PAZOPANIB CLINICAL TRIAL

ABOUT THE RANDOMIZED TRIAL FOR PAZOPANIB IN HHT-RELATED BLEEDING

Researchers want to determine if the investigational drug, Pazopanib, will lessen nosebleed severity in patients with Hereditary Hemorrhagic Telangiectasia (HHT). This 24-week randomized trial for HHT-related bleeding will occur across about 12 research centers across the United States.

Patients will either be provided active drug or a placebo (sugar - inactive pill), and be tested for nosebleed severity throughout the trial. Investigators will also test for blood loss, and as always, safety.

Adult patients with HHT in the U.S. with nose bleeding of at least 20 min per week and average hemoglobin levels less than 11 are eligible to participate.

The Pazopanib trial is funded by Cure HHT with support from a grant from the U.S. Department of Defense. Pazopanib is an oral medication currently FDA approved for the treatment of certain cancers. For the HHT study, it is an experimental drug at 1/5 the cancer dose.

At the conclusion of the 24-week randomized study, there is an option for patients who received placebo to receive Pazopanib for an extension of the clinical trial for another 24 weeks.

OBJECTIVES

Primary Objective: To determine efficacy of Pazopanib compared to placebo for the reduction in severity of epistaxis, particularly nosebleed duration, throughout the 24 weeks of the treatment period.

Secondary Objectives: To determine the safety and tolerability of Pazopanib for the treatment of HHT; To compare the number of Pazopanib and placebo patients who either show a 2-point increase in Hg at weeks 19-24 compared to baseline or show a 50% decrease in duration of nosebleeding at 19-24 weeks compared to baseline.

JOHNS HOPKINS MEDICINE	***Institutional Review Board Approval Institution***

INCLUSION CRITERIA

- Age 18-80
- Definite or probable* diagnosis of hereditary hemorrhagic telangiectasia, defined as having at least 3 of the following criteria:
    - Spontaneous and recurrent epistaxis.
    - Multiple telangiectasias at characteristic sites: lips, oral cavity, fingers, nose.
    - Visceral lesions: GI telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs.
    - A first degree relative with hereditary hemorrhagic telangiectasia according to these criteria.
    - *Probable diagnosis is two definite criteria and additional characteristics which are highly suggestive of HHT (must be discussed with medical monitoring team).
- OR a definite diagnosis of hereditary hemorrhagic telangiectasia is defined as having a gene sequencing diagnosis of hereditary hemorrhagic telangiectasia.
- Any use of IV iron and/or blood transfusions with consideration as stable for 12 weeks prior to test product initiation.
- Must agree not to undergo cautery of nasal telangiectasias or to start new therapies for HHT while on study.
- Women of non-childbearing potential; women of childbearing potential with agreement to practice abstinence or to use double method contraception until 4 weeks after drug termination with pregnancy tests prior to initiation and every 3 weeks after
- Capable of giving signed informed consent.
- Able and willing to return for outpatient visits at the protocol specified intervals.
- Able and willing to complete blood pressure monitoring at home.
- Able and willing to complete daily patient reported outcome measurements at home.

Must meet all of the inclusion criteria for either one of the below-listed cohorts:

Severe Cohort:

- Anemia mainly due to HHT (in the judgment of the PI) with average hemoglobin <9.5 g/dl regardless of gender.
- Infusion of at least 250 mg of elemental iron in the last 12 weeks, or 1 unit of blood in the last 12 weeks.
- Epistaxis averaging at least 20 minutes per week over the six-week baseline.

Moderate Cohort:

- Anemia mainly due to HHT (in the judgment of the PI) with hemoglobin 9.5 g/dl to 10.9 g/dl regardless of gender.
- Epistaxis due to HHT for an average of at least 20 minutes per week over the 6-week baseline.
- Epistaxis is clinically stable in the judgement of the ingestigator during the 12 weeks prior to Screening.
- Ability to understand and sign informed consent.

