder. Subjects will be encouraged to take their routine medication and study medication as they usually would prior to the visit, but subjects will still be instructed to bring their routine and study medications with them to each visit.

The subject will arrive at the study site outpatient clinic. The following procedures will be performed:

- Phlebotomy: complete blood count with differential, including hemoglobin, hematocrit, and platelet count, clinical chemistries, coagulation studies**.**
- Serum HCG pregnancy test (for women of childbearing potential)
- Interim medical history
- Vital signs
- Physical exam
- Review current medications
- Study drug accountability
- Reinforce instructions on recording of new medications
- Reinforce instructions on bringing the subject's routine and study medications to all visits
- Dispense supply of study drug

Blood samples for safety monitoring will be sent to the field center's laboratory.

The research coordinator will reinforce instructions on bringing the subject's routine and study medications to each visit and will also perform a pill count. The research coordinator will dispense a re-supply of study medication (encapsulated sorafenib 200 mg or placebo capsules) to the subject. The investigator or research nurse will take an interim medical history and perform a physical examination, and assess side effects.

The research coordinator will thank the subject for their attendance and reinforce compliance with the study medication and protocol. The coordinator will contact the clinician 24 hours after the study visit to discuss the clinical lab results.

5.1.6 Telephone Contacts 1 & 2: (*Week 6 ± 3 day, Week 10 ± 3 days)*

The following will be assessed during telephone contacts 1 & 2.

- Review current medications
- Study drug accountability
- Reinforce instructions on recording of new medications
- Reinforce instructions on bringing the subject's routine and study medications to all visits

and to avoid heavy exercise and smoking for 12 hours before Visits #4 and #5

The research coordinator or nurse will call the subject at Week 6 and at Week 10 to ask about the subject's general health and to review any changes in the medication they are taking. The research coordinator or nurse will also ask about any missed doses or compliance issues the subject reports.

The research coordinator will reinforce instructions on bringing the subject's routine and study medications to each visit. The research coordinator or nurse will also remind the subject of their next appointment and any remind the subject not eat or drink (except water) and to avoid heavy exercise for 12 hours prior to the next study visit. The coordinator will also request that the subject refrain from smoking for 12 hours before the next scheduled visit. Subjects will be instructed to hold their routine medications on the mornings of the visit following these telephone contacts (Visits #4 and #5) and to bring their medications and a snack with them to the visit to take at the center after blood draw.

5.1.7 Visit 4: *(Week 8 ± 3 days)*

The research coordinator will call the subject 1-2 days before the visit as a reminder. The coordinator will instruct the subject to not eat or drink (except water) and to avoid heavy exercise for 12 hours before the study day assessment. The coordinator will also request that the subject refrain from smoking for 12 hours prior to the study visit. Subjects will be instructed to hold their routine and study medication the morning of the visit and to bring a snack as well as their routine and study medications with them to the visit to take at the study center after blood draw.

The subject will arrive at the study site outpatient clinic. The following procedures will be performed:

- Phlebotomy: complete blood count with differential, including hemoglobin, hematocrit, and platelet count, clinical chemistries, coagulation studies, biomarkers, other study labs
- Serum HCG pregnancy test (for women of childbearing potential)
- Eat a small snack
- ABG (seated while breathing room air)(Optional)
- Interim medical history
- Vital signs
- Physical exam
- WHO functional class assessment
- Review current medications
- Complete SF36
- Complete Mahler Transition Dyspnea Index (TDI)
- 6MWT with Borg scores
- Reinforce instructions on recording of new medications and dose changes
- Reinforce instructions on bringing the subject's routine and study medications to all visits
- Dispense supply of study drug

Blood samples for study assays will be processed and banked or shipped, whereas samples for safety monitoring will be sent to the field center's hospital laboratory.

After the labs have been drawn, the subject will eat a snack. The investigator or research nurse will take an interim medical history and perform a physical examination including vitals, review current medications, and complete the TDI. The subject will complete the SF36.

The subject will then perform the 6MWT.

After the 6MWT, the research coordinator will perform a pill count. The research coordinator will reinforce proper administration of the study medication. The research coordinator will also reinforce instructions on bringing the subject's routine and study medications to each visit.

The research coordinator will thank the subject for their attendance and reinforce compliance with the study medication and protocol. The coordinator will contact the clinician 24 hours after the study visit to discuss the clinical lab results.

5.1.8 Visit 5: *(Week 12 ± 3 days)*

The research coordinator will call the subject 1-2 days before the visit as a reminder. The coordinator will instruct the subject to not eat or drink (except water) and to avoid heavy exercise for 12 hours before the study day assessment. The coordinator will also request that the subject refrain from smoking for 12 hours prior to the study visit. Subjects will be instructed to hold their routine and study medication the morning of the visit and to bring a snack as well as their routine and study medications with them to the visit to take at the study center after blood draw.

The subject will arrive at the study site outpatient clinic. The following procedures will be performed:

- Phlebotomy: complete blood count with differential, including hemoglobin, hematocrit, and platelet count, clinical chemistries, coagulation studies, biomarkers, other study labs
- Serum HCG pregnancy test (for women of childbearing potential)
- Eat a small snack
- ABG (seated while breathing room air)
- Contrast echocardiogram
- Interim medical history
- Review current medications
- Vital signs
- Physical exam
- WHO functional class assessment
- Complete SF36
- Complete Mahler Transition Dyspnea Index (TDI)
- 6MWT with Borg scores
- Study drug accountability and collection of remaining study drug

Blood samples for study assays will be processed and banked or shipped.

After the blood draw the subject will eat a snack. ABG and contrast echocardiography will then be performed. The investigator or research nurse will take an interim medical history and perform a physical examination including vitals, review current medications, and complete the TDI. The subject will complete the SF36.

The subject will perform the 6MWT.

After the completion of the walk test, the research coordinator will perform a pill count and collect any unused study drug. The research coordinator will thank the subject for their attendance and reinforce compliance with the protocol.

