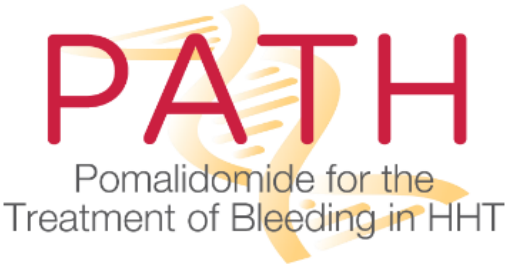
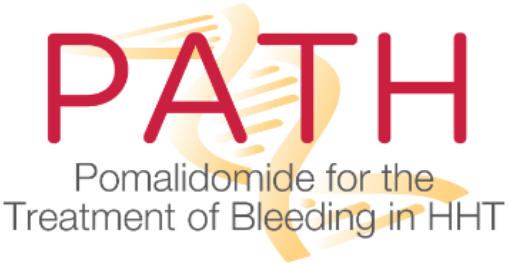


POMALIDOMIDE FOR THE TREATMENT OF BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

NCT03910244

Protocol 133646-2

Version 2.10, September 30, 2022



POMALIDOMIDE FOR THE TREATMENT OF BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

Protocol Identifying Number:	133646-2
IND Number:	133646
Study Phase:	2
Amendment:	11
Principal Investigator/IND Sponsor:	Keith R. McCrae, M.D.
Funded by:	NIH/NHLBI
Version Number:	2.10
Version Date:	September 30, 2022

Table of Contents

Version	Date	Significant Revisions
1.0	February 05, 2018	
2.0	April 05, 2019	Added epistaxis duration as a key secondary endpoint; Clarified study drug dispensation to study sites; Updated SAE reporting requirements per guidelines of NHLBI, FDA and Cleveland Clinic IRB.
2.1	June 23, 2019	Minor revisions to inclusion criteria language to make it concise and avoid repetition; included INR and aPTT tests at Screening; Clarified need for CBC with differential at study visits; corrected pregnancy testing frequency and requirements per REMS mandate; added PAX tube to biospecimen collection.
2.2	August 19, 2019	The major change is shifting the genetic testing schedule from Screening visit to Randomization/Baseline visit. Other minor changes include correcting the monthly pregnancy testing schedule as mandated by the Pomalyst REMS guidelines and correcting the incorrect number of grade 3 AEs for halting study drug administration.
2.3	May 21, 2020	The major change to the protocol is to provide flexibility to extend the screening period as needed and conduct some of the research visits remotely.
2.4	August 17, 2020	The major change to the protocol is to refine the inclusion/exclusion criteria and provide clarifications to a) reporting AE severity levels and pregnancy (if it occurs during the study); b) handling missed dose and missed study visits; and c) use of prohibitive medications.
2.5	November 09, 2020	The major changes made to the protocol were to modify the eligibility criteria to allow a) upto 2 sec deviation from normal aPTT; b) exclude only those with prior history of unprovoked thromboembolism; and c) allow those with Gilbert syndrome who typically have greater bilirubin. In addition, clarity has been provided for recommended follow-up visits after permanent discontinuation of study drug.
2.6	December 01, 2020	The major change to the protocol is to allow study participants with Grade 3 neutropenia to continue on study drug for a week if their ANC>800 x 10^6/L.
2.7	February 15, 2021	The major change to the protocol is to modify the study halting rules by only including grade 3 non-neutropenia cases. A few inclusion criteria were modified to increase pool of potential patients and to eliminate inconsistencies within protocol. Remote options have been provided to additional study visits: EOS and C3.

Version	Date	Significant Revisions
2.8	August 02, 2021	The major change to the protocol is to reduce the follow-up period post-treatment completion or post-treatment discontinuation from 12 weeks to 4 weeks. Other changes include increase in number of sites to 15, update to exclusion criterion 14, clarification regarding ET / EOS visits and visit assessments, update to biorepository sample timepoints with RNA tube, clarification regarding worsening epistaxis not to be reported as an AE, update to contraceptive methods, addition of non-leukopenia to halting rules.
2.9	April 12, 2022	Study stopping rule was modified to be as follows: randomization of new participants will be halted when eight thromboembolic events, defined as any venous thromboembolic event requiring medical intervention (grade 2 or higher) or any arterial thromboembolic event, determined to be related or "probably related" to the study drug have been reported. Other changes include updates, clarifications to exclusion criteria and prohibited medications regarding oral estrogens and progestins, use of hemoglobin for anemia determination, aPTT or PTT per local laboratory designation, genetic testing and study drug dose adjustment / discontinuation for hematologic toxicity and peripheral neuropathy.
2.10	September 30, 2022	Satisfaction with Social Roles and Activities was updated from the PROMIS to the Neuro-QOL to match the form on the eCRF, an additional Other Secondary Outcome was added for Change in iron/hemoglobin-related studies including iron saturation, ferritin, hemoglobin, hematocrit, MCV, and MCHC, the planned statistical methods for secondary efficacy outcomes amount of blood transfusions and amount of parenteral iron infusions was clarified, scoring of the HHT-QOL total score was clarified.

LIST OF ABBREVIATIONS

ACVRL1	Activin A Receptor Like Type 1 Gene
ADL	Activities of Daily Living
AE	Adverse Events
ALT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Amino Transferase
AVM	Arteriovenous Malformations
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCC	Clinical Coordinating Center
CMP	Complete Metabolic Panel
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
EDTA	Ethylene Diamine Tetra Acetic Acid
EMR	Electronic Medical Record
ENG	Endoglin Gene
ESS	Epistaxis Severity Scale
FCBP	Female of Child Bearing Potential
FDA	US Food and Drug Administration
FGF	Fibroblast Growth Factor
GCP	Good Clinical Practice
GDF2	Growth Differentiation Factor 2
GI	Gastrointestinal
HEENT	Head, Eyes, Ears, Nose and Throat
HHT	Hereditary Hemorrhagic Telangiectasia
ICH	International Conference on Harmonization
IMiD	Immunomodulatory imide Drugs
IMM	Independent Medical Monitor

INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
LLN	Lower Limit of Normal
NCI	National Cancer Institute
Neuro-QOL	Quality of Life in Neurological Disorders
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institute of Health
PI	Principal Investigator
PROMIS	Patient Reported Outcomes Measurement Information System
PTT	Partial Thromboplastin Time
QOL	Quality of life
RASA1	RAS p21 Protein Activator
REMS	Risk Evaluation and Mitigation Strategies
SAE	Seious Adverse Events
SAP	Statistical Analysis Plan
SC	Steering Committee
SMAD4	SMAD Family Member 4
TIBC	Total Iron Binding Capacity
UP	Unanticipated Problems
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Count

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the NHLBI Terms of Award, Code of Regulations on the Protection of Human Subjects (21 CFR Part 50), Institutional Review Board (21 CFR Part 56), Standards of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH E6) and all applicable regulatory requirements. The CCC and DCC Principal Investigators assure that no deviation from, or changes to the protocol will take place without prior agreement and documented regulatory approval, except where necessary to eliminate an immediate hazard(s) to the trial participants. All key personnel involved in the conduct of this study will complete both Human Subjects Protection and Study Related trainings.

We agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Lead Principal Investigator: ____Keith R McCrae, M.D.___
Print/Type Name

Signed: _____Date: _____
Signature

DCC Principal Investigator: ____Sonia Thomas, DrPH___
Print/Type Name

Signed: _____Date: _____
Signature

PROTOCOL SIGNATURE PAGE

Protocol 133646-2

The signature below constitutes the agreement to conduct the study as described in the protocol, and provides the necessary assurances that this trial will be conducted in accordance with all stipulations of this protocol including, without limitation, all statements regarding confidentiality, the Code of Federal Regulations on the Protection of Human Subjects (21 CFR Part 50), Institutional Review Board (21 CFR Part 56), and Standards of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH E6) and all applicable regulatory requirements. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

Clinical Site Name: _____

Site Principal Investigator: _____
Print/Type Name

Signature: _____

Date: _____

PROTOCOL SUMMARY

Title:	Pomalidomide for the Treatment of Bleeding in Hereditary Hemorrhagic Telangiectasia
Précis:	This is a Phase II placebo-controlled double-blind study of pomalidomide in patients with hereditary hemorrhagic telangiectasia (HHT) with moderate to severe epistaxis who have anemia and/or require parenteral iron infusions or blood transfusions. A total of 159 patients will be randomized 2:1 to treatment with oral pomalidomide or matching placebo for 24 weeks. Mean change from baseline to 24 weeks in the Epistaxis Severity Score (ESS) will be compared between treatment groups to determine pomalidomide efficacy.
Objectives:	**Primary Objective**: To determine efficacy of pomalidomide compared to placebo for the reduction in severity of epistaxis after 24 weeks of treatment. **Secondary Objectives:** To determine the safety and tolerability of pomalidomide for the treatment of HHT; to determine if pomalidomide treatment improves quality of life in HHT; to determine whether a continued response to pomalidomide is evident 4 weeks after treatment discontinuation; to develop a biorepository for future studies to define biomarkers predictive of pomalidomide response and allow investigations into the biology of HHT and mechanisms of pomalidomide.
Endpoint:	**Primary endpoint**: Change from baseline to 24 weeks in the Epistaxis Severity Score. **Secondary endpoints:** Total parenteral iron (mg) infused and packed red blood cells (units) transfused during the 24 week treatment period, change from baseline to 24 weeks in total weekly duration of epistaxis, change in quality of life (QOL) scores assessed using NIH Neuro-QOL Satisfaction with Social Roles and Activities, PROMIS Emotional Distress - Depression and PROMIS Fatigue instruments, and HHT-specific QOL questions, proportion of patients requiring no blood transfusions or iron infusions during the 24 week treatment period, change from baseline in the Epistaxis Severity Score averaged across weeks 16-24 and at each study visit, proportion of patients requiring endoscopic

	interventions for bleeding, safety assessed by adverse events and side effects.
Population:	Adults 18 years and older with moderate to severe epistaxis due to hereditary hemorrhagic telangiectasia who require parenteral iron infusions or blood transfusions.
Phase:	Phase II
Number of Sites Enrolling Participants:	up to 15
Description of Study Agent:	Pomalidomide, a third generation derivative of thalidomide, given orally at a starting dose of 4 mg/day for days 1-28 of six 28-day cycles. The dose may be reduced to 3 or 2 mg/day based on specific AE criteria.
Study Duration:	5 years
Participant Duration:	32 weeks

SCHEMATIC OF STUDY DESIGN

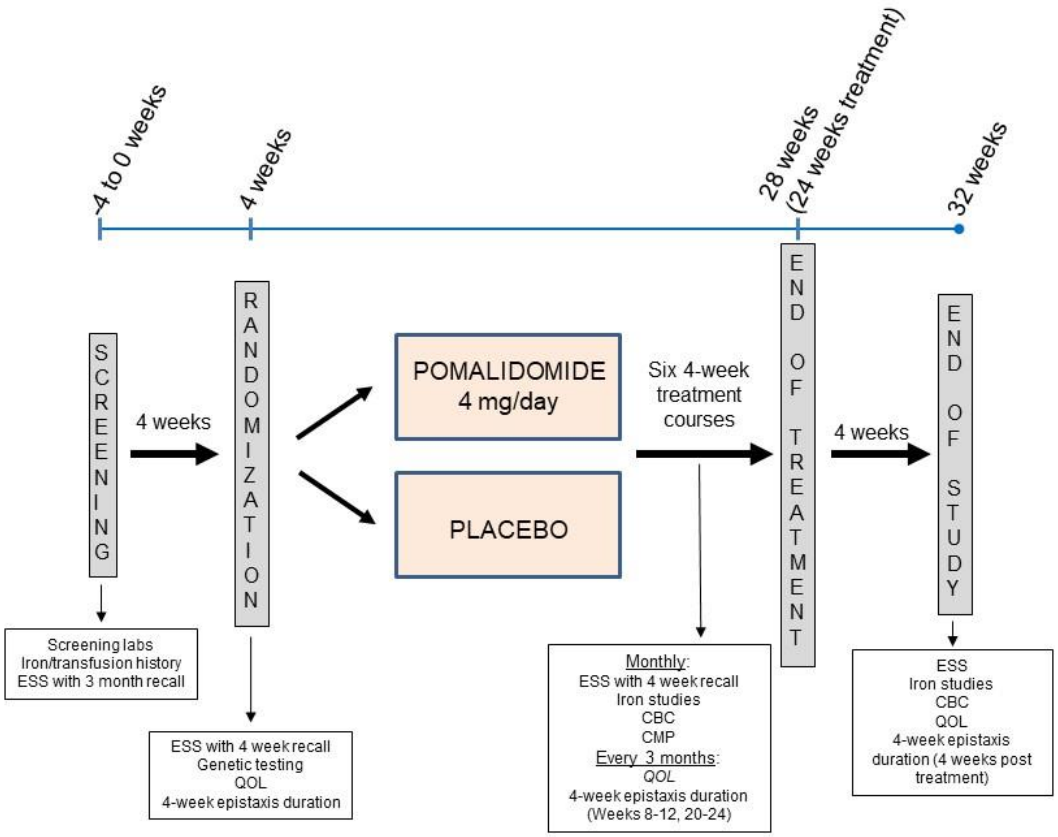


Figure 1: **Study Design Schematic.** After recruitment, patients will be screened for their iron infusion/transfusion history, undergo laboratory testing, and have the ESS with 3-month recall calculated for eligibility. After a minimum 28 day (up to 56 days allowed for scheduling flexibility) period following the screening ESS, during which patients will record the duration of each epistaxis event, eligible patients will return for genetic and QOL testing and determination of an ESS with 28 day recall to serve as the baseline for comparison with monthly ESS scores performed throughout the study. Patients will then be randomized 2:1 to pomalidomide or an identical-appearing placebo. Patients will initiate treatment after receipt of the drug/placebo, and subsequently will be seen every 4 weeks for 24 weeks, corresponding to six 4-week cycles of therapy. Pomalidomide will be discontinued after the 24 week end-of-treatment visit, and patients will be seen once more 4 weeks after treatment discontinuation to determine the stability of their response. ESS, iron studies, CBC, and CMP will be assessed monthly , and QOL will be determined at baseline, at 12 and 24 weeks after treatment initiation, and at the end of study. Patients will record the duration of each epistaxis event during the 4-week periods between weeks 8-12 and weeks 20-24 post initiation, and 4 weeks after treatment discontinuation.

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

This study will address the efficacy of pomalidomide in the treatment of epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT) who have anemia and/or require blood transfusion or iron infusion for treatment of bleeding-induced anemia and iron deficiency. HHT is an inherited disease clinically diagnosed using the Curacao criteria, which consists of 1) spontaneous and recurrent epistaxis, 2) telangiectasias at characteristic sites, 3) visceral arteriovenous malformations (AVMs) or telangiectasias, and 4) a first degree relative with HHT (inheritance is usually autosomal dominant). Patients with three criteria are considered to have definite HHT, and those with 2 criteria probable HHT, while one or no criteria make the diagnosis unlikely [1]. Patients eligible for this study will have a diagnosis of definite or probable HHT. Estimates suggest that HHT affects between 1 in 1,330 and 1 in 10,000 individuals [2]. Since many physicians are not familiar with the disease, only 10% of patients with HHT may actually be diagnosed. Significant manifestations of HHT often do not appear until the third or fourth decades, sometimes later.

Approximately 90% of patients with HHT harbor mutations in one of three genes, which encode endoglin (*ENG*), activin receptor-like kinase (*ACVRL1*) or *SMAD4*[3,4]. Additional genes such as *RASA1* and *GDF2* have been implicated in several cases, and in some patients no underlying mutations are identified[5]. While the clinical manifestations of patients with mutations in *ENG* or *ACVRL1* are generally similar, those with *SMAD4* mutations, who account for less than 5% of the HHT population, display a unique clinical phenotype characterized by the development of colonic polyps with a high incidence of neoplastic transformation, often at a young age[6]. Due to the complex management of these patients and the fact that bleeding is often not their primary clinical concern, patients with known *SMAD4* mutations will not be included in this study. Genetic testing will be confirmed or assessed in all study patients in order to determine whether genotype correlates with clinical responses to pomalidomide.

In addition to epistaxis, AVMs involving the gastrointestinal (GI) tract, particularly the small bowel, are responsible for GI bleeding as the primary symptom in 15-20% of patients with HHT[7]. HHT may also be associated with additional manifestations including brain abscesses and stroke resulting from cerebral AVMs and paradoxical right to left shunts through pulmonary AVMs[8]. Patients may also develop liver AVMs which in extreme cases may cause high output congestive heart failure[8,9].