EXCLUSION CRITERIA

- Women currently breast feeding or pregnant.
- Participant has known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Pazopanib that in the opinion of the investigator contradicts their participation.
- Currently has incompletely treated cerebral arterio-venous malformations (AVMs), cerebral arteriovenous fistulae, or cerebral cavernous malformations (CCMs) (Note: MRI scan does not need to be repeated at screening if AVMs, arterio-venous fistulas and CCMs were absent on a scan at age ≥ 18 years).
- Currently has perfused pulmonary AVMs with feeding artery diameter ≥ 3mm.
- Known significant bleeding sources other than nasal or gastrointestinal.
- Systemic use of a vascular endothelial growth factor inhibitor in the past 4 weeks, or systemic use of bevacizumab in the 6 weeks prior to enrollment due to its longer half-life.
- Active and recent onset of clinically significant diarrhea.
- Current or recent (in the last 5 years) malignancies (except non-melanoma skin cancers)
- Participant has had major surgery (e.g. surgical ligation of an AVM) or trauma within 28 days or had minor surgical procedures (e.g. central venous access line removal) within 7 days prior to dosing, the latter representing a recent wound, fracture or ulcer
- Participant has a planned surgery during the period to include active treatment and 6 weeks of follow up.
- Participant has clinically significant gastrointestinal abnormalities (other than hereditary hemorrhagic telangiectasia related vascular lesions).
- Participant during the 6 months prior to first dose of study drug has a history of cerebrovascular accident (including transient ischemic attacks), pulmonary embolism, untreated deep vein thrombosis (DVT), myocardial infarction, or any other thrombotic event.
- Presence of intrinsic heart disease as evidenced by any of the following: Echo derived left ventricular ejection fraction < 45%; Unstable obstructive CAD; history of MI, or CABG, or PCI in the last 6 months; Infiltrative and/or restrictive cardiomyopathies; Significant pericardial disease; or clinical heart failure with more than moderate mitral valve or aortic valve disease.
- Unable or unwilling to discontinue use of prohibited medications for at least 14 days or 5 half-lives of a drug (whichever is longer) prior to the randomization and for the duration of the study. List of prohibited drugs found in 6.5.2 of study protocol.
- The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the start of randomization: 4 weeks, 4 half-lives or the duration of the biological effect of the investigational product (whichever is longer).
- QT corrected interval ≥450 msec, based on averaged QT corrected interval values of triplicate ECGs obtained over a brief recording period.
    - History of familial prolonged QT.
    - Any concomitant medication which is known to prolong QT.
- Average baseline hemoglobin <6 g/dL.
- Platelets < 100,000 uL.

- International normalized ratio (INR) >1.5 x upper limit of normal and activated partial thromboplastin time (aPTT) >1.5 x upper limit of normal.
- Alanine Transaminase (ALT) >2 x upper limit of normal.
- Bilirubin >1.5x upper limit of normal (isolated bilirubin >1.5x upper limit of normal is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
- Participant has poorly controlled hypertension (defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg).
- Substantive renal disease (eGFR <30 mL/min/1.73m2calculated using the Cockcroft-Gault formula)
- Echo derived left ventricular ejection fraction < 45%.
- Thyroid stimulating hormone (TSH) > 1.5 x upper limit of normal.
- Urine protein to creatinine ratio > 0.3.
- Neutrophil count <1000 /uL.