5.1.9 Telephone contact #3 OR Visit 6 – Two Week Follow Up: *(Week 14 ± 3 days)*

Week 14 will be conducted as a telephone contact or a clinic visit should the subject have moderate to serious unresolved AE's and/or the local investigator requires a clinic visit.

For a telephone contact, the research coordinator or nurse will call the subject to ask about the subject's general health and changes in the medication they are taking. The research coordinator or nurse will also review any unresolved AE's the subject had ongoing to determine if they have resolved.

If the local investigator requires a clinic visit due to moderate to serious unresolved AE's or other concerns, the research coordinator will call the subject 1-2 days before the visit as a reminder. Subjects will be instructed to bring their regular medications with them to the visit and to take their regular medications before coming to the study center.

The subject will arrive at the study site outpatient clinic. The following procedures will be performed:

- Phlebotomy: complete blood count with differential, including hemoglobin, hematocrit, and platelet count, clinical chemistries, coagulation studies
- Interim medical history
- Vital signs
- Review current medications
- Physical exam

The investigator or research nurse will take an interim medical history and perform a physical examination including vitals and review current medications.

The research coordinator will thank the subject for his or her participation.

5.1.10 Future Research

In the future, the University of Pennsylvania may conduct candidate gene and/or genome-wide analysis (GWAS) for HPS research with research samples provided during the study. The main focus of the blood testing will be HPC and biomarker analysis as described in the aims of this study. However, we may also look for genetic determinants of the disease state or genetic predictors of drug efficacy. Any GWAS results which result from this analysis will be shared for research purposes through the National Institutes of Health (NIH) GWAS data repository in accordance with their usual policies. Information about genetic and physical characteristic information will be identified by use of a code number to protect privacy.

5.2 Study Schedule of Procedures

The table below summarizes the study procedures.

Table 1. Study Procedures

	Consent	Screen	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14
Visit #	-1	0	1	2	3		4		5	(6) §
Telephone contact #						1		2		3
Day#	-84 - -28	-28-1	0	14 ± 3	28 ± 3	42 ± 3	56 ± 3	70 ± 3	84± 3	98 ± 3
Informed consent	X									
History and physical exam										
Medical history		X								
Medications		X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X		X		X	X§
Physical exam		X	X	X	X		X		X	X§
General testing										
Chemistry, CBC with diff, LFT		X			X		X		X	X§
Prothrombin time / INR		X			X		X		X	X§
Pregnancy test (as appropriate)		X	X*		X		X		X	
Electrocardiogram		X								
Spirometry / Lung Volumes		X								
Endpoint assessment										
ABG		X					(X)‡		X	
Contrast Echo		X							X	
HPCs / Biomarkers			X				X		X	
Six-minute walk test			X				X		X	
SF-36 / MDI (BDI or TDI)			X				X		X	
WHO functional capacity		X	X				X		X	
Study procedures										
Dispense study med			X		X		X			
Assess:										
Adverse events			X	X	X	X	X	X	X	X
Med compliance				X	X	X	X	X	X	

*****At Baseline (Visit 1), pregnancy will be assessed by urine testing. All other pregnancy tests will be measured using blood samples.

(X)‡Optional at this visit.

§ Week 14 will be conducted as a telephone contact or a clinic visit should the subject have moderate to serious unresolved AE's and/or the local investigator requires a clinic visit. Testing marked "**§**" will be completed if a clinic visit is conducted.

5.3 Subject Retention and Drug Compliance

We will enforce subject retention in several ways. We will record extensive contact information for each subject at their enrollment in the trial. This will include home, work, and cellular telephone numbers. The research coordinator will call before each study visit to remind the subject to attend. Subjects will be reimbursed for their time participating in the study and for reasonable travel expenses necessary for their participation in the study (parking/mileage) in the amount of $250 per study visit that they attend (with an additional $25 at Visit 4 for allowing optional ABG to be performed). – Participants traveling over 60 miles will be also reimbursed for additional travel expenses including, mileage, hotels and meals up to an additional $300 per visit. In order to receive reimbursement, a copy of the original receipts for expenses will be required.

An adequate record of receipt, distribution, and return of all study drugs must be kept.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations.

The research coordinator and physician will explain the importance of compliance with the study protocol at each subject contact. If a subject fails to comply with a study visit, the coordinator will contact him or her by telephone. If this fails, the coordinator will send two certified express letters one week apart, to request follow-up.

We have considered how to minimize noncompliance with therapy. We will strongly emphasize the importance of complying with the study drug treatment. Nonetheless, we will perform pill counts at visits and record episodes when medication is withheld for any reason. If a subject wishes to drop-out from the treatment phase of the study or has a serious adverse event (SAE) (whether related to study drugs or not), we will continue to follow-up with the subject for study assessments to assist with safety monitoring and to avoid the problems introduced by missing data. The inclusion of such follow-up data will allow for analysis by intention-to-treat.

If a subject is withdrawn from the treatment portion of the study for any reason, the subject will be strongly encouraged to continue with the remainder of the study assessments, as scheduled. If a subject does not wish to return for the remainder of the study assessments/visits, subject will be asked to attend one more visit at week 12 to complete end of study assessments.

Chapter 6. Assessment of Efficacy and Outcome Measures

6.1 Assessments of Efficacy

The primary objective of this study is to assess the effect of sorafenib versus placebo on the $AaPO_2$ in subjects with HPS at 12 weeks.

6.1.1 Alveolar-Arterial Oxygen Gradient ($AaPO_2$)

The $AaPO_2$ (assessed by seated arterial blood gas sampling while breathing room air) is the primary endpoint of this Phase II study for several reasons. The diagnosis of HPS is predicated on abnormal gas exchange, which normalizes after LT. We have shown that interventions which decrease lung angiogenesis and intrapulmonary shunting in the animal model of HPS also improve $AaPO_2$. The $AaPO_2$ is strongly associated with the degree of intrapulmonary shunting by contrast TTE in HPS.