Treatment of HHT

There are no evidence-based guidelines for managing HHT, and there is no medical therapy universally accepted as efficacious; thus, treatment is not standardized. Historically, interventional procedures have formed the mainstay of HHT therapy[10]. However, though often effective initially, such procedures are associated with a high incidence of recurrent bleeding from new AVMs or AVMs not visualized during endoscopic procedures[10]. Epistaxis is the most common clinical manifestation of HHT, affecting ≥ 80% of patients, and leading to significant impairment in quality of life[11,12].

Hemostatic agents such as epsilon-aminocaproic acid (Amicar) and tranexamic acid, administered locally or systemically, have been used to treat epistaxis in HHT, though results have been inconsistent[13-15]. A retrospective study of tranexamic acid in 42 patients with HHT demonstrated that chronic therapy reduced the epistaxis severity score (ESS) but not the need for blood transfusion or hospitalization. Hormonal agents such as estrogens and octreotide benefit occasional patients with HHT though their limited efficacy has not led to widespread utilization[16,17]. A randomized study of high-dose estrogen failed to significantly reduce bleeding[18]. Moreover, the thrombosis risk and acceptance of estrogens, particularly in males, limits their use. For these reasons, epistaxis is often treated with temporizing approaches such as laser photocoagulation[12].

Bevacizumab, an anti-VEGF antibody, has been used as therapy for HHT based on the presumption of excessive VEGF-induced angiogenesis causing telangiectasia. Small, uncontrolled studies and, more recently, several retrospective case series demonstrate activity in HHT[19-21]. However, not all patients respond, and in some individuals responses are relatively short-lived, requiring frequent retreatment. Moreover, intravenous administration is required, and systemic toxicity may be significant, particularly the development of hypertension[20], life-threatening thromboembolism[22] and other complications. Such concerns have led to studies of bevacizumab nasal spray in HHT. However, in the ELLIPSE study, a phase I randomized, dose escalation trial of bevacizumab nasal spray in HHT, no efficacy was demonstrated at doses up to 100 mg/spray[23]. In the NOSE study, patients with HHT were randomized to twice per day use of nasal sprays containing placebo, bevacizumab, tranexamic acid or estriol[24]. Though small differences in the ESS were seen at 12 weeks in all groups, no significant differences in the ESS, or the duration or frequency of epistaxis were observed in any of the treatment groups compared to placebo.

Taken together, these considerations demonstrate the continuing need to identify efficacious agents for managing patients with HHT.

Quality of life studies in HHT and survey results

Work performed during the development of this study, funded by a *NHLBI U34 Clinical Trial Planning Grant*, as well as that of others, demonstrates a significant reduction in quality of life in patients with HHT[25], reflecting a high incidence of anxiety, depression and fear of social situations due to uncertainty of when an episode of epistaxis will occur. The ESS generally correlates well with QOL, with a minimal important difference as small as 0.7 significantly associated with decreased QOL[26].

There exists very little information concerning the effect of therapy on QOL in patients with HHT. To assess the effect of pomalidomide on QOL in HHT patients, we will administer QOL assessments before, during and after therapy. We have worked closely with the CureHHT foundation to assess the responses of HHT patients to validated NIH PROMIS QOL measures. We emailed a survey of quality of life questions to CureHHT members, and the responses to three PROMIS instruments were compared with a set of four HHT-specific questions developed during the planning of this study. An additional item recorded a self-assessment of HHT severity. Overall, 492 surveys were returned, of which 290

(59%) had all four instruments fully completed; 121 (25%) were completed in enough detail that at least one instrument could be scored, and 81 were blank or not able to be scored.

The following three NIH PROMIS instruments were used:

1. Satisfaction with Participation in Social Roles Short Form V1.0,
2. Satisfaction with Participation in Discretionary Social Activities Short Form V1.0
3. Emotional Distress – Depression Short Form V1.0

The total scores from these instruments were compared with each other, and with four HHT-specific questions developed during the design of this study:

1. How often in the past month has an activity related to your job been interrupted by a nose bleed?
2. How often in the past month has an activity with your family been interrupted by a nose bleed?
3. How often have you avoided social activities because you were worried about having a nose bleed?
4. How often do you miss work or school due to HHT related problems?

Analysis of the responses revealed the following key points:

- 29% of respondents reported their HHT as "mild", 46% as "moderate" and 25% as "severe"
- Overall, 49% of respondents indicated that HHT significantly interfered with daily activities on at least one of the HHT questions; mostly those rating their HHT as moderate or severe, similar to the patients who will be in the current study. Of those that rated their HHT moderate, 40% missed work due to HHT at least "sometimes" and 18% did not work due to HHT. Of those rating their HHT severe, 25% missed work "frequently" and 47% did not work due to HHT.
- The 3 PROMIS scores and the HHT-specific questions all correlated with HHT severity (correlations ranged from 0.40 – 0.61)
- The two PROMIS instruments related to social activities were highly correlated (r=.89). PROMIS has subsequently released a new instrument consolidating these measures called the PROMIS Satisfaction with Social Roles and Activities Short Form V2.0, which will be used in this study.
- The 4 HHT Questions were moderately correlated with each other (one pairwise correlation of 0.40, all others ranged from 0.52 to 0.64).
- The 4 HHT Questions were moderately correlated with the 3 PROMIS measures (pairwise correlations ranged from 0.35 to 0.71).

These responses confirm that HHT is indeed strongly associated with significant interference with work and social activities leading to a reduced QOL, and that these variables are captured by the selected PROMIS instruments. Additional analysis demonstrated that the subset of items comprising the PROMIS short form instruments captured these QOL responses with similar accuracy as the longer

item banks, demonstrating the feasibility of the short form NIH PROMIS measures for assessing QOL response to pomalidomide in this study.

The moderately high correlation among the 4 HHT-specific responses and between these responses and the PROMIS scores provides evidence of good convergent validity to support the use of this abbreviated HHT-specific questionnaire to capture the psychodynamic effects of pomalidomide therapy on QOL in treated patients. To enhance clarity, a revised version of the survey questions will be used in this protocol and is described in section 7.1.1.3.

2.2 RATIONALE

Rationale for the use of pomalidomide in HHT builds upon prior experience with thalidomide

Pomalidomide is an analogue of thalidomide (Figure 2), which was initially developed in Germany in the 1950s and marketed as a sedative to treat morning sickness in pregnancy. Thalidomide was withdrawn from the market in the early 1960s due to teratogenicity. Despite the clinical ban, research on its vascular and immunomodulatory effects continued, and the FDA approved its use in 1998 for the treatment of cutaneous manifestations of erythema nodosum leprosum, and in 2006 for the treatment of multiple myeloma.

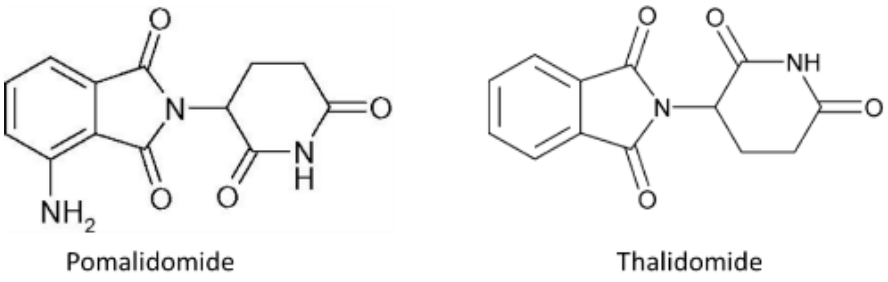

Figure 2: Structures of pomalidomide and thalidomide

The antiangiogenic activity of thalidomide is not well understood, but is thought to be due in part to the suppression of production of vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor (bFGF)[27]. This suggested potential benefit in gastrointestinal angiodysplasia, since the expression of VEGF may be increased in the bowel wall of patients with this disorder[28]. Several small studies suggested efficacy of thalidomide in patients with GI angiodysplasia, including many with associated comorbidities[29-40]. Some evidence suggests that in patients with GI angiodysplasia and refractory bleeding, thalidomide reduces serum levels of VEGF[29]. However, in none of these studies were patients assessed for HHT, which has been increasingly recognized as a cause of angiodysplasia in the GI tract over the last decade.

Several small reports also describe the use of thalidomide in patients with HHT[41-47]. In a study by Lebrin et al, five of six patients with HHT-related epistaxis had significant responses to thalidomide; none of four untreated controls showed any improvement over the same three month period[45].

Biopsies of nasal mucosa in patients with epistaxis before and after treatment demonstrated that thalidomide induced vessel maturation, characterized by enhanced mural cell coverage and improvement in vessel wall defects. Similar improvements in vessel architecture were seen in mice heterozygous for a null mutation in *ENG*[48]. A recent single arm study of thalidomide also demonstrated a high, and durable response rate in 31 HHT patients with epistaxis, with some patients treated for up to 10 years[49]. Another study reported the efficacy of a second generation thalidomide analogue, lenalidomide, in a patient with HHT and refractory GI bleeding[50]. However, there are no reports of patients with HHT treated with pomalidomide.

These results, taken together with those derived from the Principal Investigator's phase I pilot study demonstrating the activity and safety of pomalidomide in HHT, provide the rationale and evidence of feasibility for an expanded study of pomalidomide. When compared to thalidomide and lenalidomide, pomalidomide is potentially superior due to its efficacy and reduced toxicity profile, including a lower incidence of peripheral neuropathy and cytopenias.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Risks of this study include the reported toxicities of pomalidomide. These include: 1) teratogenicity, 2) thromboembolism, 3) cytopenias, 4) hepatotoxicity, 5) allergic reactions (including rash), 6) dizziness and confusional state, 7) peripheral neuropathy, 8) fatigue, 9) GI intolerance and 10) new cancers.

The data source from which these toxicies were identified consists of patients with multiple myeloma, a plasma cell neoplasm involving the bone marrow and other organs that is associated with thrombosis, cytopenias and neuropathy—among the most common toxicities seen with pomalidomide. Therefore, the incidence of these toxicities in patients with HHT and normal bone marrow function is unknown but likely to be much lower than that in myeloma patients.

The incidence of these toxicities, specifically thromboembolism, cytopenias, fatigue, and peripheral neuropathy appears to be lower with pomalidomide than with thalidomide. The only drug related AEs seen in the PI's current pilot study are Grade 1-2 fatigue, two allergic reactions and one cytopenia occurring at a pomalidomide dose (5 mg daily) that exceeds the dose that will be used in this study.

The risk of teratogenicity remains a concern and precautions to prevent exposure of pregnant women to pomalidomide are embedded in this protocol. Pomalidomide and placebo will be provided by Celgene and the study will adhere to the FDA-mandated pomalidomide risk evaluation and mitigation strategies (REMS) protocol. The study will closely monitor and if necessary manage other toxicities.

2.3.2 KNOWN POTENTIAL BENEFITS

HHT is associated with substantial morbidity, leading to a reduced quality of life, decreased rate of employment and a high incidence of depression. There currently exists no medical therapy recognized as consistently efficacious in HHT. Reports of the efficacy of thalidomide in HHT, as well as interim results of our pilot trial of pomalidomide in HHT provide evidence of efficacy with minimal toxicity. The favorable efficacy:toxicity ratio of pomalidomide suggest that it may benefit patients with HHT.

3 OBJECTIVES AND PURPOSE

3.1 PRIMARY OBJECTIVE

To determine efficacy of pomalidomide compared to placebo for the reduction in severity of epistaxis after 24 weeks of treatment.

3.2 SECONDARY OBJECTIVES

1. To determine the safety and tolerability of pomalidomide for the treatment of HHT.
2. To determine if pomalidomide treatment improves quality of life in HHT.
3. To determine whether a continued response to pomalidomide is evident 4 weeks after treatment discontinuation.
4. To develop a biorepository for future studies to define biomarkers predictive of pomalidomide response and allow investigations into the biology of HHT and mechanisms of pomalidomide.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a multi-center, double blind, placebo-controlled study that will investigate the efficacy and safety of pomalidomide in patients with HHT and chronic epistaxis leading to iron-deficiency anemia or requiring intravenous iron infusions or blood transfusion.

After recruitment, patients will be screened for study eligibility. The screening evaluation will include the ESS with three month recall, which will reflect the patient's history of epistaxis and bleeding over the prior three months, as well as detailed review of iron infusion and red cell transfusion over the preceding six months. Eligible patients will be provided a diary to record the duration of each epistaxis event that occurs during the 4 weeks prior to the baseline visit. Eligible patients will then return for the baseline randomization visit between 28 and 56 days later, at which time patients will undergo genetic testing, if this has not been previously performed or if results for ENG, ACVRL1 and SMAD4 genes are not available. A repeat ESS with 4 week recall will be performed and will be considered the "baseline" ESS. Patients will also complete QOL surveys at this visit. Patients will then be randomized 2:1, stratified by study site, to either pomalidomide, 4 mg/day for 28 days during each of six 28 day cycles (24 weeks), or placebo, administered on an identical schedule.

Patients will be seen every four weeks during the study to measure the ESS (with 4 week recall), measure iron stores, and obtain laboratory studies, which will include CBC, metabolic profile and iron studies. The iron replete state will be defined as a ferritin ≥ 50 ng/ml *and* a transferrin saturation ≥ 30% (since ferritin levels may be elevated due to concurrent inflammation). Investigators will be encouraged to replete iron stores in patients in both arms of the study based on these parameters, and the amount of iron infused (in mg) recorded. There is no mandate for the use of a particular iron preparation. Investigators will be encouraged to use iron infusions prior to blood transfusion, though the latter will be mandated for a hemoglobin below 6.5 gm/dl, and recorded as units of packed red blood cells administered. Blood transfusion may also be given at the investigator's discretion based on symptoms that may include shortness of breath, severe fatigue, or other cardiovascular manifestations. Patients will be assessed for adverse events (AE) throughout the study. Treatment dosage may be reduced, or temporarily or permanently discontinued following AE-specific guidelines related to fatigue, cytopenias or other toxicities.

The effect of pomalidomide on QOL will be assessed by measuring QOL at the baseline visit, at the 12 and 24 week visits, and at the 4 week post-treatment follow-up visit using validated NIH instruments of 1) Neuro-QOL satisfaction with social roles and activities, 2) PROMIS emotional distress – depression, and 3) PROMIS fatigue. We will also assess responses to an HHT specific questionnaire developed specifically for this study and shown to correlate with these PROMIS items. The effect of pomalidomide on duration of epistaxis will be assessed via diary between weeks 8-12, 20-24 and the 4 weeks post-treatment discontinuation.

4.2.1 PRIMARY ENDPOINT

The primary endpoint of this study is change of the Epistaxis Severity Score from baseline to week 24 in the placebo and pomalidomide-treated groups. The ESS at baseline and each follow-up visit will reflect the patient's symptoms and bleeding over the previous 4 weeks.

4.2.2 SECONDARY ENDPOINTS

Key Secondary endpoints

1. Amount of parenteral iron administered (in mg) during the 24 week treatment period in the pomalidomide and placebo groups (calculated as average mg/4-week interval to account for patients who discontinue early).
2. Amount of packed red blood cell transfusions (in units) during the 24 week treatment period in the pomalidomide and placebo groups (calculated as average units/4-week interval to account for patients who discontinue early).
3. Change in Neuro-QOL™ Satisfaction with Social Roles and Activities Short Form (V1.1) T-score from baseline (randomization visit) to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups. Although developed as part of an assessment system for people with neurological conditions, the Satisfaction with

Social Roles and Activities is scored relative to a general population sample, supporting its use in non-neurologic health conditions.

4. Change in the HHT-specific QOL total score from baseline to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
5. Change in average weekly epistaxis duration from the four week screening period prior to baseline to weeks 8-12 and to weeks 20-24 (key timepoint), and to the 4 weeks post-treatment in the pomalidomide and placebo groups.

Other Secondary endpoints

6. Change in PROMIS® Emotional Distress – Depression Short Form (V1.0) T-score from baseline (randomization visit) to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
7. Change in PROMIS® Fatigue Short Form (V1.0) T-score from baseline (randomization visit) to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
8. Proportion of patients requiring no red blood cell transfusion or parenteral iron infusion during the 24 week treatment period in the pomalidomide and placebo groups.
9. Change in the ESS from baseline to that recorded at each individual patient assessment, including the 4 week post-treatment follow-up visit.
10. Change in the ESS from baseline to the average of the week 16, 20 and 24 assessments.
11. Proportion of patients requiring endoscopic interventions for management of bleeding during the 24 week treatment period in the pomalidomide and placebo groups.
12. Incidence and severity of adverse events in the pomalidomide and placebo groups including but not limited to:
    - Venous thromboembolism
    - Arterial thromboembolism
    - Thrombocytopenia
    - Neutropenia
    - Peripheral neuropathy
    - Fatigue
    - Constipation/diarrhea
    - Rash
    - Any other AEs or SAEs of at least moderate severity that are possibly related to pomalidomide
13. Change in iron/hemoglobin-related studies including iron saturation, ferritin, hemoglobin, hematocrit, MCV, and MCHC.