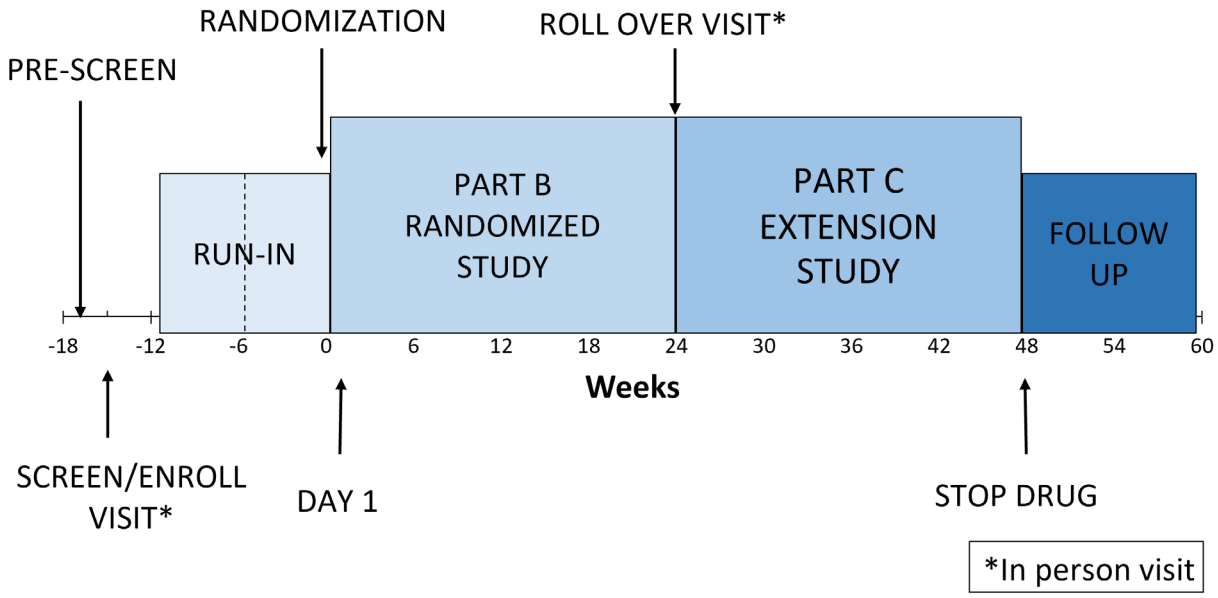
STUDY SITES

Approximately 12 HHT Centers of Excellence across the U.S. states will participate. Sites actively recruiting are listed below:

Augusta University	Melissa James, RN	mejames@augusta.edu	706-721-5599
John Hopkins University	Eugene Bosworth	eboswor1@jhmi.edu	443-974-8071
Mayo Clinic	Sue Donlinger	donlinger.sueann@mayo.edu	507-284-9259
Oregon Health & Science University	Lori Russell BSN CCRP	watsonlo@ohsu.edu	503-494-7226
	Eleanor Lottsfeldt	lottsfel@ohsu.edu	503-494-3199
University of Utah	Mac McPherson, CRC		801-585-7295
Washington University in St. Louis	Kristine Kempf	kempf@wustl.edu	314-273-8131
Yale	Katharine Henderson	katharine.henderson@yale.edu	203-737-1427

SCHEDULE OF EVENTS

Total duration	8 months
# Study Visits	2 in-person visits at the start and week 24; Virtual visits every 3 weeks (22 total)
Drug	Take study drug every day
Diaries / Surveys	Record blood pressure and nosebleeds every day; Fill out electronic questionnaires every 3 weeks
Fe/Bld	Blood and urine test at local lab every 3 weeks
Other tests	Finger electrocardiogram every 6 weeks



STUDY COSTS

Nothing for most patients.

- Study drug and regularly scheduled lab will be provided for free.
- Travel expenses will be partially compensated based on distance traveled.
- Blood pressure cuff and EKG device will be provided for free.

IMPORTANT PRECAUTIONS

The most common risks of Pazopanib include increased blood pressure, increased liver enzymes in the blood, changes to the heart rhythm, infections – sometimes serious, gastrointestinal symptoms like diarrhea, low energy, and protein in the urine.

CLINICALTRIALS.GOV

The Pazopanib study is registered with clinicaltrials.gov. More information on the study design and status can be found here: https://www.clinicaltrials.gov/ct2/show/NCT03850964?cond=hereditary+hemorrhagic+telangiectasia+Pazopanib&draw=2&rank=2