6.2 Secondary Outcome Measures

There are several secondary objectives of this study. They include:

- To assess the effect of sorafenib vs. placebo on intrapulmonary shunting at 12 weeks
- To assess the effect of sorafenib vs. placebo on plasma HPC levels and other angiogenesis biomarkers
- To assess the effect of sorafenib vs. placebo on six-minute walk distance at 8 and 12 weeks
- To assess the effect of sorafenib vs. placebo on SF-36 questionnaire scores and Mahler dyspnea index at 8 and 12 weeks
- To assess the effect of sorafenib vs. placebo on PaO_2 and oxygen saturation by pulse oximetry at 8 and 12 weeks
- To assess the effect of sorafenib vs. placebo on $AaPO_2$ at 8 and 12 weeks (for those with available ABG at 8 weeks)
- To assess the effect of sorafenib vs. placebo on functional class at 8 and 12 weeks
- To assess the safety and side effects associated with sorafenib administration in subjects with HPS

6.2.1 HPC Levels

We will assess the effect of sorafenib on HPC levels as biomarkers of angiogenesis in subjects with HPS.

6.2.2 Intrapulmonary Shunting

Intrapulmonary shunting will be assessed using contrast TTE in a standardized fashion. A decrease in arterio-venous dilations in the lungs with the administration of sorafenib should be associated with a decrease in the degree of intrapulmonary passage of bubbles using agitated saline.

6.2.3 Six-Minute Walk Distance

Walking is the most basic form of exercise and is integral to daily activities. The 6MWT is a standardized, timed submaximal test of unencouraged, self-determined distance walked which is reliable and valid. Standardized test methods and scripted and timed statements have been established in prior studies and will be used. The 6WMT is also non-invasive and safe.

The 6MWT will be performed at baseline, 8 weeks and 12 weeks. The subject will be instructed to wear comfortable clothing and shoes. The test will be performed at approximately the same time of day at each visit. The Borg score for dyspnea and oxygen saturation will be recorded at the beginning and conclusion of each test.

6.2.4 SF-36 / Mahler Dyspnea Index

The SF36 is one of the most widely used generic measures of subjective health status. The SF36 includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical and emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Subjects will complete the SF36 at baseline and weeks 8 and 12.
The Mahler Dyspnea Index (MDI) is an interview-administered instrument that allows patients to assess their level of dyspnea. Baseline scores are called the BDI and depend on ratings for three different categories: functional impairment, magnitude of task and magnitude of effort. Limitation of ability in each of these three categories of dyspnea is graded from 0 (severe) to 4 (unimpaired) in each category. The ratings for the three categories are added to form the total baseline score, ranging from 0 (severe) to 12 (no dyspnea). The TDI score ranges from −3 (major deterioration) to +3 (major improvement) for each domain (compared with the same domain of the BDI) with the TDI focal score being the sum of scores for the three domains (−9 to +9).

Chapter 7. Statistical Considerations

7.1 Study Design

The proposed research project involves one primary and several secondary objectives. To address these aims, we will conduct a double-blind, randomized, placebo-controlled trial. Blood sampling and 6MWT will be performed at baseline, 8 weeks, and 12 weeks. Contrast TTE and ABG will be performed at screening/baseline and at 12 weeks, with an optional ABG at 8 weeks.

7.2 Disposition of Subjects and Baseline Comparisons

Summaries of all subjects screened, recruited, and randomized and the number who complete visits at 8 and 12 weeks post-randomization will be provided, according to the CONSORT guidelines. The treatment groups will be compared at baseline with respect to demographics and baseline measurements related to efficacy and safety without formal statistical testing.

7.3 Statistical Procedures

7.3.1 Data Analysis

The intent-to-treat analysis will include all randomized subjects. Hypothesis testing will use two-sided α level 0.05 without correction for multiplicity. We will summarize demographics and baseline and follow-up endpoints.

7.3.2 Univariate Analysis

Continuous variables will be summarized by the mean, median, standard deviation, and range, as appropriate. We will use contingency tables for discrete and dichotomous variables.

7.3.3 Analyses of Treatment Assignment and Outcome Measures

The primary analysis will compare the absolute change from baseline to 12 weeks in $AaPO_2$ between the blinded treatment arms using a two-sample t-test. This will be supplemented with mixed analysis of variance methods to allow inclusion of the baseline value (fixed) and clinical site (random). If the data are not normally distributed, they will be transformed. For dichotomous outcomes, logistic regression will be used. For secondary outcomes with additional longitudinal assessments, including 8- and 12-week results of the plasma biomarker assessments, 6MWT, SF-36, ABG, and the Mahler Dyspnea Index, linear mixed effects models or generalized estimating equations will be used as appropriate.

All patients will be assessed for toxicity and included in the safety analysis. This analysis will include summaries of the incidence and grade of toxicities. Patients will be evaluated for serious adverse events. Safety interim analyses will be performed and reported at each DSMB meeting.

7.3.4 Survival Analysis

A log-rank statistic will be used to compare time to death, although there are expected to be few events.

7.3.5 Missing Data and Dropouts

We will attempt to minimize missing data, however we have planned for its occurrence. For subjects lost to follow-up, we will use all of the information available until the end of follow-up. This protocol will continue to be followed and test procedures performed as prescribed even if a subject drops out of the therapeutic portion of the study. That is, if a subject decides that he/she does not wish to continue taking the study drug(s), the subject will stop the investigational treatment, but will still be strongly encouraged to continue to follow up with the study personnel for all scheduled study procedures (e.g., phlebotomy, echocardiography), so that missing data (and assumptions regarding these data) will be minimized.

For patients lost to follow-up, we will use all the information available up to the time of loss to follow-up. For the primary end point, we will perform an analysis of completers only. We will also perform additional sensitivity analyses using imputation to assess the impact of missing data for the primary and secondary end points.