4.2.3 EXPLORATORY ENDPOINTS

1. Rate of relapse at the 4 week post-treatment follow-up visit, where relapse is defined as a return of the ESS to the baseline value or greater in pomalidomide (or placebo)-treated subjects.
2. Median time after initiation of pomalidomide to obtain a decrease in the ESS of at least 1.0 in the in pomalidomide-treated subjects compared to placebo.
3. Effect of genotype on the response to pomalidomide.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. A clinical diagnosis of HHT as defined by the Curacao criteria
2. Age ≥ 18 years
3. Platelet count ≥ 100 x 10^9/L
4. WBC ≥ 2.5 x 10^9/L
5. INR ≤ 1.4 and normal ± 2 sec activated partial thromboplastin time (aPTT or PTT per local laboratory designation) by local laboratory criteria (except for patients on a stable dose of warfarin or direct oral anticoagulants)
6. Epistaxis severity score ≥ 3 measured over the preceding three months, measured at the screening visit
7. A requirement for anemia, as determined by local laboratory hemoglobin assessment and normal ranges, and/or parenteral infusion of at least 250 mg of iron or transfusion of 1 unit of blood over the 24 weeks preceding the screening visit
8. All study participants must agree to be registered into the FDA mandated POMALYST REMS® program, and be willing and able to comply with the requirements of the POMALYST REMS® program
9. Females of childbearing potential (FCBP)[†] must adhere to the pregnancy testing schedule mandated by the POMALYST REMS® program (see Section 8.4.5)
10. Ability to understand and sign informed consent

[†]A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Women currently breast feeding or pregnant
2. Renal insufficiency, serum creatinine > 2.0 mg/dl
3. Hepatic insufficiency, bilirubin > 2.0 (or >4.0 in the setting of a prior clinical or genetic diagnosis of Gilbert's syndrome) or transaminases > 3.0x normal
4. Prior treatment with thalidomide or other Immunomodulatory imide drugs (IMiDs) within previous 6 months
5. Prior treatment with bevacizumab (systemic or nasal) within previous 6 weeks*

6. Prior treatment with pazopanib within previous 6 weeks*
7. The use of octreotide or oral estrogens within the previous month*
8. History of prior unprovoked thromboembolism confirmed by venous ultrasound or other imaging modalities
9. Known peripheral neuropathy, confirmed by neurologic consultation
10. Known underlying hypoproliferative anemia (i.e. myelodysplasia, aplastic anemia)
11. Currently enrolled in other interventional trials
12. Known hypersensitivity to thalidomide or lenalidomide
13. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs
14. Known *SMAD-4* mutation, unless there has been a colonoscopy with normal (negative) results, or in which the patient has had no more than 5 small (in the opinion of the gastroenterologist) colonic polyps completely removed within the preceding 18 months
15. Anything that in the investigator's opinion is likely to interfere with completion of the study

* Use of these treatments is not permitted during study participation. See protocol section 7.6 for additional details regarding prohibited treatments.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

We estimate that we will need to screen 200 patients in order to enroll and randomize 159 participants (106 treated with pomalidomide, 53 with placebo), assuming 80% of screened patients will enroll.

To meet this recruitment goal, patients will be recruited at each of up to 15 institutions all of which are nationally-designated HHT Centers of Excellence; three of these centers contributed patients to the NOSE study, with our Utah site being the highest enroller. A national recruitment process will also be employed through the outreach of CureHHT, an international patient advocacy group that communicates regularly with more than 10,000 HHT patients. Details describing the trial will be posted on the CureHHT website and the study website maintained by the DCC after approval from the central IRB at the Cleveland Clinic. CureHHT will publicize the trial through regular email blasts to its constituency and mailings. The trial will also be listed on www.clinicaltrials.gov.

Randomization will be performed in a 2:1 manner to enhance patient enthusiasm for participation in the trial. To alleviate the risk of exposure to COVID-19, site PIs will be given the flexibility to conduct some of the research visits remotely. We anticipate that half of the patients will be recruited from existing populations treated at the study sites, and that half of the patients will respond to communications issued through CureHHT and other mechanisms. Original study timelines were that enrollment would be completed within 2.5 years, with each site screening 9 to 10 patients and randomizing 6-8 patients per year. However, the COVID-19 pandemic has impacted enrollment prolonging study timelines.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 WITHDRAWAL OR TERMINATION OF SUBJECTS FROM THE STUDY

Subjects will be encouraged to remain in the study until completion, but informed that they have the right to stop taking medication or withdraw from the study at any time without compromise to their subsequent care. Causes for study withdrawal may include unacceptable side-effects, a decision to pursue another treatment modality, or personal issues that preclude continued study participation. If a subject elects to stop taking study medication or if study medication is permanently stopped by the study PI due to toxicity concerns, they should be encouraged to complete follow-up visits after stopping study medication as indicated in Section 7.3.5.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

For subjects who withdraw from the study, data collected up to the time of study withdrawal will remain in the trial database and will be used in the analysis. A discussion of how data from subjects with early treatment stop or early study withdrawal will be handled in the statistical analysis is described in Section 10, Statistical Considerations.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the clinical coordinating center to NHLBI and the FDA. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. In the case of unanticipated, unacceptable risks to participants, the Principal Investigator will make the determination to terminate or suspend the study based on recommendations of the Medical Monitor or Data Safety Monitoring Board (DSMB).

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping (per DSMB review of interim analysis)
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility (per DSMB review of interim analysis)

If suspended, the study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the sponsor, DSMB, IRB and/or FDA.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Pomalidomide (POMALYST®) or placebo will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard POMALYST REMS™ program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

Drug will be shipped on a per patient basis by a contract pharmacy to the clinic site or research subject. In accordance with the POMALYST REMS™ program, only enough pomalidomide for one cycle of therapy (i.e., 28 days) will be supplied to the subject.

6.1.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Pomalidomide or matching placebo will be supplied as 4.0 mg capsules for oral administration. Capsules of 3.0 and 2.0 mg pomalidomide or matching placebo will also be provided for patients who experience hematologic toxicity, fatigue or muscle cramping thought to be drug related, per guidelines described in Section 6.1.8. The new dose may be initiated after the unused capsules from the previous dose are collected.

Pomalidomide is dispensed to research subjects as individual bottles containing capsules. Each bottle will identify the contents as study medication. It is suggested as a component of the pomalidomide REMS program that patients not open or extensively handle pomalidomide capsules. All bottles will contain the following warning label: "WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS."

Placebo will contain Microcrystalline Cellulose (Type PH-102) (Compendia: NF, Ph Eur, JP) and the Swedish Orange (6180) Opague Global Capsule Shell (Coni-Snap). Placebo will be indistinguishable from pomalidomide.

6.1.3 PRODUCT STORAGE AND STABILITY

The study drug and placebo should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

6.1.4 PREPARATION

No preparation of pomalidomide is necessary.

6.1.5 DOSING AND ADMINISTRATION

Females of child bearing potential must have two negative pregnancy tests to enter this trial, the first test being 10-14 days before and the second test within 24 hours prior to prescribing study drug. The dose of pomalidomide is 4 mg per day for days 1-28 of a 28 day cycle. For the purposes of this study, one cycle will be defined as 28 days. Subsequent cycles may begin within 5 days of completion of the

previous cycle, to allow time for patient assessment and provision of new drug to the study participant.

6.1.6 ROUTE OF ADMINISTRATION

Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal (water is allowed), preferably around the same time each day.

6.1.7 DOSING SCHEDULE

This study employs a fixed dose of 4 mg of pomalidomide daily. This is the FDA approved dose for multiple myeloma, and has been shown to be active in a pilot trial of pomalidomide for patients with HHT. In the event that patient experiences adverse events that cannot be managed, the dose may be reduced stepwise to 3 mg or 2 mg/day at the site PI's discretion.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Study drug dose may be reduced, or temporarily or permanently discontinued following the guidelines specified in the sections below.

6.1.8.1 MISSED DOSE

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day, within 6 hours. If it is missed for the entire day, it should not be made up the next day. The regular dose should be taken on the next day. Vomitted doses should be considered as dose missed for the entire day.

6.1.8.2 OVERDOSE

Patients who take more than the prescribed dose of pomalidomide should be instructed to contact study staff immediately to review the dose taken and symptoms, and determine if urgent medical care is necessary.

6.1.8.3 DOSE ADJUSTMENT FOR HEMATOLOGIC TOXICITY

The primary toxicity of pomalidomide is hematologic. Hematologic toxicity will be monitored monthly during the study. Dose adjustments will be undertaken any time the hematologic parameters dictate, as described in the tables below. Table 1A lists the NCI CTCAE grading of adverse event severity related to neutropenia and thrombocytopenia. Table 1B lists the interventions that will be used for neutropenia or thrombocytopenia according to NCI CTCAE grade. There is a lower threshold for intervention and/or discontinuation of pomalidomide for either neutropenia or thrombocytopenia than in multiple myeloma, as HHT is not a malignant disease.

TABLE 1A: NCI CTCAE FOR NEUTROPENIA AND THROMBOCYTOPENIA ‡					
	Grade				
Adverse Event	***1***	***2***	***3***	***4***	***5***
Neutrophils (ANC)	<LLN-1.5 x 10^9/L	<1.5-1.0 x 10^9/L	<1.0-0.5 x 10^9/L	<0.5 x 10^9/L	Death
Platelets	<LLN-75 x 10^9/L	<75-50 x 10^9/L	<50-25 x 10^9/L	<25 x 10^9/L	Death

‡ Units for blood cells counts are expressed as 10^9/L, which is equivalent to 10^3/µl or 10^3/mcl. ANC = absolute neutrophil count.

TABLE 1B: INTERVENTIONS FOR NEUTROPENIA AND THROMBOCYTOPENIA BY NCI CTCAE GRADE					
	Grade				
Adverse Event	***1***	***2***	***3***	***4***	***5***
Neutrophils (ANC)	None	None	Interrupt pomalidomide treatment, follow CBC weekly Resume pomalidomide when ANC is >1.0 x 10^9/L, at 1 mg/day less than previous dose*	Interrupt pomalidomide treatment, proceed as for Grade 3	Off study
Platelets (thrombocytopenia)	None	None	Interrupt pomalidomide treatment, follow CBC weekly Resume pomalidomide when platelets are >0.5 x 10^9/L, at 1 mg/day less than previous dose	Off study drug permanently	Off study

* For Grade 3 neutropenias in which the ANC is > 0.8 x 10^9/L, patient may remain on the same dose of drug for up to 1 week at which time a repeat CBC should be obtained. If the ANC is persistently less than 1.0 x 10^9/L, study drug should be discontinued until recovery of the ANC to > 1.5 x 10^9/L and the patient then restarted on the next lower dose.

6.1.8.4 DOSE DISCONTINUATION BASED ON INVESTIGATOR'S DISCRETION

Pomalidomide may be held for an indefinite period at the discretion of the investigator for reasons including but not limited to safety and/or patient benefit (for example, surgery or other drug or disease related or unrelated medical problem). Study drug can be resumed at the discretion of the investigator based on the investigator's opinion that it is safe to do so. Patients should still attend regular study visits while study drug is held.

If the study drug is held during a cycle, the patient may begin the next dose cycle even if the previous cycle was not completed, assuming that the reason for holding the drug was not due to an adverse event requiring dose adjustment.

6.1.8.5 SURGERY

In the specific case of surgery it is recommended that pomalidomide be stopped at least 7 days prior to surgery. Pomalidomide may be restarted 14-21 days after surgery, at the investigator's discretion.

6.1.8.6 FATIGUE

Fatigue may be observed in some patients. This may be difficult to separate from fatigue due to underlying HHT/anemia. For fatigue of CTCAE Grade 3 or higher (*https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, version 4.0*), pomalidomide may be stopped for 1-2 weeks at the investigator's discretion and then resumed at a dose of 3 mg daily, or simply reduced to a dose of 3 mg/daily. This dose may be continued for the remainder of the study or further reduced to 2 mg daily if fatigue is persistent.

6.1.8.7 RASH

The incidence of rash in patients with myeloma treated with pomalidomide is < 10%, though in one study of myeloma patients only 1 of 70 patients were forced to stop drug because of rash. The rash usually develops at the time of drug initiation, and involves the trunk and extremities and may be intensely pruritic. It may sometimes resolve with continued therapy, and is often not of sufficient severity to require drug cessation. Recommended therapies include topical hydrocortisone, oral corticosteroids, antihistamines, cimetidine, oatmeal baths, and ketoconazole shampoo.

6.1.8.8 MUSCLE CRAMPING

In the case of muscle cramping, which may occur in some patients on higher doses of pomalidomide, treatment with over-the-counter quinine water as well as muscle relaxants such as cyclobenzaprine is allowed. If these do not diminish the intensity of symptoms to a tolerable level, the dose of pomalidomide may be reduced to 3 mg/day for two weeks, and the effect on cramping assessed. If this is unsuccessful in improving symptoms, the dose may be reduced to 2 mg/day. If symptoms remain intolerable, the patient will be removed from the study.

6.1.8.9 THROMBOEMBOLISM

Thromboembolic disease has been associated with pomalidomide in patients with multiple myeloma, who are often on concomitant high-dose corticosteroids and have a predisposition to thrombosis due to their underlying cancer. Thrombosis has not been observed in a pilot study of HHT treated with pomalidomide with approximately 60 pt-months of exposure. The development of thrombosis in a patient on this study being treated with pomalidomide warrants study drug discontinuation.

6.1.8.10 HEPATOTOXICITY

Pomalidomide hepatotoxicity is rare. Elevations in bilirubin or transaminases > 3 times the baseline value should prompt temporary discontinuation of pomalidomide. Laboratory testing should be

performed two weeks after discontinuation to assure that abnormalities have resolved. If so, therapy may be resumed at a dose of 3 mg/day.

6.1.8.11 RENAL TOXICITY

Renal toxicity of pomalidomide is rare. Renal toxicity is defined by CTCAE version 4.0 criteria. An increase of creatinine of > 0.3 mg/dl, or a baseline creatinine > 1.5 with an increase at least 2x above baseline define Grade 1 nephrotoxicity. If these abnormalities are confirmed, the pomalidomide dose should be reduced to 3 mg/day. For higher levels of nephrotoxicity, the drug will be discontinued until the abnormalities have resolved and pomalidomide will then be reintroduced at a dose of 3.0 mg/day.

6.1.8.12 DOSE ADJUSTMENT FOR PERIPHERAL NEUROPATHY

Dose adjustments will be undertaken for peripheral motor neuropathy and peripheral sensory neuropathy as described in the tables below. Table 1C lists the NCI CTCAE Version 4.0 grading of adverse event severity for peripheral motor neuropathy and peripheral sensory neuropathy. Table 1D lists the intervention that will be used for each type of neuropathy according to NCI CTCAE grade.

TABLE 1C: NCI CTCAE FOR PERIPHERAL NEUROPATHY

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Peripheral Motor Neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral Sensory Neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

TABLE 1D: INTERVENTIONS FOR PERIPHERAL NEUROPATHY BY NCI CTCAE GRADE					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Peripheral Motor Neuropathy	None	Hold Pomalidomide treatment for up to 4 weeks; restart at next lowest dose if symptoms resolve or improve to Grade 1	Off study drug permanently	Off study drug permanently	Off study
Peripheral Sensory Neuropathy	None	Hold Pomalidomide treatment for up to 4 weeks; restart at next lowest dose if symptoms resolve or improve to Grade 1	Off study drug permanently	Off study drug permanently	Off study

6.1.9 DURATION OF THERAPY

The duration of pomalidomide therapy will be 24 weeks.

6.1.10 TRACKING OF DOSE

Only enough pomalidomide capsules for 1 cycle (i.e., 28 days) of therapy will be provided to the patient each cycle. Patients will be instructed to return empty bottles or unused capsules at each in-person visit.

Returned empty bottles or unused study drug will be disposed by the clinical site (according to site procedures) after documentation. If any study drug is lost or damaged, its disposition should be documented in the source documents.