7.4 Sample Size and Power Calculations

We have considered the effects of the intervention (sorafenib) on the primary and secondary outcome measures as independent hypotheses, setting α=0.05 for each. We expect 30 patients to enroll in the study and anticipate a 10% drop-out rate, accounted for in our power calculations. Assuming that 1 standard deviation in $AaPO_2$ is ~10 mm Hg, we have sufficient power to detect a difference of 11.5 mm Hg in the change of $AaPO_2$ over 12 weeks between active treatment and placebo.

7.5 Interim Monitoring Guidelines

Regular reports of safety will be compiled and presented to the DSMB at six months and then yearly; there are no planned formal interim analyses of efficacy using either upper or lower boundary or other methods. Our reason for this choice is based on the relative speed of accrual relative to the sample size and length of follow-up. An interim analysis which included enough subjects to provide credible data on early stopping for benefit would have to occur so late in recruitment so as to have little or no effect on trial conduct. Between meetings of the DSMB, information regarding issues deemed critical to the trial or participants' safety will be provided to the Chair of the DSMB by the PI. As this is a Phase II study with multiple secondary end points and the first study of sorafenib for this indication, there will be no formal stopping rules for futility.

7.6 Protocol Violations

Serious protocol violations such as discontinuation of experimental treatment unrelated to adverse events (AEs) will be carefully recorded and regularly reviewed by the Principal Investigator. Remedial changes in procedure will be recommended where feasible to reduce the incidence of such violations. The causes and circumstances of all violations will be documented where known for purposes of future secondary analyses and interpretation. Because all primary analyses will be intent-to-treat, it is essential that violations be kept to a minimum, especially where it is possible to influence their rate of occurrence.

7.7 Safety Analysis

All patients will be assessed for toxicity and included in the safety analysis. This analysis will include summaries of the incidence and grade of toxicities. Safety interim analyses will be performed and reported at each DSMB meeting. Patients will be evaluated for SAEs.

Chapter 8. Quality Control and Data Handling

Design strategies and monitoring activities throughout the study will ensure the integrity and high quality of the data. Design strategies include randomization of treatment assignment, masking, and training and certification of personnel. The rigorous monitoring program includes data queries and performance monitoring over the time of the trial.

8.1 Personnel Training

Prior to randomization of the first subject in the study protocol, the PI will ensure that the staff has completed appropriate training and that all documentation including IRB approval is completed and available. The purpose of training is to ensure that study personnel are carrying out the protocol in a consistent way and adhering to good clinical practice guidelines. Staff will have current Human Subjects Training Certification on file. Before enrollment begins, study coordinators and research assistants who will perform the outcome assessments will be trained in all procedures, including completion of the web-based database.

The PI and research staff will constitute the first line of monitoring of the safety of the human participants. Surveillance for AEs will consist of questioning subjects about potential AEs at every study contact, having subjects report any AE to the study team, and having subjects undergo vital sign checks and physical exams during each study visit. Laboratories will be performed at selected visits and checked.

All study personnel are required to read the consent form, the protocol and the manual of procedures.

8.2 Data Quality

The PI will perform continuous monitoring of data quality and completion of CRFs. The Data Coordinating Center (DCC) will create computer modules to identify discrepancies and incomplete data. These reports are sent to the sites and tracked until each problem is resolved and corrected in the database.

On-site audits of each enrollment site will be conducted by CCC staff when 2-4 subjects are enrolled at the site. The necessity of further visits will be determined according to study performance by each site. During these visits, the monitoring staff reviews all subjects' eligibility criteria, primary end point, SAEs, and a random sample of at least 10% of database forms against source documents to ensure that the information on the forms is complete and consistent with the source documents. Confirmation of missing visits and documentation will be performed, as will the recording of the disposition of participants who complete or exit the study. All consent forms and screening logs will be audited. Summary statistics from the screening logs will be sent to the CCC quarterly or as requested. Finally, the CCC staff reviews the reporting, documentation and follow-up of SAEs to assure that these events were handled according to required study procedures.

8.3 Audit and Inspection

Inspections by regulatory health authority representatives [i.e., FDA and IEC(s)/IRB(s)] are possible.

8.4 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

Chapter 9. Participant Safety and Confidentiality

9.1 Consent

Consent will be obtained for enrollment from participants. For each consent process, study personnel will discuss the details of the study, the risks and benefits, and the subject's rights and responsibilities if they choose to participate in the trial and their right to refuse to participate. It will be made clear that their clinical care will not be affected by their decision.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

2. For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The ICF and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written ICF. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB's approval in advance of use.

9.2 Institutional Review Board Process

Study staff at each site will obtain IRB approval before any study procedures are initiated.

9.3 Laboratory Values

The following clinical laboratory tests will be measured at screening and repeated at time points specified in schedule of procedures (section 5.2) and as clinically indicated.

9.3.1 Hematology

Complete blood count with differential including hemoglobin, hematocrit, platelets and absolute neutrophil count.

9.3.2 Chemistry

Comprehensive metabolic panel including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, potassium, total and direct bilirubin, albumin, and phosphate.

9.3.3 Coagulation Studies

Prothrombin time, international normalized ratio (INR).

9.3.4 Pregnancy Testing

Blood and urine pregnancy tests will be performed (as appropriate) per the schedule of procedures (section 5.2).

9.4 Sorafenib-Related Laboratory Abnormalities and Drug Interactions

Laboratory Abnormalities
The following laboratory abnormalities were observed in studies done with sorafenib and patients with hepatocellular carcinoma and cirrhosis:

Hypophosphatemia was a common laboratory finding, observed in 35% of sorafenib-treated patients compared to 11% of placebo patients; CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 11% of sorafenib-treated patients and 2% of patients in the placebo group; there was 1 case of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with sorafenib is not known.

Elevated lipase was observed in 40% of patients treated with sorafenib compared to 37% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients treated with sorafenib compared to 29% of patient in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. Many of the lipase and amylase elevations were transient and in the majority of cases sorafenib treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 sorafenib treated patients(Grade 2).

Hypoalbuminemia was observed in 59% of sorafenib-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

INR elevations were observed in 42% of sorafenib-treated patients and 34% of placebo patients; CTCAE Grade 3 INR elevations were reported in 4% of sorafenib-treated patients and 2% of placebo patients; there was no CTCAE Grade 4 INR elevation in either group.

Lymphopenia was observed in 47% of sorafenib-treated patients and 42% of placebo patients.

Thrombocytopenia was observed in 46% of sorafenib-treated patients and 41% of placebo patients; CTCAE Grade 3 or 4 thrombocytopenia was reported in 4% of sorafenib-treated patients and less than 1% of placebo patients.

Effect of Cytochrome P450 Inducers on Sorafenib
Rifampin, a strong CYP3A4 inducer, administered at a dose of 600 mg once daily for 5 days with a single oral dose of sorafenib 400 mg in healthy volunteers resulted in a 37% decrease in the mean AUC of sorafenib. Other inducers of CYP3A4 activity (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort) can increase the metabolism of sorafenib and thus, decrease systemic exposure of sorafenib.

Effect of Cytochrome P450 Inhibitors on Sorafenib
Ketoconazole, a strong inhibitor of CYP3A4 and P-glycoprotein, administered at a dose of 400 mg once daily for 7 days did not alter the mean AUC of a single oral dose of sorafenib 50 mg in healthy volunteers.

Effect of Sorafenib on Other Drugs
Sorafenib 400 mg twice daily for 28 days did not increase the systemic exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate).

9.5 Dose Modification for Management of Adverse Events

9.5.1 Dose Reduction Levels

The starting dose of sorafenib is 400 mg once daily. Study medication will be administered daily on a continuous basis.

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained on the study visit day.

Table 1. Dose modification levels for sorafenib

Dose	Sorafenib
Starting Dose (Baseline)	400 mg once daily
-1	200 mg once daily
-2	200 mg every other day

9.5.2 Dose Modification for Hematologic Toxicities

Table 2. Recommended dose modification for hematologic toxicities

Toxicity	ANC (x 10^9/L)	Hemoglobin (g/dL)	Platelets (x 10^9/L)	Sorafenib
Grade 1	< LLN - 1.5	< LLN – 10.0	< LLN to 75	Treat on time No change
Grade 2	< 1.5 to 1.0	< 10.0 – 8.0	< 75 to 50	Treat on time No change
Grade 3	< 1.0 to 0.5	< 8.0 – 6.5	< 50 to 25	Treat on time Reduce by one dose level
Grade 4	< 0.5	Life-threatening consequence; urgent intervention indicated	< 25	Delay sorafenib until toxicity resolves to Grade 2 or less then reduce by two dose levels
Febrile Neutropenia				Sorafenib held until toxicity has resolved to Grade 2 or less; when sorafenib is restarted, reduce by one dose level

ANC - absolute neutrophil count

- If no recovery after 30 day delay, study treatment should be permanently discontinued.

9.5.3 Dose Modification for Non-Hematologic Toxicities

Table 3. Recommended dose modification for non-hematologic toxicity (excluding hypertension and HFSR, diarrhea and fatigue)

Grade	Dose Interruption	Dose Modification
Grade 0-2	Treat on time	No Change
Grade 3	Interrupt until ≤ Grade 2	DECREASE one dose level
Grade 4	OFF protocol therapy	OFF protocol therapy
• If no recovery after 30 day delay, treatment will be discontinued.		

Prevention/management strategies for diarrhea and fatigue

Diarrhea and fatigue are common side effects of sorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea and fatigue should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status for diarrhea).

9.5.4 Hand-Foot-Skin Reaction

Table 4. Recommended dose modification for HFSR

Toxicity Grade		Suggested dose modification
Grade 1	Any occurrence	Maintain dose level and consider topical therapy for symptomatic relief
Grade 2	1st occurrence	Maintain dose level and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level
	3rd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level
	4th occurrence	Discontinue treatment permanently
Grade 3	1st occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level
	2nd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level
	3rd occurrence	Discontinue treatment permanently

Recommended prevention/management strategies for skin toxicities consistent with HFSR are summarized below.

Table 5. Recommended prevention/management strategies for skin toxicities consistent with HFSR

Toxicity Grade	Practical Prevention / Management Strategies for HFSR
Grade 0 (Preventive strategies)	• Maintain frequent contact with trial physician to ensure early diagnosis of HFSR. • Practical prevention strategies o Subjects should avoid hot water, and clothing or activities that can cause friction on the skin. o Subjects will be encouraged to wear appropriately fitted shoes with cushioned socks (e.g., tube socks) o Urea-based moisturizing cream (supplied by the study) should be applied to hands and feet twice daily liberally. • Padded gloves and open shoes with padded soles should be worn to relieve pressure points.
Grade 1 Any occurrence	• Continue preventive strategies and in addition: o Soak hands in cool water. o Apply petroleum jelly to moist skin. • In the case of hyperkeratotic lesions, exfoliate the hands or feet and apply moisturizing cream immediately afterwards.
Grade 2 Any occurrence or **Grade 3** Any occurrence	• Continue supportive/management measures and add analgesic(s) for pain.

9.5.5 Treatment-Emergent Hypertension

Hypertension is a known and potentially serious AE associated with sorafenib treatment. Subjects will undergo brief physical examinations, including blood pressure monitoring, at each clinic visit.

Blood pressure measurements that are out of the normal range must be noted. Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 140 mm Hg, or a 20 mm Hg increase in diastolic pressure if the previous measurement was within normal limits.