6.1.11 DRUG/DEVICE SPECIFIC CONSIDERATIONS

Pomalidomide (POMALYST®) or matching placebo will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the POMALYST REMS™ program. Per the standard POMALYST REMS™ program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Patients will be instructed to return all empty bottles or unused capsules at each of the 6 treatment visits. Pill counts will be conducted at every treatment visit to determine compliance.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

7.1.1.1 EPISTAXIS SEVERITY SCORE

The epistaxis severity score (ESS) was developed by Hoag et al and is a clinically-validated score for quantifying epistaxis in HHT which correlates inversely with QOL[11,26]. The ESS takes only 1-2 minutes to perform and will be obtained during screening to assess for eligibility, at the start of therapy, and at each study visit. The ESS will be determined by the study nurse, coordinator or investigator. At screening, the ESS will assess symptoms and bleeding over the previous 3 months. All other time points will assess symptoms and bleeding over the prior 4 weeks. Questions comprising the ESS are depicted in Table 2. The ESS captures the frequency, duration and severity of epistaxis. Clinical characteristics of the bleeding frequency and severity are collected and assigned a numerical score, which is added and multiplied by specific coefficients to determine the final ESS. Historically, sixty percent of patients with an ESS of 4-7 have required invasive treatment. The maximum ESS score is 10, with patients in the 7-10 range being considered to have severe epistaxis. Calculations for determining the ESS are depicted in Table 3, and an automated determination of the ESS may be obtained in real time through electronic entry of scores as depicted in Table 2 (*https://curehht.org/resource/epistaxis-severity-score/*). Question 4 "have you sought medical attention for your nose bleeding" will not include scheduled study visits UNLESS the participant would have sought medical attention had the study visit not been scheduled-we suggest that this question refer to emergent visits for bleeding, such as those to an emergency department. Question 5 "are you anemic (low blood counts) currently" will be based upon the hemoglobin results of laboratory testing related to that particular study visit. The presence of anemia will be defined using local laboratory cutoffs as used for study eligibility.

Please answer each of the following questions as they pertain to your TYPICAL (usual or most common) symptoms during the past 4 weeks.

1. How often did you TYPICALLY have nose bleeding during the past 4 weeks?
   - ☐ Less than monthly [0]
   - ☐ Once per month [1]
   - ☐ Once per week [2]
   - ☐ Several per week [3]
   - ☐ Once per day [4]
   - ☐ Several per day [5]

2. How long did your nose bleeding episodes TYPICALLY last during the past 4 weeks?
   - ☐ Less than 1 minute [0]
   - ☐ 1 to 5 minutes [1]
   - ☐ 6 to 15 minutes [2]
   - ☐ 16 to 30 minutes [3]
   - ☐ More than 30 minutes [4]

3. How would you describe your TYPICAL nose bleeding intensity during the past 4 weeks?
   - ☐ Not Typically Gushing or Pouring [0]
   - ☐ Typically Gushing or Pouring [1]

4. Have you sought medical attention for your nose bleeding during the past 4 weeks?
   - ☐ No [0]
   - ☐ Yes [1]

5. Are you anemic (low blood counts) currently?
   - ☐ No [0]
   - ☐ Yes [1]
   - ☐ I don't know [2]

6. Have you received a red blood cell transfusion SPECIFICALLY for nose bleeding during the past 4 weeks?
   - ☐ No [0]
   - ☐ Yes [1]

Table 2: Questions comprising the epistaxis severity score.

Question	Response	Multiplied by		Coefficient	Result
1	Less than monthly	0	X	0.14 (0.70 Den)	
	Once per month	1			
	Once per week	2			
	Several per week	3			
	Once per day	4			
	Several per day	5			
2	< 1 minute	0	X	0.25 (1.00 Den)	
	1-5 minutes	1			
	6-15 minutes	2			
	16-30 minutes	3			
	>30 minutes	4			
3	No	0	X	0.25 (0.25 Den)	
	Yes	1			
4	No	0	X	0.30 (0.30 Den)	
	Yes	1			
5	No	0	X	0.20 (0.20 Den)	
	Yes	1			
	I don't know	Drop		0	
6	No	0	X	0.31 (0.31 Den)	
	Yes	1			
Total				**Denominator (Sum Den)**	**Raw Score**
Normalized HHT-EES = [Raw Score / Denominator (2.76)] X **10**					

Table 3: Sample table for calculation of the ESS.

7.1.1.2 EPISTAXIS DURATION

In addition to the ESS, subjects will be asked to determine the total duration of epistaxis at several four week intervals during the study (4 weeks prior to baseline, and between weeks 8-12 (C2-C3), 20-24 (C5-C6), and 4 weeks after treatment discontinuation (C6-EOS)) using an electronic diary with paper backup. The total weekly epistaxis duration averaged over these four week intervals will be assessed as a secondary endpoint as described in sections 4.2.2 and 10.2.

7.1.1.3 QUALITY OF LIFE INSTRUMENTS

QOL instruments will be performed at baseline, after 12 and 24 weeks of treatment, and 4 weeks after the end of treatment. The QOL is assessed using three validated NIH instruments as well as the HHT-specific questionnaire developed during the design of this study (described in Section 2.1):

The three NIH instruments are:

1. ***Neuro-QOL Satisfaction with Social Roles and Activities Short Form*** *V1.1*. 8 questions. Total score is calculated as a T score using Neuro-QOL scoring engine.
2. ***PROMIS Emotional Distress – Depression Short Form 8b V1.0***. 8 questions. Total score is calculated as a T score using PROMIS scoring engine.
3. ***PROMIS Fatigue Short Form 6a V1.0***. 6 questions. Total score is calculated as a T score using PROMIS scoring engine.

The HHT-specific survey [56] (see Appendix 1) includes the following four questions:

1. How often in the past 4 weeks has an activity related to your work, school, or regularly scheduled commitments been ***interrupted by a nose bleed***?
2. How often in the past 4 weeks has an activity with your partner, family, or friends been ***interrupted by a nose bleed***?
3. How often in the past 4 weeks have you ***avoided social activities*** because you were ***worried about having a nose bleed***?
4. How often in the past 4 weeks have you ***had to miss*** work, school, or regularly scheduled commitments because of ***HHT related problems <u>other than</u> nosebleeds***?

A total score is calculated by summing the items 1-4 (each ranging from 0-4). The total score ranges from 0 (no limitations) to 16 (severe limitations). If any items are not answered, the total score will not be calculated.

7.1.1.4 COUNSELING

Patients will be provided with their laboratory results and interpretation at each visit. Their symptoms will be reviewed and they will be counseled concerning the relationship of these symptoms, if any, to pomalidomide and/or HHT.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

7.1.2.1 MEDICAL HISTORY

A full medical history will be taken during the screening visit. An interval history including questions to allow calculation of the ESS will be taken at all subsequent visits.

7.1.2.2 PHYSICAL EXAMINATION

A full physical examination including vital signs, examination of the nasal mucosa, examination of the heart, lungs, abdomen and extremities, as well as a brief neurologic examination with emphasis on peripheral neuropathy will be performed at screening, at month 3 of the treatment period, at the end of treatment (cycle 6) and at the end of study. A limited physical examination including vital signs, HEENT and cardiopulmonary examinations will be performed during all other visits. At remote visits, physical exam will be performed to the extent possible. If the screening visit is performed remotely, the baseline visit will include a full physical examination.

7.1.2.3 CONCOMITANT MEDICATION

Patients will be allowed to use any concomitant medications that they require except those listed in the exclusion criteria and section 7.6 Prohibited Medications, Treatments and Procedures. They may remain on HHT-directed medications other than those listed in the exclusion criteria if they were taking these when eligibility was determined. If they remain on such medications, they must remain on a stable dose during the study. Concomitant medications will be reviewed at screening, and at each study visit.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

7.2.1.1 STANDARD OF CARE LABORATORY STUDIES

CBC

A CBC with differential will be performed at the screening visit and at all other study visits. Hematologic toxicities of pomalidomide and their grading are discussed in Table 1A. The Hgb, WBC, absolute neutrophil count (ANC) and platelet counts at all study visits will be recorded.

Complete Metabolic Profile

A complete metabolic profile including renal and liver function studies will be performed at screening, at the initiation of therapy, each month during pomalidomide therapy, and at the end of treatment. The ALT, AST, alkaline phosphatase, total bilirubin, creatinine and BUN at all study visits will be recorded.

Iron Studies

Ferritin, iron and total iron binding capacity (TIBC) (to determine iron saturation) will be obtained at screening, at the initiation of therapy, each month during treatment, at the end of treatment and at the end of the follow-up period.

PT/INR (International Normalized Ratio) and Activated Partial Thromboplastin Time

Hemostasis will be assessed by measuring the PT/INR and activated partial thromboplastin time (aPTT or PTT per local laboratory designation) tests. These two tests will only be done at screening and are not required at other study visits. For study entry, the INR should be ≤1.4 and aPTT should be within the normal range (± 2 sec) per local laboratory guidelines (except for patients on a stable dose of warfarin or direct oral anticoagulants).

7.2.1.2 NON-STANDARD OF CARE LABORATORY STUDIES

Genetic Testing

All patients who provided consent for genetic testing will undergo testing for at least the three primary genes associated with HHT (endoglin (ENG), ACVRL1 and SMAD4) if they have not had prior testing or if the results for these three genes are not available. Genetic testing will be performed at Ambry Genetics, Aliso Veijo, CA. Samples will be shipped to Ambry, who will determine whether genetic testing costs will be covered by the patient's health care insurer. If not, Ambry will perform genetic testing at a reduced rate that will be covered by this study.

Pregnancy Testing

As mandated by the POMALYST REMS® program, all FCBPs must follow pregnancy testing requirements. In FCBP, pregnancy tests will be performed 10-14 days before, and within 24 hours of first study drug order. During the first treatment cycle, weekly pregnancy testing is mandated. Thereafter, pregnancy testing will be performed once every 4 weeks, during each cycle of treatment, preferably during the middle of the treatment cycle, or every 2 weeks for irregular menses.

Biorepository Samples

Biorepository blood samples will be obtained at the following times: 1) screening visit, 2) randomization (baseline) visit, 3) at 12 and 24 week treatment period visits, 4) at the 4 week post-treatment (end of study) visit, and 5) early termination visit (if this occurs). These will be shipped to the lead PI's lab for storage. If a study visit is conducted remotely, sample collection for biorepository at that visit will be skipped.

7.2.2 OTHER ASSAYS OR PROCEDURES

7.2.2.1 ASSESSMENT OF STUDY AGENT ADHERENCE

Adherence to pomalidomide will be conducted by direct questioning and by pill counts at each study visit. Deviations from the prescribed dosage regimen should be recorded.

Patients who are signficantly noncompliant may be discontinued from the study. A patient will be considered significantly noncompliant if he or she misses more than 5 consecutive days of study drug or more than 10 cumulative days of study drug during the study. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of study drug.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Biorepository samples will consist of one serum (SST) vacutainer tube, one citrate plasma tube and one EDTA plasma tube. At the randomization (baseline) visit, end of cycle 3 visit (week 12), end of cycle 6 visit (week 24) and early termination visit (if this occurs) we will also obtain one PAXgene blood RNA tube. When study visits involving biorepository sample collection are conducted remotely, sample collection will be skipped. Samples will be processed on site to isolate plasma and serum. PAXgene tubes do not require processing. Samples including the unprocessed PAXgene tube will be stored at -80° C and shipped to the PI's lab semi-annually. Samples to be shipped should include all samples collected from enrolled subjects up to the shipment date. Detailed instructions regarding processing, storing and shipping of biorespository and genetic testing samples will be described in the Manual of Procedures.

7.2.4 SPECIMEN SHIPMENT

Shipping information, including shipping labels will be provided to each site. Samples for biorepository will be shipped overnight in dry ice and stored at -80°C upon receipt until the time of analysis.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Each patient will require a screening visit to determine study eligibility. During the screening period the following information will be obtained.

- Informed consent of potential participant verified by signature on written informed consent
- Review enrollment criteria
- Review medical history
- Review of medication history
- Complete ESS with 3-month recall
- Documentation of packed red blood cell transfusions and/or iron infusions over the previous six months
- Performance of a detailed physical exam

- Collect blood for CBC, ferritin, iron and TIBC, renal and liver function, INR and aPTT (or PTT per local laboratory designation), and pregnancy testing for women of child bearing potential.
- Collect biorepository blood samples (if visit is in-person)
- Determine need for parenteral iron therapy based on results of iron studies.
- Provide participants with instructions for recording epistaxis duration between screening and enrollment/baseline visit.
- Schedule study visits for eligible patients.
- Provide participants with instructions for attending the baseline visit.

At the site PI's discretion, the screening visit may be conducted remotely. Obtaining signed informed consent prior to collecting any information for the study is mandatory for a remote screening visit as well. Physical examination may be limited to the extent possible at a remote visit; vital signs and biorepository sample collection will be skipped for remote screening visit. Screening laboratory studies may be obtained within 2 weeks before and after the screening visit.

Participants who do not initially meet eligibility criteria, but may meet criteria at a later time may be rescreened. Screening study procedures should be repeated per protocol and Manual of Procedures for rescreening. Baseline visit (if participant meets eligibility criteria) should be scheduled based on the rescreen date.

7.3.2 BASELINE/RANDOMIZATION

A period of at least 28 days after the screening visit will be required before the baseline/randomization visit, which must be conducted in-person. The baseline visit will be synonymous with the day of randomization and will include the following:

- Verification of inclusion/exclusion criteria
- Obtain ESS with 28-day recall
- Complete QOL instruments
- Perform pregnancy testing for women of child bearing potential
- Review of concomitant medications and adverse events
- Record vital signs, results of physical exam
- Collect laboratory samples for CBC, iron studies, and genetic testing
- Collect biorepository blood samples
- Collect epistaxis duration information
- Randomization and study drug order
- Study drug dispensation

Results from the laboratory assessments at baseline should not to be used to re-establish eligibility criteria; study eligibility is determined by assessments completed at the screening visit.

If the screening visit was done in-person and study eligibility is confirmed, randomization and study drug order may be done 3-5 days before the baseline visit to ensure that study drug is available on site for dispensation on the day of visit. Patients may be instructed to initiate the drug the same day or the following day.

If the screening visit was done remotely, randomization and study drug order will be done at the baseline visit. A detailed physical examination will be performed at the baseline visit and biorepository sample collection tube will include PAXgene RNA tube in addition to the SST, sodium citrate and EDTA plasma tubes.

After randomization, study drug will be shipped overnight to the study site (or directly to the patient) from the experimental pharmacy. Patients will be instructed to initiate the drug upon receipt or the following day.

7.3.3 TREATMENT FOLLOW-UP

Follow up studies and procedures during the treatment phase are as noted in the Schedule of Events (Section 7.3.7). At the follow-up treatment visits, study drug order may be initiated 3-5 days before the scheduled visit day to ensure that study drug is available for dispensation on visit day. Patients will be asked to bring empty bottles and remnant capsules (if any) at each in-person treatment visits for drug accountability. Laboratory studies may be completed ± 1 week of the study visit; however, it is strongly recommended that laboratory assessments be completed and test results be available at the study visit to evaluate safety.

At the site PI's discretion, visits at the end of treatment cycles 1, 2, 3, 4 and 5 may be conducted remotely. At the remote visits, vital signs recording will be skipped and physical exam may be limited to the extent possible. Biorepository sample collection at remote visits will also be skipped. At remote visits, study drug will be directly shipped to the patient from the experimental pharmacy. Information related to drug return and accountability will be collected at the remote visit with a reminder for the patient to bring remnant pills and empty bottles at the next in-person visit. If required, patient may be requested to ship the previously dispensed bottle (empty or with remnant pills) to site. The visit at the end of treatment cycle 6 (C6, key timepoint) will be conducted as an in-person visit.

Visit schedule will not be paused or altered for any missed follow-up visit; study follow-up should resume at the next scheduled study visit.

7.3.4 FINAL STUDY VISIT

Data to be gathered at the final study visit (EOS, end of the 4 weeks post-treatment observation period) is listed in the Schedule of Events table (Section 7.3.7). This visit may also be conducted remotely according to site PI's discretion. In addition, the following will be addressed.

- Record final adverse events as reported by participant or observed by investigator.
- Provide final instructions and/or follow up information to participant.

- Obtain final biorepository sample (if visit is in-person)

7.3.5 DISCONTINUATION OF STUDY MEDICATION

Study medication may be stopped by the study PI due to toxicity concerns or a subject may elect to stop study medication due to personal reasons. For temporary study drug discontinuations, study drug should be restarted after toxicity/safety concerns are resolved. In case of permanent study drug discontinuation, subjects should complete the visit associated with their current treatment cycle and then complete the EOS visit 4 weeks later (e.g. if a subject permanently stops study drug in the middle of their second treatment cycle, they will complete the end of treatment cycle visit 2 (C2) followed by an EOS visit 4 weeks later) (Figure 3). Subjects who do not agree to complete the 4 week post-treatment follow-up must be discontinued due to withdrawn consent and the Early Termination visit should be completed per Section 7.3.6 in place of the current treatment cycle visit.