The dose-modification schedule to be followed in the event of treatment-emergent hypertension is outlined below. The choice of anti-hypertensive medication to be used in cases of treatment-emergent hypertension will be at the investigator's discretion and based on guidelines provided in the MOP (amlodipine will be recommended). All anti-hypertensive medications used for the management of treatment-emergent hypertension should be recorded in the subject's records.

Once a dose-reduction modification has been made for treatment-emergent hypertension, NO dose re-escalation will be allowed.

Table 6. Management of treatment-emergent hypertension

Grade of Event (NCI-CTCAE v4.0)	Management/ Next Dose
Grade 1	Consider increasing blood pressure monitoring. Continue sorafenib/placebo dosing as scheduled.
Grade 2 asymptomatic and diastolic pressure 90-99 mm Hg	Begin anti-hypertensive therapy (amlodipine recommended). Continue sorafenib/placebo dosing as scheduled.
Grade 2 (symptomatic/persistent) **OR** **Grade 2** symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits **OR** **Grade 3** systolic BP >= 160 mm Hg or diastolic BP >= 100 mm Hg	Sorafenib/placebo should be held until symptoms resolve and diastolic blood pressure < 90 mm Hg; also treat subject with anti-hypertensives and when sorafenib/placebo is restarted, reduce by 1 dose level. If diastolic blood pressure is not controlled (< 90 mm Hg) on anti-hypertensive therapy, reduce another dose level.
Grade 4 life threatening consequences; urgent intervention indicated	Discontinue sorafenib

9.6 Other Events

We will not discontinue study drug for clinical events not thought to be serious drug-related AEs. For example, a hospitalization for clinical worsening will not result in cessation of trial participation. Such events could result in missing data for primary and secondary endpoints, comprising the integrity of the analysis. This trial does prohibit certain therapies, thus there may be a reason to stop study drug participation under such circumstances. Even if subjects are withdrawn from the study drug, outcome assessments will continue, allowing analysis by intent-to-treat.

9.7 Safety and Adverse Events

9.7.1 Definitions

Unanticipated Problem (UP): Any incident, experience, or outcome that meets **all** of the following criteria:

1) 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, informed consent document, or investigators brochure; and b) the characteristics of the subject population being studied;

2) related or possibly related to participation in the research (Possibly related to participation in the research means there is a reasonable possibility that the AE, experience, or outcome may have been caused by the procedures involved in the research.); and

3) 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.

Adverse event (AE): Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious adverse event (SAE): Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All AEs that do not meet any of the criteria for serious should be regarded as ***non-serious AEs***.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug/investigational product caused the adverse event. For reporting purposes, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug/investigational product and the adverse event.

Internal adverse event: Adverse events experienced by subjects enrolled by the investigator(s) at their own Field Center.

External adverse event: Adverse events experienced by subjects enrolled by investigators at other Field Centers in the clinical trial.

9.7.2 Classifying Adverse Events

Severity

The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

CTCAEv4 Grade 1: **mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.
CTCAEv4 Grade 2: **moderate**; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
CTCAEv4 Grade 3: **severe** or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
CTCAEv4 Grade 4: **life-threatening** consequences; urgent intervention is indicated.
CTCAEv4 Grade 5: **death** due to an AE.

Expectedness

AEs must be assessed as to whether they were expected to occur or were unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label.

Expected: an AE known to be associated with the intervention or condition under study.

Unexpected: an AE for which the nature or severity is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.

OHRP defines an **unexpected AE** as any AE occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and b) other relevant sources of information, such as product labeling and package inserts; or

2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

Relatedness

1) **Definite:** the AE is clearly related to the research procedures
2) **Probably:** the AE is likely related to the research procedures
3) **Possible:** the AE may be related to the research procedures
4) **Unlikely:** the AE is doubtfully related to the research procedures
5) **Unrelated:** the AE is clearly not related to the research procedures

For each identified AE, an entry on the AE form will be completed. Reporting procedures should be started
immediately upon learning of a SAE.

9.7.3 Interpretation of Definitions

AE Reporting Period

The study period during which AEs must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the end of study treatment follow-up is Week 14.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Post-Study AE
All unresolved AEs considered possibly, probably or definitely related to the study drug should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an AE if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is considered clinically significant by the local PI and is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a serious AE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for and AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.7.4 Reporting Procedures for Unanticipated Problems and Adverse Events

Participating investigators should notify the local IRB, in an expedited manner, of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. Researchers should submit reports of the following problems :

- Any AE or UP (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:
  1.) Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  2.) Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

  AND

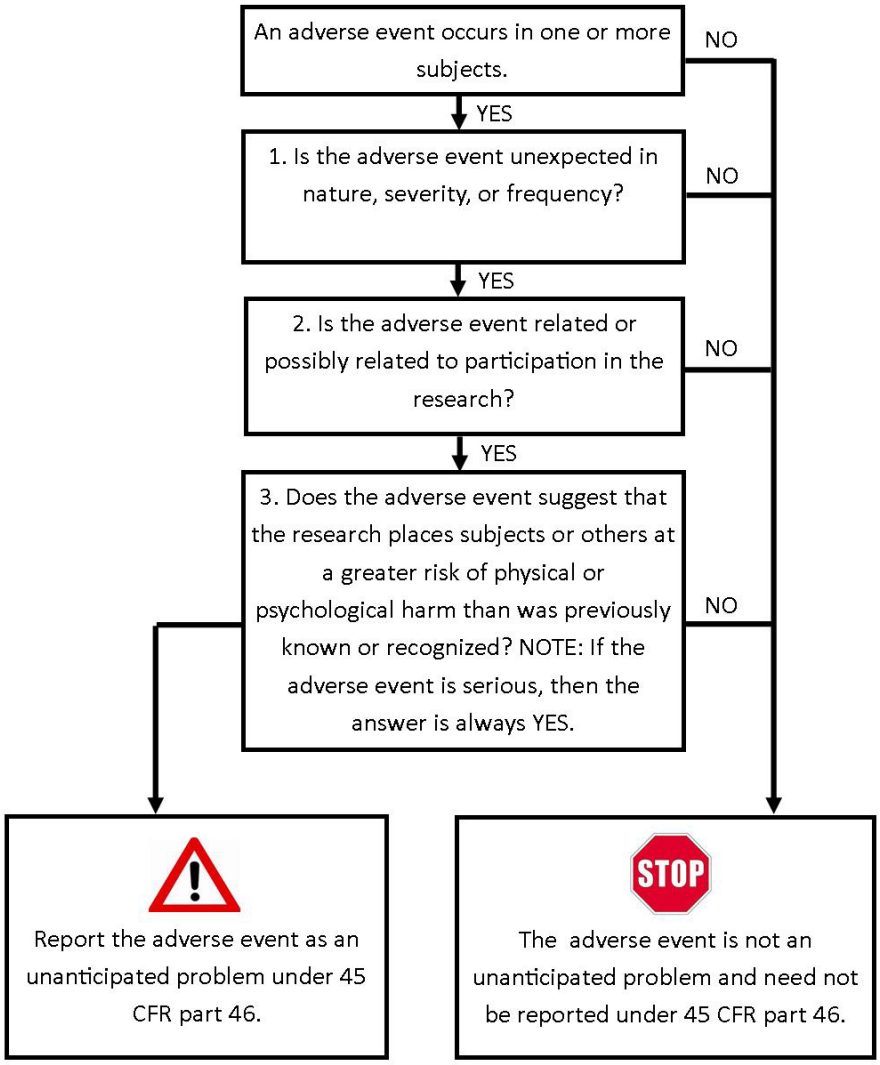
  3.) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Serious and unanticipated AEs which are fatal and indicates that participants or others are at increased risk of harm must be reported within 24 hours to the CCC, as well as to the local IRB per their requirements.

What Event is Reported	Internal/ External	By Whom is Event Reported	To Whom is Event Reported	When is Event Reported
Fatal unexpected, suspected serious adverse event *(SAE – death that is unexpected and poss/prob/def related to the research)*	Internal Event	Local Investigator	• CCC	Within **24 hours** of initial receipt of information
			• Local IRB	Within **24 hours** of initial receipt of information
		CCC	• All participating Investigators	Within **24 hours** of initial receipt of information from Field Center Investigator reporting the local event
			• NHLBI, DSMB	Within **7 calendar days** of local Field Center's initial receipt of information
	External Event	Field Center Investigators	• Field Center IRBs	Within **3 calendar days** of Field Center's initial receipt of information from CCC unless otherwise instructed by Field Center's IRB*
Life-threatening unexpected, suspected serious adverse reactions *(SAE- life-threatening, unexpected, poss/prob/def related to the research)*	Internal Event	Local Investigator	• CCC	Within **2 calendar days** of initial receipt of information
			• Local IRB	Within **5 calendar days** of initial receipt of information
		CCC	• All participating Investigators	Within **2 calendar days** of initial receipt of information from Field Center Investigator reporting the local event
			• NHLBI, DSMB	Within **7 calendar days** of Field Center's initial receipt of information
	External Event	Field Center Investigators	• Field Center IRBs	Within **5 calendar days** of Field Center's initial receipt of information from CCC unless otherwise instructed by Field Center's IRB*
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions *(SAE – unexpected, poss/prob/def related, non-life-threatening hospitalization, prolonged hospitalization, disability/incapacity/birth defects, important medical event)*	Internal Event	Local Investigator	• CCC	Within **2 calendar days** of initial receipt of information
			• Local IRB	Within **5 calendar days** of initial receipt of information
		CCC	• All participating Investigators	Within **2 calendar days** of initial receipt of information from Field Center investigator
			• NHLBI, DSMB	Within **15 calendar days** of Field Center's initial receipt of information
	External Event	Field Center Investigators	• Field Center IRBs	Within **5 calendar days** of Field Center's initial receipt of information from CCC unless otherwise instructed by Field Center's IRB*
Unanticipated Problem that is not an SAE *(AE or non-AE, unexpected, poss/prob/def related and suggests greater risk of harm)* *e.g. Development of moderate hypersomnia that resolve after discontinuing drug. This AE although not-serious, is not listed as an expected event in the consent. Thus it is an AE that is unexpected, possibly related (resolved after coming off drug), and places subject(s) at greater risk of harm than previously known*	Internal Event	Local Investigator	• CCC	Within **2 calendar days** of initial receipt of information
			• Local IRB	Within **5 calendar days** of initial receipt of information
		CCC	• All participating Investigators	Within **2 calendar days** of initial receipt of information from Field Center investigator
			• NHLBI, DSMB	Within **14 days** of Field Center's initial receipt of information
	External Event	Field Center Investigators	• Field Center IRBs	Within **5 calendar days** of Field Center's initial receipt of information from CCC unless otherwise instructed by Field Center's IRB*

Modified from the NHLBI Adverse Event and Unanticipated Problem Reporting Policy.
*Investigators should also take into account local IRB guidance if reporting timelines for UPs are shorter than the above guidance.

Investigators should follow the below guidance to help determine if an Adverse Event represents an UP that should be reported.



http://www.hhs.gov/ohrp/policy/adveventguid.html

Reporting Process

UPs posing risks to subjects or others as noted above will be reported to the local IRB using the institution required form or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

The participating Investigator is expected to report any serious and unexpected adverse experiences, whether or not they are considered related to the CCC, usually within 24 hours.