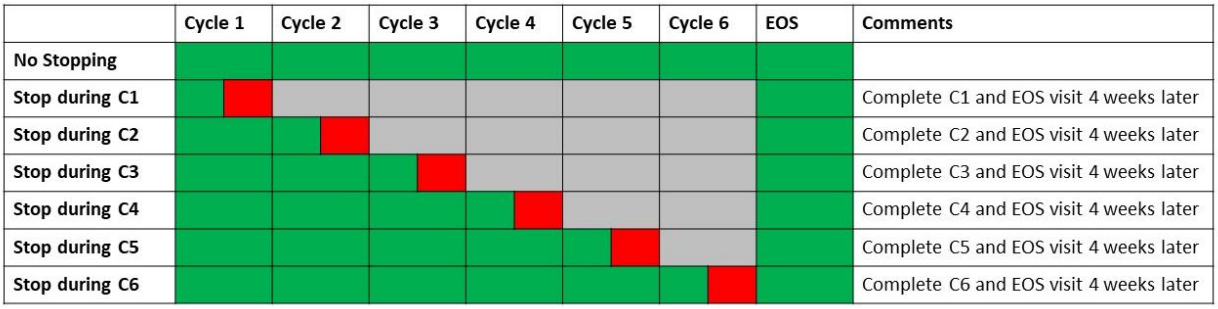

Figure 3. Follow-up visit schedule after permanent study drug discontinuation. Dark Green: completed visits; Red: stop study medication mid-cycle.

7.3.6 EARLY TERMINATION VISIT

If a subject wishes to withdraw consent for study participation, study drug is to be stopped and the early termination visit should be completed as soon as possible. Parameters dictated by the Schedule of Events (Section 7.3.7) for an early termination visit will be obtained.

7.3.7 TABLE 4: SCHEDULE OF EVENTS TABLE

	Screen and Baseline		Treatment Period						End of Study	
Visit	**SC**	**BL**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**EOS**	**ET[12]**
Study Procedures	**Week -4 to -8[13]**	**Week 0**	**Week 4 0-5 Days***	**Week 8 0-5 Days***	**Week 12 0-5 Days***	**Week 16 0-5 Days***	**Week 20 0-5 Days***	**Week 24 0-5 Days**	**Week 28 (4 week follow up) 0-7 Days**	**Only for withdrawn consent**
Informed Consent	X									
Enrollment Criteria	X									
Demographics	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X[1*]	X[1]	X[1]	X	X[1]	X[1]	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X
Genetic Testing[3]		X								
Iron Infusion	X[4]	X	X	X	X	X	X	X	X	X
Blood Transfusion	X[4]	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
ESS	X[5]	X	X	X	X	X	X	X	X	X
Epistaxis Duration Diary	X	X[6]		X	X[6]		X	X[6]	X[6]	X[6]
CBC with differential	X	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X		X
Iron Studies[7]	X	X	X	X	X	X	X	X	X	X
INR and aPTT (or PTT per local lab designation)	X									
Biorepository Collection	X	X[8]			X[8]			X[8]	X	X[8]
QOL[9] surveys		X			X			X	X	X
Pregnancy Testing[10]	X	X	X	X	X	X	X	X		X[10]
Randomization		X								
Drug Dispensation		X	X	X	X	X	X			
Drug Return			X[11]	X[11]	X[11]	X[11]	X[11]	X		X

SC = Screening; BL = Baseline; C = End of cycle; ESS = Epistaxis severity score; CBC = Complete blood count; CMP = Complete metabolic panel; EOS = End of study Visit; ET = Early termination; QOL = Quality of life; Gray boxes: flexibility to perform visits remotely in which case physical exam may be mofified; vital signs and biorepository samples may not be collected.

* Window to begin study drug dosing cycle (see Section 6.1.5)

[1] Limited physical examination; *A detailed physical exam if screening visit was remote.

[2] Vital signs will include height (only at first in-person visit), body weight, blood pressure, pulse and O2 saturation.

[3] Genetic testing will be performed only if not done previously or if results for ENG, ACVRL1 and SMAD4 genes are not available and consent is obtained.

[4] Information on Iron infusion and Blood transfusion over the past 6 months to be collected at screening visit.

[5] ESS will be a 3-month recall for these visits; for all other visits, it will be a 4-week recall.

[6] Epistaxis Duration Diary will be collected at these visits and if applicable a new diary will be dispensed for the next set of epistaxis recording. For ET visit, diary will be collected if dispensed for the previous visit. See MOP for additional details.

[7] Iron studies include ferritin levels, serum iron and total iron binding capacity.

[8] One PAXgene RNA tube is included at these visits.

[9] QOL questionnaires will include 3 NIH instruments (Neuro-QOL Satisfaction with Social Roles and Activities Short Form V1.1, PROMIS Emotional Distress - Depression Short Form V1.0 and PROMIS Fatigue Short Form V1.0) and a HHT specific questionnaire.

[10] In FCBP, pregnancy tests will be performed 10-14 days before, and within 24 hours of first study drug order. During the first treatment cycle, weekly pregnancy testing is mandated. Thereafter, pregnancy testing will be performed once every 4 weeks, during each cycle of treatment, preferably during the middle of the treatment cycle, or every 2 weeks for irregular menses. For subjects completing an ET visit, pregnancy testing is only required if study medication was taken after the last pregnancy test.

[11] Information on remaining drug and empty bottles will be collected over phone, email, or other means, if visit is remote.

[12] Early Termination visit should be scheduled as soon as possible not to exceed 4 weeks post study drug discontinuation.

[13] Strongly recommended that BL be scheduled 4 weeks after SC. Additional days up to 8 weeks to be used only for scheduling purposes.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications, treatments and procedures taken during study participation will be recorded on case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

- Patients who are on chronic anticoagulation with warfarin or a direct acting oral anticoagulant at a stable dose are eligible for the study.
- Patients on chronic aspirin are eligible for the study.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Several drugs may interact with pomalidomide, either directly or indirectly, increasing the risk of toxicity. The use of other agents may potentially obscure the therapeutic effect of pomalidomide. Therefore, the following restrictions on the use of specific medications must be followed during the study.

- The use of concomitant octreotide, which may be used for management of gastrointestinal angiodysplasia, is prohibited.
- Initiation or changing the dose of oral epsilon-aminocaproic acid or tranexamic acid is not allowed while the patient is on study. However, if the patient is already on a stable dosing (at least a month before study start) of an antifibrinolytic agent he/she may be evaluated for study eligibility.
- The use of propanolol, timolol, epsilon aminocaproic acid or tranexamic acid nasal sprays will be allowed if the patient is already on a stable dosing regimen of one of these agents and continues to have epistaxis of a severity that qualifies him/her for this trial. The initiation or administration of increased doses of any intranasally-administered agent will not be permitted while the patient is on study.
- Bevacizumab, either administered intranasally/topically, or systemically, will not be allowed while the subject is on study.
- Erythropoetic agents and oral estrogen and/or progestin therapy are not allowed. Nasal estriol is allowed if the patient was using this agent before study entry and does not change the dose during the study. Nasal estriol cannot be added during the study.
- Ciprofloxacin, fluvoxamine, ketoconazole are not allowed (decreased metabolism and potential increase in pomalidomide toxicity).

- Carbamazepine is not allowed (decreased pomalidomide effect)
- Initiation of pazopanib will not be allowed while the subject is on study

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Since this is an investigational drug for treatment of HHT, study drug will not be available to patients once the treatment period ends.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

A secondary objective of this study will be to define the incidence of toxicities potentially attributable to pomalidomide. These include

- Venous thromboembolism
- Arterial thromboembolism
- Thrombocytopenia
- Neutropenia
- Peripheral neuropathy
- Fatigue
- Constipation/diarrhea
- Rash/pruritis

Venous and arterial thromboembolism will be considered serious adverse events and result in study drug discontinuation. Thrombocytopenia and neutropenia will be managed as outlined in Section 6.1.8. Peripheral neuropathy will be managed as outlined in Section 6.1.8.12. Management of fatigue will involve temporary withholding and/or dose reduction of study drug at the investigator's discretion.

The incidence of these toxicities has been determined in studies of patients with multiple myeloma, who have compromised bone marrow function, a predisposition to thrombosis, and reduced immunity. Therefore, estimates of toxicity based on this population are likely not relevant to the current study. However, subjects taking pomalidomide will be continuously monitored for these toxicities.

8.1.1 DEFINITION OF ADVERSE EVENTS

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

For the purposes of this protocol, worsening of epistaxis, and seeking medical attention for epistaxis is not to be reported as an AE, as epistaxis is part of the disease being studied and evaluated for primary and secondary endpoints.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of this protocol, worsening of epistaxis and seeking medical attention for epistaxis is not to be reported as an SAE unless it results in death.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems are defined as including any incident, experience, or outcome that meets all of the following criteria:

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

Corrective actions or changes that will be considered in response to an UP include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

National Cancer Institute (Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) for use in reporting adverse events. The website for the CTCAE is: *https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm*.

The CTCAE includes a grading (severity) scale for each adverse event term. Grades were developed using the following guidelines:

- Grade 1 –Mild adverse event
- Grade 2 –Moderate adverse event
- Grade 3 –Severe or disabling adverse event
- Grade 4 - Life threatening adverse event
- Grade 5 –Fatal adverse event

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically

reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTEDNESS

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent. Determination of the expectedness of an adverse event will be made by the site PI after evaluating the study subject. All AE reports will be reviewed by the IMM, who will make the final determination concerning relatedness of the event to the drug.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed by the site PI or his/her designee), and time of resolution/stabilization of the event and any additional medical treatment employed in its management (assessed by the site PI or his/her designee). All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

If there are changes to severity of an AE during a single episode, the maximum severity experienced for that episode should be recorded. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study site will record all adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study drug . At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

Reporting requirements of AEs are calibrated to the seriousness of the event and the perceived relationship to the study treatment. This study will be using the descriptive terminology developed by the National Cancer Institute (Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) for use in reporting adverse events. The website for the CTCAE is: *https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm*. The site needs to be aware of the distinction between a severe AE and serious AE: severe refers to the intensity of the AE whereas serious refers to the AE that fulfils the criteria as defined in section 8.1.2. During the trial, occurrence of all AEs and SAEs will be documented on dedicated eCRFs (and the corresponding paper version, if applicable) on an ongoing basis in a manner consistent with ICH Requirements.[51] Reporting timelines and requirements for AEs that are deemed to be serious or non-serious differ and the site must follow the appropriate reporting procedures.

8.4.1 NON-SERIOUS ADVERSE EVENT REPORTING

For AEs that are non-serious the site should use the AE eCRF within Medidata RAVE to enter all event information within 5 working days of becoming aware of the event. All reported AEs will be followed until resolution or study completion, whichever occurs first. After review by the study monitor, the site may be requested to provide additional details. The site should additionally follow local IRB guidelines for submission of these AEs to their local IRBs.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

SAEs will be promptly reported by the site to the DCC using the SAE eCRF within Medidata RAVE, within 24 hours of becoming aware of the event. The DCC may contact the site for additional information on the SAE, if required. All SAEs must also be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable, whichever occurs first. All updates to SAEs must also be promptly provided within 48 hours of becoming aware of the updates. The DCC will review and categorize all SAEs with the independent medical monitor to facilitate reporting by the CCC.

All sites are expected to adhere to the specified timelines and procedures for SAE reporting in order to facilitate SAE reporting by the CCC to meet specific timelines mandated by the FDA, NHLBI (https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-

unanticipated-problem-reporting-policy), DSMB, Celgene Drug Safety, and the Cleveland Clinic IRB, as applicable.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the DCC and institution IRB (as applicable) within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the DCC and institution IRB (as applicable) within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IRB's receipt of the report of the problem from the investigator.

8.4.4 EVENTS OF SPECIAL INTEREST

AEs of special interest are listed in Section 8.1.

8.4.5 REPORTING OF PREGNANCY

1. All FCBP are screened for pregnancy at the screening visit, and subsequently managed as mandated by the pomalidomide REMS. The REMS has the following requirements for pregnancy screening throughout the study.
2. Females taking Pomalidomide must avoid pregnancy during active treatment and for at least four weeks after taking pomalidomide.
3. Female patients of reproductive potential must either completely abstain from heterosexual sexual contact or must use two effective methods of contraception (at least one highly effective method and one effective method) at the same time (see Table 2 below).
4. The 2 effective contraceptive methods include using at the same time at least 1 highly effective method and at least 1 additional method of birth control every time they have sex with a male.

5. The 2 effective contraceptive methods must be started at least 4 weeks before POMALYST therapy, during therapy (including dose interruptions), and for at least 4 weeks following discontinuation of therapy.
6. The subject will undergo pregnancy testing twice prior to pomalidomide initiation. They must obtain a negative pregnancy test 10 to 14 days before first study drug order and again within 24 hours before study drug order even if continuous abstinence is the chosen method of birth control.
7. Pregnancy testing must occur weekly during the first four weeks of use.
8. During subsequent cycles, pregnancy testing must occur every 4 weeks if they have regular menses or every two weeks if menses are irregular.
9. The sensitivity of the pregnancy test should be at least 50mIU/ml.
10. Since oral estrogen may have a potential therapeutic effect in HHT, oral contraceptives are not considered an acceptable means of contraception during this study.

Table 2. REMS Program Contraceptive Methods

Highly Effective Methods	Additional Effective Methods	Unacceptable Methods
• Intrauterine device (IUD) • Hormonal methods: - Hormonal patches - Injections - Vaginal rings - Implants • Tubal ligation • Partner's vasectomy	• Male latex or synthetic condoms • Diaphragm • Cervical cap	• Progesterone-only "mini-pill" • IUD progesterone T • Female condoms • Natural family planning (rhythm method) • Breastfeeding • Fertility awareness • Withdrawal • Cervical shield*

*A cervical shield should not be confused with a cervical cap which is an effective secondary form of contraception.

Pomalidomide is present in semen of males taking the drug and therefore males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide and for up to 4 weeks after discontinuing pomalidomide, even if they have undergone a successful vasectomy. Male patients taking pomalidomide must not donate sperm.

Study subjects must not donate blood during treatment with pomalidomide and for 1 month following discontinuation.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on pomalidomide, or within at least 28 days of the subject's last dose of pomalidomide, are considered reportable events. Pomalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the DCC and institutional IRB (as applicable) as an SAE. The subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The Investigator will follow the female subject until completion of the pregnancy, and must notify the DCC and institutional IRB (as applicable) about the outcome of the pregnancy (either normal or abnormal outcome) within 15 days.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the pomalidomide should also be reported to the DCC and institutional IRB (as applicable) within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking pomalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider.

8.5 STUDY HALTING RULES

Randomization of new participants will be halted when eight thromboembolic events, defined as any venous thromboembolic event requiring medical intervention (grade 2 or higher) or any arterial thromboembolic event, that are determined to be related or "probably related" to the study drug are reported to the DCC.

The DCC will notify the study monitor, study sponsor, PI and investigators immediately when the eighth thromboembolic event (as defined above) is reported and randomization functionality will be deactivated. The PI will inform the DSMB members within 24 hours of this occurrence and the DCC will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor/NIH. The clinical coordinating center will inform NHLBI and the FDA of the temporary enrollment halt and the disposition of the study.

8.6 SAFETY OVERSIGHT

This study will be reviewed for safety by an independent data safety monitoring board (DSMB) who are familiar with HHT, selected by NHLBI (per protocol), work independently of the PI, and thus have the appropriate expertise to monitor the safety and risk/benefit ratio of pomalidomide for HHT. Serious adverse events that arise in this study will be brought to the attention of the PI, DCC, IRB, FDA, NHLBI, and Celgene. The DSMB will meet every 6 months during the study. Two meetings will include a planned interim analysis for efficacy or futility after 50% and 75% of subjects have completed the 24 week treatment period. See section 10.4.7 for further details.

9 CLINICAL MONITORING

Site monitoring visits will be conducted by the Data Coordinating Center to inspect study data, informed consent forms, subjects' medical records, and Case Report Forms, pursuant to US GCPs and other federal and local regulations. Monitoring visits will occur in the first year after site activation and every other year thereafter. The study site principal investigator will permit authorized representatives of the FDA, NHLBI, and local health authorities to inspect relevant facilities and records.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

A detailed statistical analysis plan (SAP) will be prepared by the study statistician and approved by the trial Steering Committee and the DSMB prior to database lock and unblinding of the study data. Details of all analyses including data reduction steps, calculation of derived variables, primary, secondary, subgroup, and confirmatory analyses will be provided in the SAP. The SAP will have table templates as appropriate. The SAP will also fully specifiy the criteria to make decisions at the interim and final analyses, including:

- Definition of the endpoint(s) that will be considered when deciding if the trial should continue beyond the pre-planned interim analysis. These endpoints will include the primary efficacy and safety endpoints, but may also include other outcome measures.
- Decision criteria. The rules that pre-specify the criteria for recommending that the trial stop at the interim analysis. The decision criteria will be specified using established methods for group sequential trial design that will assure that the pre-trial statistical operating characteristics are not altered by the interim analysis.
- Methods for implementing the interim analyses: often the pre-trial timing of the interim analysis must be altered to accommodate differences from the pre-trial assumptions about event rates and timing of DSMB meetings. The SAP will pre-specify the procedures that will be used to modify the decision rules to accommodate changes in the timing of the interim analysis.
- Bias-adjusted inference: the SAP will specify the method for reporting of trial results that will adjust for the bias that is introduced by the interim analysis.