The participating Investigator is expected to provide as much of the following information as is available to the CCC:

- Protocol name and number
- Subject identifiers
- Demographic data
- Nature of the event
- Severity of the event
- Probable relationship (causality) of AE to study procedure
- Date and time of AE onset
- Date and time of AE resolution, if available
- Concomitant medications that the participant was taking for an underlying medical condition or disease and the therapeutic agents used for the treatment of the adverse event
- Clinical assessment of participant conducted at time of SAE/AE
- Results of any laboratory and/or diagnostic procedures, and treatment
- Follow-up plan
- Outcome
- Autopsy findings (if appropriate)

The participating Investigator will provide details about the AE to the CCC as they become available. If additional information cannot be obtained for whatever reason, this will be documented. The participating Investigator should inform the CCC when no other information is expected. The participating Investigator should provide the CCC with a logical, complete, and accurate narrative description of the SAE based upon the above information.

The participating Investigator should promptly determine an assessment of causality.

The participating Investigator should communicate to the CCC if the IRB requires revisions to the informed consent form or other measures.

The CCC will determine if any corrective actions should be initiated as a result of any known specific or collective SAE/AE(s) and inform all participating Investigators of the corrective action (e.g., revision of informed consent form, protocol, CRF).

The participating Investigator/designee should keep originals or photocopies of all relevant documentation, including facsimile confirmations, and file them in the participant's file.

All participating Investigators should ensure that their sites report all routine AE(s) as part of the periodic or annual reporting requirements to the IRB of record.

The CCC and any participating Investigator should file copies of all correspondence with the IRB in the appropriate section of the Regulatory Master File or site study file.

Other Reportable events:
The following events are also reportable to the IRB:

- Any adverse experience that, even without detailed analysis, represents an unexpected SAE that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis).
- Any AE that would cause a modification to the investigators brochure, protocol or ICF, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

9.7.5 Subject Withdrawal

A subject has the right to withdraw from the study entirely at any time for any reason without prejudice to future medical care by the investigator or other physician. The investigator also has the right to withdraw subjects from the study in the event of concurrent illness, AEs, or other reasons deemed to be in the subject's best interest.

Subjects **must be withdrawn** from the trial (treatment and procedures) for the following reasons:

- Subject withdraws consent for study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a

subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Death.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

In order to preserve the integrity of the intention-to-treat analysis, even if the subject is withdrawn from the treatment portion of the protocol (either due to subject, physician, or investigator decision), it is imperative to continue with the scheduled follow-up assessments both for the safety of the subject and for completeness of data collection. This will be explained to potential subjects at the time of informed consent. The importance of compliance with study visits will be reinforced throughout the trial. If the treatment is permanently withdrawn, the subject will return to the center for safety assessment (history, physical examination, and clinical laboratories, if necessary).

In the event of clinical worsening, subjects will be continued on their assigned study medication. There is no evidence that the medication under study is effective in subjects with HPS, so that there is neither reason to unmask the study therapy nor to initiate treatment with sorafenib in such subjects.

9.8 Confidentiality of Study Data

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Should direct access to medical records require a waiver or authorization separate from the subject’s statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

9.9 Potential Risks

There are several areas of potential risk in this study. We will obtain several blood samples from each subject. There is a risk of bruising, hematoma, and infection after phlebotomy, which are possible but not considered serious AEs. Fainting may occur, which is unlikely but considered a serious AE. The removal of <70 cc of blood every 2-4 weeks during the twelve-week period is a potential risk; however this amount is routinely taken from subjects for clinical indications without adverse effect. Study medications will be delayed until after phlebotomy on each study day.

Under some circumstances, it can be a risk for genetic information to be known. To help ensure confidentiality, samples will be coded and stored in a secured facility. While situations cannot be foreseen where potentially sensitive genetic information is revealed or where people who should not have this information could obtain it (representing a loss of confidentiality), however, it is possible that presently unforeseen situations may arise where this could happen.

The risks of spirometry and lung volumes are minimal. There is a small risk of temporary shortness of breath. The test should not be given to someone who has experienced a recent heart attack or who has certain other types of heart disease.

The risks of obtaining an arterial blood sample for the ABG are blood flow problems at puncture site (rare), bruising, hematoma, and infection. Some people may feel lightheaded, faint, dizzy, or nauseated. On-going bleeding can be a problem for people with bleeding disorders. On rare occasions, the needle may damage a nerve or the artery, causing the artery to become blocked.

The risks associated with an electrocardiogram (ECG) are often none or include mild skin irritation or rash at the site of electrode placement.

The risks associated with a contrast echocardiogram are that the probe used on the chest during the echocardiogram may lead to mild soreness in the area for about a day. The risks of inserting an IV for the saline (salt-water) contrast are the same as for blood draws. The risk of agitated normal saline contrast is extremely low.

The 6MWT may cause light-headedness, chest pain, or musculoskeletal discomfort, however the risks of this study to subjects are minimal.

The administration of sorafenib poses a risk of fatigue, weight loss, rash/desquamation, HFSR, hair loss (alopecia), diarrhea, anorexia, nausea, vomiting, constipation, hemorrhaging, hypertension, infection, and abdominal pain.

Studies have shown some additional and more serious risks of the administration of sorafenib such as cardiac ischemia/infarction, GI perforations, drug induced hepatitis, thromboembolism, transient ischemic attack, and liver failure.

Studies with sorafenib have shown subjects may have an increased risk for hypertension, bleeding, wound healing complications, and myocardial ischemia. Sorafenib can prolong the QT/QTc interval. QT/QTc interval prolongation increases the risk of ventricular arrhythmias.

The other risk to the subjects is the potential loss of confidentiality during data collection.

9.10 Potential Benefits

The results from the study could be applied in the future to subjects (including those in the study) who stand to benefit from the information. There may be clinical benefits to the use of sorafenib in subjects with HPS. As the study involves the risks of randomization to sorafenib, phlebotomy, echocardiography, exercise testing, and loss of confidentiality, and there is a potential for future benefit for both subjects in the study and for future subjects, the risk/benefit ratio is favorable.

9.11 Alternatives

The use of the medications for this study requires that certain other medications not be used. Therefore, the alternative is to not participate in this study and to continue having the option to take these medications.

9.12 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB in agreement with local legal prescriptions for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the NIH before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

10.0 References

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