10.2 STATISTICAL HYPOTHESES

Primary efficacy endpoint:

The primary efficacy endpoint is the change from baseline to Week 24 in the ESS total score.

Null hypothesis: There is no difference in the mean change in ESS score at Week 24 between the pomalidomide and placebo treatment groups.

Alternative hypothesis: There is a difference in mean change in ESS score at Week 24 between the pomalidomide and placebo treatment groups. Specifically, pomalidomide will have a larger improvement from baseline than placebo.

Secondary efficacy endpoints:

The pomalidomide and placebo treatment groups will be compared for the following secondary endpoints:

Key Secondary endpoints

1. Amount of parenteral iron administered (in mg) during the 24 week treatment period in the pomalidomide and placebo groups (calculated as average mg/4-week interval to account for patients who discontinue early).
2. Amount of packed red blood cell transfusions (in units) during the 24 week treatment period in the pomalidomide and placebo groups (calculated as average units/4-week interval to account for patients who discontinue early).
3. Change in Neuro-QOL™ Satisfaction with Social Roles and Activities Short Form (V1.1) T-score from baseline (randomization visit) to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
4. Change in the HHT-specific QOL total score from baseline to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
5. Change in average weekly epistaxis duration from the four week screening period prior to randomization to weeks 8-12 and to weeks 20-24 (key timepoint), and to 4 weeks post-treatment in the pomalidomide and placebo groups.

Other Secondary enpoints

6. Change in PROMIS® Emotional Distress – Depression Short Form (V1.0) T-score from baseline (randomization visit) to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
7. Change in PROMIS® Fatigue Short Form (V1.0) T-score from baseline (randomization visit) to weeks 12 and 24 (key timepoint), and the 4 week post-treatment follow-up visit in the pomalidomide and placebo groups.
8. Proportion of patients requiring no red blood cell transfusion or parenteral iron infusion during the 24 week treatment period in the pomalidomide and placebo groups.
9. Change in the ESS from baseline to that recorded at each individual patient assessment, including the 4 week post-treatment follow-up visit.
10. Change in the ESS from baseline to the average of the week 16, 20 and 24 assessments.
11. Proportion of patients requiring endoscopic interventions for management of bleeding during the 24 week treatment period in the pomalidomide and placebo groups.
12. Change in iron/hemoglobin-related studies including iron saturation, ferritin, hemoglobin, hematocrit, MCV, and MCHC.

Null hypothesis: For each secondary endpoint, there is no difference between the pomalidomide and placebo treatment groups.

Alternative hypothesis: There is a difference between between the pomalidomide and placebo treatment groups. Specifically, pomalidomide will have a larger improvement

10.3 ANALYSIS DATASETS

Modified Intention-to-Treat Analysis Dataset: Randomized participants who took at least one dose of double-blind study medication and have at least one post-baseline efficacy measurement.

Per-Protocol (PP) Analysis Dataset: Randomized participants who complete the study with no major protocol violations and took at least 80% of the prescribed double-blind medication.

Patients who withdraw consent for further follow-up will be treated as lost to follow-up at the time that consent was withdrawn, and data will be used up to the time of study withdrawal.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This is a Phase II trial in which the primary goal is to evaluate the safety and efficacy of pomalidomide in the treatment of epistaxis in patients with HHT.

For descriptive statistics, categorical data will be presented as proportions and 95% confidence intervals and continuous data as means with standard deviations, median, and range. Estimates from linear models will be presented by mean, standard error, and 95% CI. Estimates from logistic regression will be presented by odds ratios and 95% CIs. All statistical tests will be 2-tailed.

Checks of assumptions (e.g., normality) underlying statistical procedures will be performed and corrective procedures such as use of a transformation or application of nonparametric tests will be applied.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analysis will be fully pre-specified in a written SAP.

Treatment groups will be compared for the change from baseline in the ESS Total Score at Week 24 using a mixed effects analysis of covariance model for repeated measures (MMRM). The observed change from baseline score at each scheduled post-baseline visit (Weeks 4, 8, 12, 16, 20, 24, and 4 Weeks post-treatment) is the dependent variable. The model will include the baseline ESS score as a covariate, with fixed effect categorical factors for treatment group (Active and Placebo), site, visit, and the treatment × visit interaction. The interaction remains in the model regardless of significance, and treatment group comparisons at each visit are estimated by differences of least squares (LS) means. A heterogeneous Toeplitz covariance pattern will estimate the variance-covariance of the within-subject repeated measures, and the Kenward-Roger method will be used to calculate denominator degrees of freedom. Estimates, p-values and 95% confidence intervals will be presented for treatment group comparisons at each visit. In an intent-to-treat fashion, all data will be included in the primary model, regardless of the treatment actually taken by the patient.

This model assumes missing data (such as due to a missed visit or due to early study discontinuation) is missing at random. Sensitivity analyses to this assumption to be specified in the SAP will be explored, including methods that assume that data are missing not at random, such as imputation of missing outcomes in the pomalidomide treatment group based on data from the placebo group (control-

based imputation). We will also investigate if the season of the year of enrollment is a relevant baseline covariate, given that there may be seasonal variation of epistaxis during colder months due to drier room air and increased prevalence of upper respiratory infections.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

A Hochberg multiple comparison adjustment will be applied to the 5 key secondary endpoints to maintain the overall Type 1 error rate, as described in Section 10.4.9. Treatment groups will be compared for the secondary endpoints as follows:

Treatment groups will be compared for the total amount of packed red blood cell transfusions (average units/4-week interval) and iron (average mg/4-week interval) infused during the 24 week treatment period, using an analysis of covariance or rank analysis of covariance if not normally distributed, with adjustment for baseline value, defined as the average amount over the 6 months prior to the screening visit and clinical site. Missing data from early discontinuations will be addressed assuming MAR by averaging each subject's available data. Sensitivity analyses will be specified in the SAP. If packed red blood cell transfusions are rare, then we will switch to either a zero-inflated Poisson regression model or logistic regression.

Groups will be compared for the proportion of patients relapsed, requiring no blood or iron, and requiring endoscopic interventions using logistic regression with adjustment for baseline assessment (ESS score, whether the patient had required a blood transfusion or required an iron infusion of at least 250 mg in the 6 months before the screening visit, and ESS score, respectively), and study site.

Treatment group comparisons of the ESS score averaged over the week 16, 20, and 24 week visit assessments and at each study visit will be assessed in the same model as the primary outcome.

Change from baseline in weekly epistaxis duration averaged over weeks 8-12, 20-24, and 4 weeks after treatment, and Quality of Life scores at weeks 12, 24, and 4 weeks after treatment will be analyzed using the same MMRM model as the ESS score.

10.4.4 SAFETY ANALYSES

In addition to expedited reporting of unexpected SAEs outlined in Section 8.4.2, the DCC will determine the frequency of toxicities potentially attributable to pomalidomide treatment that were described in Section 8.1 (e.g., venous/arterial thromboembolism, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, constipation/diarrhea, rash/pruritis). The DCC will determine the number of subjects experiencing each type of event and the frequency with which each occurs in the affected subjects. Treatment and resolution of all safety endpoints will also be documented. Treatment groups will be compared for incidence of events with a chi-squared or Fisher's exact test, and incidence density (events per person-months of exposure) will be calculated for toxicities in the pomalidomide group. Adverse event incidence rates will be included in semi-annual safety reports to the DSMB and annually to the FDA.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Missing data and missed visits will be monitored in real-time. In the event a scheduled visit is missed, site coordinators will contact the patient before the follow-up period closes to encourage them to at least obtain measurements relevant to the primary endpoint. For any missing data that do occur, we will record and describe the reasons the data are missing when reporting results.

In the event that one or more ESS or QOL score is missing during the treatment, or post-treatment periods, the MMRM analysis approach which assumes data are missing at random (MAR) will be used to compare treatments based on the available data and the correlation between observations with a person. To guard against bias if the MAR assumption is incorrect, sensitivity analyses will be explored, as specified above in section 10.4.2.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

10.4.7 PLANNED INTERIM ANALYSES

The Data Coordinating Center will prepare regular data reports, and the DSMB will review those findings to ensure that patients are not exposed unnecessarily to clearly inferior or dangerous treatments and to accelerate scientific and clinical progress if clear evidence can be obtained much earlier than originally expected. DSMB reports prepared by the DCC will include summaries of AEs and SAEs, primary endpoint measures, and metrics of study enrollment, retention, and data quality on which the DSMB can base their recommendations. Biostatisticians from the DCC will develop a DSMB Charter and an interim statistical analysis plan (ISAP) detailing interim stopping criteria and the DSMB will review and amend as needed. We plan to have DSMB reviews once each 6 months, with a formal interim analysis for efficacy after 50% and 75% of patients have completed the 24 week treatment period or discontinued from the study.

10.4.7.1 SAFETY REVIEW

Safety reviews will take place every 6 months corresponding to DSMB meetings. In addition to the interim safety reviews, all adverse events will be reviewed by the trial independent medical monitor, Dr. Jason Valent, who will also refer all major events to the DSMB chair for potential consideration and discussion by the DSMB.

Study halting rules are described in Section 8.5. Briefly, randomization of new study participants will be halted when eight thromboembolic events, defined as any venous thromboembolic event requiring medical intervention (grade 2 or higher) or any arterial thromboembolic event, that are determined to be related or "probably related" to the study drug are reported to the DCC.

Safety monitoring is described in detail in Section 8.

10.4.7.2 EFFICACY REVIEW

We will perform a formal interim analysis to evaluate for early overwhelming efficacy based on the change in ESS score from baseline to 24 weeks after 50% and 75% of subjects have completed the 24 week visit or discontinued the study. Futility will also be assessed at 75%, and each formal interim analysis will include a full DSMB safety review.

For assessing early efficacy, the significance level for the interim and final analysis will be based on Lan-DeMets α-spending functions with O'Brien-Fleming boundaries in order to maintain the study-wise α level at 0.05. The α level will be 0.0031 at 50%, 0.0183 at 75% and 0.0440 at the final analysis. The exact α level at the interim will be determined based on the actual percent of data available at the interim. Assuming 90% power at the end of the study, there is a 26% chance of meeting the stopping boundary at the 50% interim, and a 69% chance at the second interim. If the study actually has 80% power (for example, due to higher than expected discontinuation rate or ESS standard deviation), then there is a 54% chance of meeting the stopping boundary at the second interim. Conversely, if the study actually has power > 95% (for example if treatment group difference in ESS change is 1.2 rather than 1.0 or lower than expected standard deviation), then the chance of stopping is 41% at the first interim and 84% at the second interim.

Futility will be assessed at 75% based on conditional power of the primary efficacy variable. The DSMB may recommend study stop due to futility if the upper limit of the 80% confidence interval for conditional power does not exceed 50%.

With our planned enrollment rate, we expect approximately 6 months of randomization visits to take place after the 50% interim analysis (Table 5), and so there is a potential to decrease the overall study sample size in the event that the DSMB recommends stopping enrollment based on the interim analysis results. If enrollment proceeds as planned, then randomization will be essentially complete by the time of the 75% interim analysis. In this case, we will request the DSMB to skip the second interim analysis in order to maximize the alpha level at the end of the study. Otherwise, if enrollment is slower than expected, then the results of the second interim analysis still provide a chance to decrease the study sample size.

Protocol Timeline	Y1				Y2				Y3				Y4				Y5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Recruitment*				x	x	x	x	x	x	x	x	x	x							
Randomized after screening (1-2M)					x	x	x	x	x	x	x	x	x	x						
24W visit (end of treatment)							x	x	x	x	x	x	x	x	x	x				
28W visit (4W post-trt follow-up)								x	x	x	x	x	x	x	x	x	x			
Interim - 50% completed 24W												x								
Interim - 75% completed 24W														x						
Database lock																		x		
Analysis																	x	x	x	x
*assumes 10 patients randomized at the end of the first year, and 7 patients/year at 10 sites in subsequent years. (6 patients/site/year would add an extra 3 months to recruitment period).																				

Table 5. Timing of interim analysis relative to planned Study Milestones

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

We will evaluate treatment group comparisons for the primary outcome and key secondary outcomes in subgroups of participants defined by genetic confirmation of HHT (yes or no), gender and race (per NIH guidelines).

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

For inferential tests, the p-value for determination of statistical significance (Type I error) for the single primary efficacy outcome (change in ESS from baseline to week 24) will be evaluated relative to 0.044 to adjust for the interim efficacy analysis.

Significance of the treatment group comparison for 5 key secondary outcomes will be evaluated as follows: If the primary endpoint is found statistically significant at $p < 0.044$, then the key secondary endpoints will be evaluated for statistical significance with a Hochberg[52] modification to the Bonferroni adjustment, in which the p-values of the 5 outcomes will be ordered. The largest p-value will be compared relative to $p < 0.05$, and if met, all 5 endpoints will be considered significant. If not, then the second largest p-value will be assessed relative to $p < 0.05/2 = 0.025$, and if met then it and the other three endpoints will be considered significant, and so on for the 3rd p-value compared at $0.05/3 = 0.017$, the fourth compared to $0.05/4 = 0.012$, and the firth compared to $0.05/5 = 0.010$. Results from analyses of all other secondary endpoints and subgroup analyses will not be evaluated relative to statistical significance.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Subject-level data will be produced internally at the DCC that will allow detection of potential issues that could only be detected by examining trends across multiple visits. For example, such reports could enable rapid identification of patterns in missed visits or missed entries for patient-reported data (ESS, QOL data), medical incongruencies, or data outliers, or trends in the number of adverse events.

10.4.11 EXPLORATORY ANALYSES

Exploratory analyses include estimating the rate of relapse at the 4 week post-treatment follow-up visit, where relapse is defined as a return of the ESS to the baseline value or greater in pomalidomide-treated subjects, and estimating the median time after initiation of pomalidomide to obtain a decrease of at least 1.0 in the ESS in pomalidomide-treated compared to placebo subjects. To try to understand which demographic or biomarkers are predictive of greater response to pomalidomide we will fit generalized linear models to predict treatment response based on presence of the specific mutations in the endoglin (*ENG*) or activin-like kinase (*ACVRL1*) genes. In future studies, the biorepository specimens obtained in this study may be analyzed for the predictive value of growth factors, proteins, microRNAs, or other potential biomarkers measured in participant biospecimens.

10.5 SAMPLE SIZE

We will randomize 159 patients, 106 on pomalidomide, 53 on placebo.

Design: Since HHT is a rare disorder and our study is unlikely to be repeated, we wish to power the study at 90%. To assist in participant recruitment, we will randomize in a 2:1 ratio of pomalidomide to placebo in order to maximize active intervention for study participants and also maximize the amount of safety data for pomalidomide. Treatment group comparison for the single primary endpoint will be evaluated for statistical significance relative to alpha <0.0444, reduced from 0.05 to adjust for two planned interim analyses after 50% and 75% of patients complete the treatment period (see section 10.4.7.2).

Effect Size: The primary endpoint is ESS change from baseline to 24 weeks. We wish to power the study to identify a difference between pomalidomide and placebo of 1.0. Table 6 provides a summary of ESS scores from available HHT studies. In our small pilot study of patients with moderate to severe epistaxis treated with pomalidomide, we found an average reduction in ESS score at 24 weeks of 2.7. On the other hand, the NOSE study[53] of 121 HHT patients identified an improvement in ESS across all study participants receiving placebo or non-effective treatments of 1.5 at 12 weeks. Although we anticipate a difference of at least 1.2 between groups in our study, we have planned the sample size to detect a difference of 1.0. This value is above the estimated minimally important difference of 0.7 as determined by patient's assessment of QOL[54]. We conservatively estimate that the standard deviation for the ESS change from baseline score will be 1.7, based on standard deviations from the

recent large double-blind NOSE trial and with support from other small studies in Table 6, many of which range from 1.5 to 1.7.

Discontinuation Rate: Table 6 also summarizes early study discontinuation rates for HHT study participants, either due to drop-out (from placebo or treatments with minimal side effects), or due to AEs (from our pilot study of pomalidomide and studies of the more toxic thalidomide). Based on an average of these sources, we anticipate a 10% discontinuation rate during the 24-week treatment interval. Patients with HHT regularly see their doctors and are not expected to be lost to follow-up, and so we anticipate being able to obtain post-baseline ESS scores even for participants who stopped taking the double-blind study drug before that time. We also expect to minimize study discontinuations by allowing patients with some side effects to temporarily halt study drug and then re-start with a lower dose. Nevertheless, it is likely that some participants may discontinue the study without providing any post-baseline data, and it is possible that discontinuations due to AE may be larger than 10%. By planning for 90% power with a 10% discontinuation rate, we plan to have sufficient sample size so that the study would still be well powered if the study discontinuation rate were as high as 30%.

Author	**Treatment**	**N**	**ESS Baseline mean (SD)**	**Post-trt assessment time**	**Rate of Discontinuation, dose-limiting AEs or missing data**	**ESS Post-BL mean (SD)**	**ESS Change from baseline Mean (SD), N**	**Source of SD for change from baseline**
McCrae pilot study of Epistaxis and GI bleeding	Pomalidomide	9 (8 with epistaxis, 1 with GI bleeding)	5.9 (1.47) N=7 (1 recent enrollment not yet included)	12W	**22%** (2/9) due to rash at 2W.	3.5 (0.99) N=5	-2.5 (2.11), N=5	Calculated from data
				24W		3.3 (0.61) N=5	-2.7 (1.92), N=5	
Whitehead NOSE study (JAMA 2016) Randomized, double-blind	Bevacizumab, estriol, tranexamic acid, or placebo nasal spray (There were no differences between the 4 TRT groups)	121	5.4 (1.38) N=120	12W	**12%** (**6%** patient decision, 6% missing diary data or protocol violation)	3.7 (1.68) N=105	-1.5 (1.48), N=105 By trt grp: B: -1.6 (1.2) E: -1.4 (1.5) TA:-1.4 (1.6) Placebo: -1.7 (1.6)	Calculated from data provided by Author
				12W after TRT stop		4.1 (1.65) N=83	-1.0 (1.53), N=83 SD varied by trt grp: (1.3, 1.3, 1.7, 1.8)	
Dupuis-Girod ELLIPSE study (JAMA 2016) Randomized double-blind	Bevacizumab or placebo nasal spray	80	N/A	6 months	**8 %** (6% patient decision, 2% missing data or protocol violation)	N/A	N/A	N/A
Vivek 2018 Retrospective review	IV Bevacizumab	34	6.6 (2.2) N=30	3 months	N/A – not a study	4.4 (1.8) N=14	-2.4 (3.0), N=14	SD is higher, perhaps due to standard of care vs study ESS scores
Thompson, 2014 Non-rand.	Bevacizumab low dose infusion	6	7.2 (2.1) N=6	24W	**0%**	3.3 (1.9) N=6	-3.9 (1.7), N=6	Calculated from data in manuscript
Invernizzi, Non-rand.	Thalidomide	31	N/A	4 months	**10%** dose-limiting AEs	N/A	N/A	N/A
Fang, 2017	Thalidomide	7	5.3 (2.05) N=7	Varied 8W-18W	**30%** (2/7) due to AEs	0.9 (0.84)	-4.4 (1.55), N=7	Calculated from data

Author	Treatment	N	ESS Baseline mean (SD)	Post-trt assessment time	Rate of Discontinuation, dose-limiting AEs or missing data	ESS Post-BL mean (SD)	ESS Change from baseline Mean (SD), N	Source of SD for change from baseline
McCrae pilot study of Epistaxis and GI bleeding	Pomalidomide	9 (8 with epistaxis, 1 with GI bleeding)	5.9 (1.47) N=7 (1 recent enrollment not yet included)	12W	**22%** (2/9) due to rash at 2W.	3.5 (0.99) N=5	-2.5 (2.11), N=5	Calculated from data
				24W		3.3 (0.61) N=5	-2.7 (1.92), N=5	
Whitehead NOSE study (JAMA 2016) Randomized, double-blind	Bevacizumab, estriol, tranexamic acid, or placebo nasal spray (There were no differences between the 4 TRT groups)	121	5.4 (1.38) N=120	12W	**12%** (**6%** patient decision, 6% missing diary data or protocol violation)	3.7 (1.68) N=105	-1.5 (1.48), N=105 By trt grp: B: -1.6 (1.2) E: -1.4 (1.5) TA:-1.4 (1.6) Placebo: -1.7 (1.6)	Calculated from data provided by Author
				12W after TRT stop		4.1 (1.65) N=83	-1.0 (1.53), N=83 SD varied by trt grp: (1.3, 1.3, 1.7, 1.8)	
Dupuis-Girod ELLIPSE study (JAMA 2016) Randomized double-blind	Bevacizumab or placebo nasal spray	80	N/A	6 months	**8 %** (6% patient decision, 2% missing data or protocol violation)	N/A	N/A	N/A
Vivek 2018 Retrospective review	IV Bevacizumab	34	6.6 (2.2) N=30	3 months	N/A – not a study	4.4 (1.8) N=14	-2.4 (3.0), N=14	SD is higher, perhaps due to standard of care vs study ESS scores
Thompson, 2014 Non-rand.	Bevacizumab low dose infusion	6	7.2 (2.1) N=6	24W	**0%**	3.3 (1.9) N=6	-3.9 (1.7), N=6	Calculated from data in manuscript
Invernizzi, Non-rand.	Thalidomide	31	N/A	4 months	**10%** dose-limiting AEs	N/A	N/A	N/A
Non-rand.				3M after trt. Stop		2.0 (1.34)	-3.3 (1.35), N=7	listed in manuscript
Yin	N/A	604	5.3 (2.03)	N/A	N/A	N/A	N/A	N/A

Table 6. ESS scores and discontinuation rates from HHT studies

Analysis Method: We conservatively conduct initial sample size calculations based on a T-test with equal variances (using the Power procedure within SAS). Since the primary analysis is an MMRM model with adjustment for baseline score, we next perform sensitivity power calculations which account for expected improvement in power based on the analysis plan. Data provided from the NOSE study indicated that the correlation between baseline and change from baseline at post-baseline visits is likely to be -0.4, and correlation between post-baseline visits is likely to be 0.5. Adjustment for baseline would reduce the standard deviation of the residual from 1.7 to 1.6. To evaluate power of the MMRM model in the face of increasing percent of missing data across study visits, we compute power using the formula by Lu, Luo, and Chen[55].

Calculation and Sensitivity Analysis: A total sample size of 159 patients (106 pomalidomide, 53 placebo) will provide 90% power to identify a treatment group difference in ESS change from baseline at 24 weeks of 1.0 with $p<0.044$, assuming a standard deviation of 1.7 and 10% early discontinuation rate. Power will remain above 80% if there is a substantially higher than expected study discontinuation rate of 30% (with 10% providing no post-baseline data): 81% based on a conservative

T-test, or 90% with the planned MMRM analysis. If the standard deviation is 1.8 instead of 1.7, the power for the planned MMRM analysis would be 91% with 10% discontinuation, and 87% with 30% discontinuation. Table 7 provides calculations for sample size selection, and Table 8 provides sensitivity of the power for the selected sample size.

Pomalidomide vs placebo Mean difference in ESS change from BL at W24	Std Dev of ESS change from BL at W24	Effect size = (mean difference) /SD	Power	Planned sample size with post-baseline data	Planned study early D/C rate	**Total sample size.**
-1.0	1.9	0.526	90%	180 (120:60)	10%	**198 (132:66)**
-1.0	1.8	0.556	90%	162 (108:54)	10%	**178 (119:59)**
-1.0	1.7	0.588	90%	144 (96:48)	10%	**159 (106:53)**
-1.0	1.6	0.625	90%	129 (86:43)	10%	**141 (94:47)**
-1.2	1.7	0.706	**97%**	144 (96:48)	10%	159 (106:53)
-0.7	1.7	0.412	**62%**	144 (96:48)	10%	159 (106:53)
Note: In each row, the bolded number was calculated. All other items in the row were fixed. Calculations based on a 2-sample T-test						

Table 7. Sample size calculations for 2:1 randomization and Alpha = 0.044.

Calculation Method	Std Dev	Planned study early D/C rate	Power
T-test	1.7	10%	90%
MMRM*	1.7	10%	94%
T-test	1.7	20%	87%
MMRM*	1.7	20%	92%
T-test	1.7	30%	81%
MMRM*	1.7	30%	90%
T-test	1.8	10%	87%
MMRM*	1.8	10%	91%
T-test	1.8	20%	83%
MMRM*	1.8	20%	89%
T-test	1.8	30%	76%
MMRM*	1.8	30%	87%
Note: MMRM includes adjustment for baseline assuming a correlation of -0.4 between baseline and change from baseline, and assumes 10% have no post-baseline data, and half of the remaining drop-outs occur between the first and second post-baseline visits.			

Table 8. Power Sensitivity Analysis for N=159, Mean Difference=-1.0 and Alpha = 0.044.

With 159 patients, we will also have at least 90% power to identify a treatment group difference of 30% for a binary secondary endpoint of proportion of participants requiring at least one packed red blood cell transfusion or iron infusion at any time during the 24-week treatment period with $p < 0.05$, whether assuming a rate in the placebo and pomalidomide groups of 90% and 60%, or 50% and 20%, as demonstrated in Table 9.

Total sample size.	Planned discontinuation rate	Planned sample size (completers)	Power for selected proportions (Pomalidomide vs placebo)	
			60% vs 90%	20%vs 50%
159 (106:53)	10%	144 (96:48)	98%	96%
159 (106:53)	20%	126 (84:42)	97%	93%
159 (106:53)	30%	111 (74:37)	94%	90%

Table 9. Power for comparison of treatment groups for proportion of patients with at least one packed red blood cell transfusion or iron infusion during the treatment period for 2:1 randomization with Alpha = 0.05.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

This study is double-blind. The placebo capsule will be identical in appearance to the pomalidomide capsule. After eligibility and consent are confirmed, designated staff will randomize the patient by accessing the randomization system through the Medidata Rave electronic data collection system. The DCC will create randomization tables for each center that include randomization numbers and treatment assignments in a randomly permuted block design. Randomization will be in a 2:1 ratio and will be stratified by site. All patients and protocol staff will remain masked to study treatment, except the DCC statistician responsible for randomization and submission of reports to the DSMB.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Any intentional or unintentional unmasking will be reported as a protocol deviation in the data management system.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

In the event of an emergency, the site PI and/or study coordinator will be able to unmask a patient's treatment assignment through a report from the DCC. Such unmasking should only happen in a true emergency where knowing the treatment assignment would alter the course of treatment for the participant.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents for standard of care laboratory measures, medical history, concomitant medications, and HHT-specific interventions such as blood transfusions and iron infusions will be the

site's electronic medical record (EMR). Source documents for data collected directly from the patient including items from the ESS, quality of life instruments, and reporting of adverse events will be the place upon which this data was first recorded by the site (such as a paper version of the CRF).

12 QUALITY ASSURANCE AND QUALITY CONTROL

The quality assurance (QA) and quality control (QC) program will be based on procedures for monitoring the quality of data and procedures implemented at the clinical sites. The QC Committee will have monthly conference calls to discuss issues that arise and review QA/QC reports. The DCC will work with the QC Committee to develop and provide support for its activities.

QA activities refer to steps that are taken prior to collection of data that ensure unified data collection standards across clinical sites. These QA procedures will include the following:

- **Detailed Manual of Procedures (MOP) Development**. The MOP contains detailed instructions on study procedures, such as recruitment and screening, training, certification, data collection, quality control procedures, and specimen collection and transfer. The MOP serves as a reference guide for study staff, including investigators, coordinators, technicians, and data managers and clearly describes the functions of the DCC and CCC. To ensure quality and compliance with GCP guidelines, all documents created by the DCC (e.g., data collection forms, MOP, and analysis plan) will be reviewed and approved following procedures consistent with RTI's SOPs and ITP guidelines developed in collaboration with NHLBI and network investigators. Final version controlled study documents will reside in the private portion of the ITP website.
- **Training**. The DCC will lead the training of site investigators, clinical coordinators, and data capture and reporting system users in collaboration with the CCC and NHLBI. Before study initiation and prior to randomizing any patients, each staff member must review the randomization instructions and confirm that they understand the procedures via the private portion of the ITP website. The DCC will use short quizzes at the end of training sessions to ensure participants understand the information covered during the training session and targeted training is provided for missed items. If face-to-face training of lead investigators is necessary (i.e., a train-the-trainer approach resulting from a need identified through DCC or CCC committees), then this will be conducted in conjunction with national meetings (e.g., American Society of Hematology). For training in use of the data capture and reporting system, each staff member will complete an e-learning module provided by Medidata and attend a live online demonstration of the system by RTI staff and practice session afterward. We use chat rooms to allow rapid responses to questions throughout the practice period.
- **Certification**. The DCC certifications will focus on ensuring that the site staff are knowledgeable about the protocol and procedures and can demonstrate proficiency in use of the data capture and reporting system prior to study initiation.
- **Trial Operations**. The Steering Committee will provide a regular forum for discussing and resolving issues, activities and processes related to trial operations, whether they are system-

wide or site-specific. The Steering Committee will play a central role in ensuring procedures are followed and communicating new and revised procedures to the clinical sites.

QC activities refer to steps that are taken during data collection to ensure unified data collection standards across clinical sites. The QC Committee will be responsible for overseeing the development of QA/QC reports. The QC Committee will have membership from the DCC and CCC and will hold monthly conference calls to discuss issues that arise and review QA/QC reports. These QC procedures will include the following:

- **Monitoring of Data Quality and Implementing Corrective Action**. The DCC will conduct site monitoring throughout the life of the study, at both the level of the individual data item and form and at a more global level, to ensure high-quality data. We focus on high-risk areas such as safety and efficacy data, and human subjects issues. Other trial-specific monitoring includes adherence to study eligibility criteria and protocol violations. Recent research suggests that a vast majority of issues can be identified and resolved cost-efficiently through central monitoring. Using the reporting capabilities of Medidata Rave, the DCC will produce reports that may signal poor data quality and has reduced the need for repeated costly site visits. These reports evaluate performance against SC-established metrics and contain detailed information on screening, recruitment, retention, staff training/certification, protocol violations, study implementation, data receipt, delinquent data, data quality, and edit failures. We identify errors, missing forms, or missing items and produce reports so that the site staff can investigate the issue. These routine reports enable us to evaluate general site performance and to quickly initiate corrective actions when needed.
- **Site Visits**. Onsite monitoring through site visits helps identify data entry errors (e.g., discrepancies between source records and electronic case report forms and missing data in source records or electronic case report forms; provide assurance that study documentation exists; assess the familiarity of center staff with the protocol and required procedures; and assess compliance with the protocol). The DCC and CCC will conduct site visits to clinical sites as needed or at the request of NHLBI. CCC focus is to ensure that treatment procedures and follow-up assessments are following the specifications in the protocol and MOP. The DCC focus is to ensure data quality and to ensure uniform data collection, management, and reporting procedures across the sites, using established checklists and report templates. DCC will focus on facilities review to ensure that sites have the needed resources and reviewing research records and regulatory documents. Data capture and reporting system reports, such as those mentioned previously, are used to guide discussions with study staff. Following the site visit, the DCC and CCC will provide a unified written report to the site and NHLBI.
- **Creation of Statistical Products**. The DCC will adhere to written Standard Operating Procedures (SOPs) that cover such topics as the purpose and content of analysis plans; the steps required when producing sample size estimates, analyses, derived data sets, tables and graphs, and macros; or the process for developing and implementing an allocation or randomization scheme for clinical studies. Each SOP emphasizes a 3-step process for creating statistical products: specification (analysis details are specified in an analysis plan), creation

(all programs must use good programming standards to ensure well-documented code), and validation (e.g., review of data listings and tables of summary statistics, independent code review, independent programming). The analysis plans for each statistical product must specify validation requirements, and all analysis plans will be reviewed by the DCC PI.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

This study will adhere to the seven main principles used to guide the conduct of ethical research, as outlined by the NIH clinical center. The study has been and will continue to be analyzed and reviewed for adherence to each of these principles by the PI, study monitor, DSMB, DCC, and all participating physicians.

- Social and clinical value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

13.2 INSTITUTIONAL REVIEW BOARD

This study will use a single IRB (Cleveland Clinic) as dictated by Notice Number: NOT-OD-16-094, effective May 25, 2017, applying to all NIH-funded multicenter clinical trials.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

All potential study subjects will be approached by a physician (site PI or CoI), research nurse or any assigned site personnel who will review the full consent form with the potential study subject. This consent form will include a full discussion of the potential benefits as well as risks of pomalidomide therapy, a description of all study procedures and implemented methods to protect patient confidentiality. Study subject will be given opportunity to ask questions and all questions will be answered by the site study personnel. When study subject expresses their desire to participate in the study, the informed consent will be signed by both the study subject and site study personnel obtaining consent. Assent will not be used since this study will only enroll adult patients. Informed consent document may be translated to a non-English speaking language upon request and will have to be approved by the IRB. If a translated consent is used, the translated version will be signed by the

participant and the English version will be signed by both the person obtaining consent and the interpreter.

Consent is typically obtained on the day of screening visit in a face-to-face setting. In case of a remote screening visit, the consenting process may be conducted over telephone or any approved virtual platform. The consenting process should be completed (i.e., signed by both research subject and person obtaining consent) before the screening visit, with no more than 10 days between consent and the screening visit.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent procedures are described in 13.3.1. The signed consent form will be collected by the research coordinator at each site and stored in a locked cabinet.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

The confidentiality of all study subjects will be strictly maintained. Electronic data will be entered using a highly secure, password protected system (iMedidata). All study personnel will undergo training in patient confidentiality procedures at the study initiation meeting. No patient files will be shared by email.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Biorepository samples will be sent to the laboratory of the lead study PI, where they will be stored in a locked -80° freezer. Samples will be used to answer study-specific questions, specifically the identification of biomarkers that predict responses to pomalidomide. Refer to MOP for details.

13.5 FUTURE USE OF STORED SPECIMENS

Requests from investigators who may have participated or not participated in the study will be entertained after study-specific testing has been completed on the collected samples. These will be considered on a case-by-case basis by the Steering Committee.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Medidata Rave is the primary data collection system for the study. Rave is a commercial, web-based data collection system that enables streamlined study design and setup with integrated real-time reporting and analysis tools. This enables continuous data monitoring and analysis.

Because Medidata Rave is web-based and supports direct data entry, the status of data collection can be assessed in real time. In addition, Rave supports the integration of data and metadata with systems

for randomization and capitation, and can also accommodate sophisticated within- and between-form edit checks to ensure the accuracy of data. Real-time reports are available through the web interface to monitor open data queries. The DCC's data management staff and the staff at the sites can use these reports to identify and resolve data issues in real time. A complete audit trail of data entered and any subsequent changes to the data is available on demand. Both data management staff and site staff will be able to routinely monitor data for these issues and resolve them directly in the system. Study documentation, including data dictionaries, can be automatically generated from the data management system and data can be exported at any time in a variety of standard formats (e.g., SAS data sets).

Web Portal. A well-designed, easy-to-use, comprehensive project website is essential to the success of the study. The project website is the central hub to allow easy collaboration and communication among study investigators, clinical sites, and other study members. Role-based access (e.g., core member, study coordinator, calendar administrator, and access administrator) will be tightly controlled by requiring users to log in using credentials supplied by the DCC, with different users having access to different portions of the website, depending on their role on the project. The website will include project materials (protocols, manuals, forms), a project calendar, the EDC system, and graphical dashboards to track study progress and milestones. Site staff will be allowed to access reports for their own site, but will not be allowed to see reports or data from another site. The DCC will comply with all aspects of Americans with Disabilities Act and Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements when designing our websites, and we test websites with established tools to ensure that we meet those requirements.

Reporting (Study Monitoring). A centralized, integrated data management system provides the information needed to assess overall progress of the study and site performance through real-time data on enrollment, follow-up, data quality (completion of all data collection, outstanding queries, overdue or missing data and visits). Subject-level reports will also be available to allow detection of potential issues that could only be detected by examining trends across multiple visits. Because of the real-time nature of the data collection system, all communication regarding data issues can occur through the integrated data querying system. In this way, data can be corrected quickly and efficiently, and, as with initial data entry, a complete audit of changes is maintained.

14.2 STUDY RECORDS RETENTION

See section 14.4, Data Sharing.

14.3 PROTOCOL DEVIATIONS

Protocol deviations will be reported to the single IRB of record and will be recorded in the Medidata web-based data management system.

14.4 PUBLICATION AND DATA SHARING POLICY

The DCC will work with the Steering Committee (SC) and the funding agency to develop acceptable plans for resource sharing (including protocols, manuals, training materials, and study data with researchers and other members of the public), while maintaining acceptable levels of patient confidentiality. Upon approval from the NHLBI and the SC, we have shared study materials (e.g., protocols, manuals, training materials, CRFs that are not copyrighted by other organizations) through secure means (e.g., FTP server, encrypted and password protected DVD or email). In some cases, these materials have been openly available to the public. In other cases, the SC has limited release of some of these materials, and RTI staff have developed procedures to implement the limitations set by agreement of the SC. We will work with NHLBI, and the SC to develop plans for release of study materials.

The data collected through the DCC are expected to provide a wealth of information regarding treatment for HHT with the potential for translating these findings to practice. The DCC will be responsible for working with NHLBI, the SC, and the clinical centers to develop a plan and schedule for distributing this valuable resource to both internal and external researchers. The plan for sharing the data demands a carefully developed strategy that is cognizant of the importance of protecting participants' rights to individual privacy and is compliant with HIPAA regulations and other compliance requirements.

The DCC will prepare de-identified data files for sharing. Shared data may be aggregated at the individual study center level. Data may be shared with investigators, their institutions and with outside investigators. Each level of aggregating and sharing data carries its own level of disclosure risk. Wherever appropriate, we will work with NHLBI, the SC, and the clinical centers to develop a data sharing plan that will strike a balance between the protection of participants' rights and the desire for scientific collaboration. The plan will address the following issues: the expected disclosure risk level for each type of data sharing, which data types can be shared, the types of people (within the study or outside the study) who can access data at various levels, the form of participant informed consent required for each level of data sharing, and procedures for review and approval of data access request applications.

The DCC will take great care to ensure that participant confidentiality is maintained in all shared data. Several options to protect privacy of the data include releasing only part of the data, altering the data in ways that will not compromise analyses, requiring outside researchers to adhere to strict confidentiality requirements, or providing access to the data through a controlled data enclave. At a minimum, the DCC will create data sets that have undergone de-identification processes that ensure the data satisfy all HIPAA and any related international requirements for protecting participant identity by producing de-identified data that conform to both HIPAA requirements and NIH policy on data sharing. The DCC will follow procedures developed in our other data coordinating projects, to release restricted or public-use data sets. Examples of these procedures include:

- replacing the unique participant identification variable in the original data sets with a new unique participant identifier produced by a random number generator;

- removing any personal information from the data set (much of this type of data is not included in the data submitted to the DCC by the clinical sites);
- removing or recoding other distinguishing parameters, such as dates, research sites identification numbers, and hospitals where surgery was performed (e.g., dates can be recoded relative to a participant-specific reference point, and specific locations can be replaced by more general geographic codes). Interviewer or technician identifiers will be deleted or recoded;
- removing verbatim responses and especially sensitive variables, such as information on sensitive medical conditions or sexual activity; and
- combining subgroups with low frequencies or truncating distributions to ensure that there are a minimum number of participants for each category or value within each gender/ethnicity cell.

Data Sharing With Trial Investigators. The first level of data sharing will be with trial investigators once data from the trial have been cleaned and closed, and preliminary analyses indicate that the data are ready to be shared among trial investigators. Appropriate documentation will be provided including labeled versions of CRFs, raw data sets, edited analysis data sets, format files for variables, and data dictionaries. The data can be provided in SAS data sets and export files and documentation will be in PDF format. These files can be developed on a periodic basis determined by the SC, for instance, 6 months after closed data sets for the trial have been prepared for final analysis or 1 month after results of the protocol are published in a peer-reviewed journal. The purpose of granting limited access is for researchers to develop appropriate analysis approaches and identify preliminary indications of findings.

Data Sharing With the Broader Research Community. In addition, the DCC will be responsible for sharing study data with outside researchers, if approved by NHLBI and the SC. De-identified limited-access data sets will be created for this purpose. Although the data sets will be stripped of identifiers and otherwise modified to prevent easy identification of patients in the study, the narrow focus of the population to be analyzed and the possible rarity of some outcome measures and risk factors might make it possible for an identification to be made. To protect the confidentiality and privacy of the participants, investigators granted access to these data must adhere to strict requirements. The SC will define these requirements and establish criteria for access to data by outside researchers. This information will be incorporated into a standard Data Distribution Agreement to which investigators must adhere. The agreement will be subject to review by legal and IRB departments of RTI and the clinical sites, and approved by the SC. In accordance with NHLBI policies, outside researchers will be required to submit an approval from their IRB.

If directed by the NIH, instructions for obtaining access to the trial data and eligibility criteria can be publicized and provided through the study website. We can develop a request form to collect information deemed necessary by the SC and NIH, including applicant name, organization, and purpose of research. Investigators will submit the request form, Data Distribution Agreement, and IRB approval to designated DCC staff. The SC or its designated Committee will review each application,

and if the requestor meets established criteria for access to the data and provides the required documents, the requested data sets and associated documentation will be disseminated by a mode agreed upon by the SC in accordance with NHLBI policy. The data can be provided in SAS data sets and export files and documentation will be in PDF format. At the close of study funding, RTI staff will work with NHLBI and the SC to develop plans for providing continued access to the data. De-identified data files will be prepared by the DCC in accordance with NHLBI's Limited Access Data Policy and Health Insurance Portability and Accountability Act (HIPAA) privacy standards and made available for use by investigators not associated with the trial, within three years after study completion. The DCC will emphasize a clear and searchable documentation of the limited access database, including transparent vocabularies and metadata, and its linkage to the pertinent study protocols and forms so that researchers of diverse backgrounds can make effective use of this resource. Inclusion of standardized derived variables will minimize the need for elaborate data manipulation and facilitate standardization of definitions and other technical details across manuscripts.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

In addition to the clinical centers, the trial is implemented through a Clinical Coordinating Center (CCC) at Cleveland Clinic; a Data Coordinating Center (DCC) located in Research Triangle Park, NC at RTI International; and various collaborators providing specific expertise as described below and depicted in Figure 4.

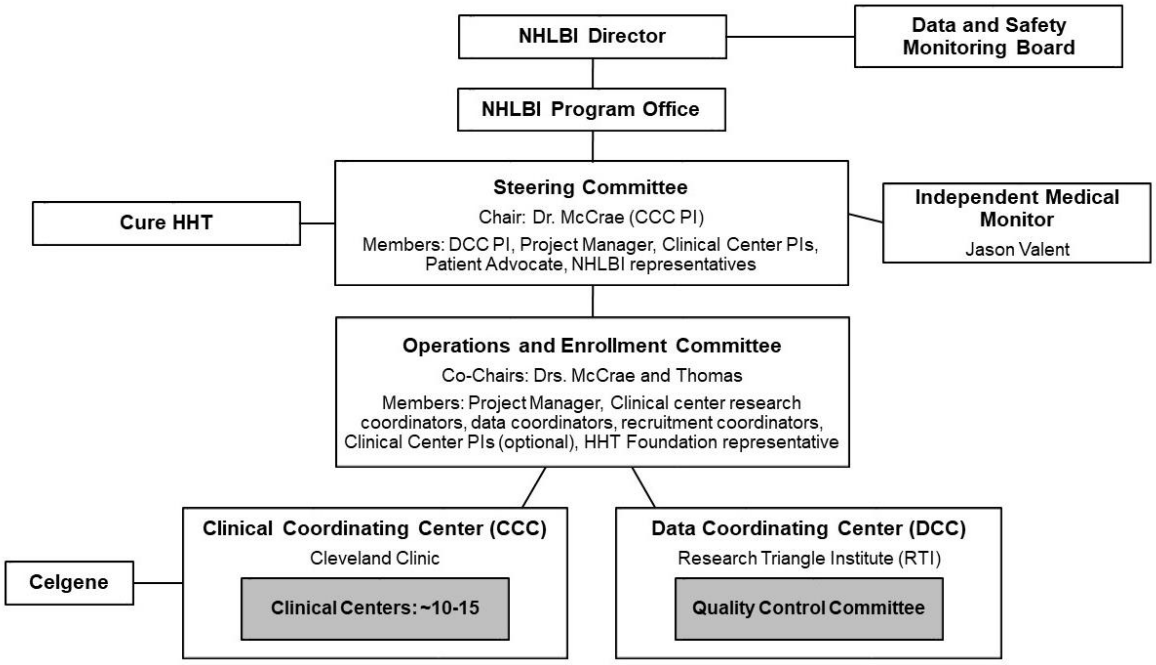

Figure 4. Organizational Structure of the Pomalidomide for the Treatment of Bleeding in Hereditary Hemorrhagic Telangiectasia Study

The National Heart, Lung, and Blood Institute (NHLBI) will serve as study sponsor. The Steering Committee will consist of NHLBI representatives, and a subset of site investigators who provided input to the design of the study as part of the NHLBI U34 Planning Grant. This leadership team will be responsible for all major scientific and operational decisions. Other trial committees will report to the Steering Committee at regular monthly meetings held by teleconference (or in person if necessary).

Cure HHT, directed by Ms. Marianne Clancy, is a critical component of the overall structure of this trial. The HTTFI maintains a database of more than 10,000 HHT patients, many of whom are not followed at HHT Centers of Excellence and thus do not overlap with the rosters maintained by sites participating in this study. Cure HHT will serve as the primary marketing and information distribution tool for this study, and will work closely with the PI to develop materials for dissemination to patients with HHT, and to physicians who treat HHT patients.

The ***Data Safety Monitoring Board*** (DSMB) will consist of approximately seven members and be directly appointed by NHLBI following recommendations of qualified individuals by the PI. Individuals on the DSMB will be familiar with the conduct of clinical trials, and have expertise in the management of HHT. The role of the DSMB will be as follows:

- To meet biannually by teleconference with the CCC and DCC PIs who will update trial progress.
- As a component of this teleconference, the DSMB will hold a closed-door discussion of progress, with specific focus on all AEs, as well as any SAEs that may have occurred.
- Following review and discussion of this data, the DSMB will determine whether any potential safety issues exist that would preclude the trial from continuing, or that need to be addressed.
- The DSMB will provide their recommendations (including continuation/discontinuation of the trial) to the NHLBI Director.
- The DCC will be responsible for documenting the proceedings of the DSMB meetings, and obtaining the signature of the designated DSMB chair.

Dr. Jason Valent will serve as the ***Independent Medical Monitor*** (IMM) for this study. His role will be as follows:

- To review all AEs that occur during the trial. In particular, he will review all SAEs within 24 hours of their occurrence.
- To prepare regular reports concerning SAEs and submit to the CCC PI, and subsequently to the DSMB and, as appropriate, to FDA as required by the IND.
- Like the DSMB, decisions of the IMM will be made independently of the PI, and he will have the authority to recommend that the trial be placed on hold if he observes an SAE that s/he considers trial-related that is of sufficient severity to threaten patient safety.
- The IMM may participate in DSMB reviews if he wishes, though this will not be compulsory, and in some cases he may wish to seek consultation from the DSMB.
- In situations in which the trial is put on hold or terminated, the IMM will communicate this directly to the PI and DCC, as well as to NHLBI.

- If the IMM is unavailable for an extended period of time (i.e., extended vacation, sabbatical, illness) a backup IMM will be nominated by the CCC PI and approved by the NHLBI Program Official.

The ***Quality Control (QC) Committee*** will include experts from the DCC and CCC. Involvement of clinical center PIs is optional. The roles of the QC committee will be as follows:

- Establish and oversee the development, implementation and monitoring of the essential trial quality control processes, including both informatics QC and clinical site QC.
- Review regular QC reports and work with the Steering Committee and Operations and Recruitment Committee to assure trial quality.
- Provide reports on overall trial quality to the Steering Committee on a semiannual basis.
- Provide reports on overall trial quality to the PIs for inclusion in annual NIH progress reports.

16 CONFLICT OF INTEREST POLICY

All investigators will be expected to comply with institution-specific conflict of interest procedures that could potentially impact this trial. When these occur, they may most commonly be addressed by full disclosure. If this is felt to be insufficient, then the investigator will be replaced.

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APPENDIX 1

HHT-SPECIFIC QOL QUESTIONNAIRE

1. How often in the past 4 weeks has an activity for your work, school, or regularly scheduled commitments been ***interrupted by a nose bleed***?

0=Never

1=Rarely

2=Sometimes

3=Often

4=Always

2. How often in the past 4 weeks has an activity with your partner, family, or friends been ***interrupted by a nose bleed?***

0=Never

1=Rarely

2=Sometimes

3=Often

4=Always

3. How often in the past 4 weeks have you ***avoided social activities*** because you were ***worried about having a nose bleed***?

0=Never

1=Rarely

2=Sometimes

3=Often

4=Always

4. How often in the past 4 weeks have you ***had to miss*** your work, school, or regularly scheduled commitments because of ***HHT-related problems other than nosebleeds?***

0=Never

1=Rarely

2=Sometimes

3=Often

4=Always

Scoring:

A total score is calculated by summing the items (each scored from 0-4). The total score ranges from 0 (no limitations) to 16 (severe limitations). If any items are not answered, the total score will not be calculated.