PATH

Pomalidomide for the Treatment of Bleeding in HHT

POMALIDOMIDE FOR THE TREATMENT OF BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

NCT03910244

Protocol 133646-2

Part 1 Master Consent

Version 2.9, October 25, 2022

Consent to Participate in a Research Study

PART 1: Master Consent

Study Title:	**PATH-HHT:** Pomalidomide for the Treatment of Bleeding in Hereditary Hemorrhagic Telangiectasia (HHT)
IND Sponsor and Grant Holder:	Keith McCrae, MD
Funding Source:	National Heart, Lung, and Blood Institute

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

A research study is designed to answer specific questions about new ways to prevent, detect, and treat disease. Being in a research study is different from being a patient. The purpose of this document is to provide a written summary of the discussion and exchange of research information you had with the research team. It is also for use as a reference during the study.

KEY INFORMATION

The following is a short summary of this research study to help you decide whether or not to be a part of this research study. More detailed information is included later on in this document.

What should I know about a research study?

- Someone will explain this research study to you.
- You can choose whether or not to take part.
- You can agree to take part and then later change your mind.
- Your decision whether or not to participate will not be held against you.
- You can ask all the questions you want before you decide.

What is the purpose, procedures and duration of this study?

We invite you to take part in a research study because you have been diagnosed with hereditary hemorrhagic telangiectasia (HHT). The purpose of this study is to learn whether pomalidomide is effective as a treatment for HHT.

After ensuring that you are eligible to participate in the study, you will be asked to complete 6 cycles of pomalidomide treatment. At each of the 6 visits, the severity of your nosebleed will be calculated,

blood samples will be collected and at several of the visits you will be asked to complete a questionnaire about how you feel.

Your participation in the study will last approximately 8 months, though you will be on active treatment for only 6 months.

Some of the research visits may be conducted remotely, to accommodate for the ongoing COVID-19 pandemic. This means that the study visit may be completed using virtual software applications (such as facetime, zoom, etc.) or a telephone call. More detailed information can be found under the section labeled: 'Information on the Research'.

Why might you choose not to participate in this research study?

Pomalidomide has been reported in some individuals to cause muscle cramps, constipation, and a decrease in red blood cell, white blood cell and platelet counts. Additionally, the effect of pomalidomide on a fetus is unknown and therefore safety precautions to avoid pregnancy would be required.

More detailed information can be found under the section labeled: 'Risks'.

Why might you choose to volunteer for this study?

In a pilot study, pomalidomide was shown to significantly decrease epistaxis and bleeding in patients with HHT. Personally, you may or may not receive direct benefit from being in this study. However, your participation in this study will help to obtain new information about developing effective therapy for HHT.

More detailed information can be found under the section labeled: 'Benefits'.

What are my other choices if I do not take part in this study?

- The alternative to being in this study is to not take part.

More detailed information can be found under the section labeled: 'Alternatives'.

DETAILED INFORMATION

1. INFORMATION ON THE RESEARCH

Why is the research study being done?

You are being asked to take part in this research study because you have hereditary hemorrhagic telangiectasia (HHT) with nosebleeds (epistaxis) and have anemia or require periodic infusions of iron or blood transfusion. The purpose of this study is to learn whether pomalidomide is safe and effective as a treatment for HHT. Approximately 159 patients from about 15 sites (all in United States) will participate in this study.

Pomalidomide is currently approved by the FDA for the treatment of refractory and relapsed multiple myeloma, a disease caused by a type of cell in the bone marrow called plasma cells, which have become cancerous. It is not currently approved for treatment of HHT, though a small pilot study has demonstrated that it has been helpful in reducing the frequency and severity of nosebleeds in HHT patients. The use of pomalidomide in this study is investigational.

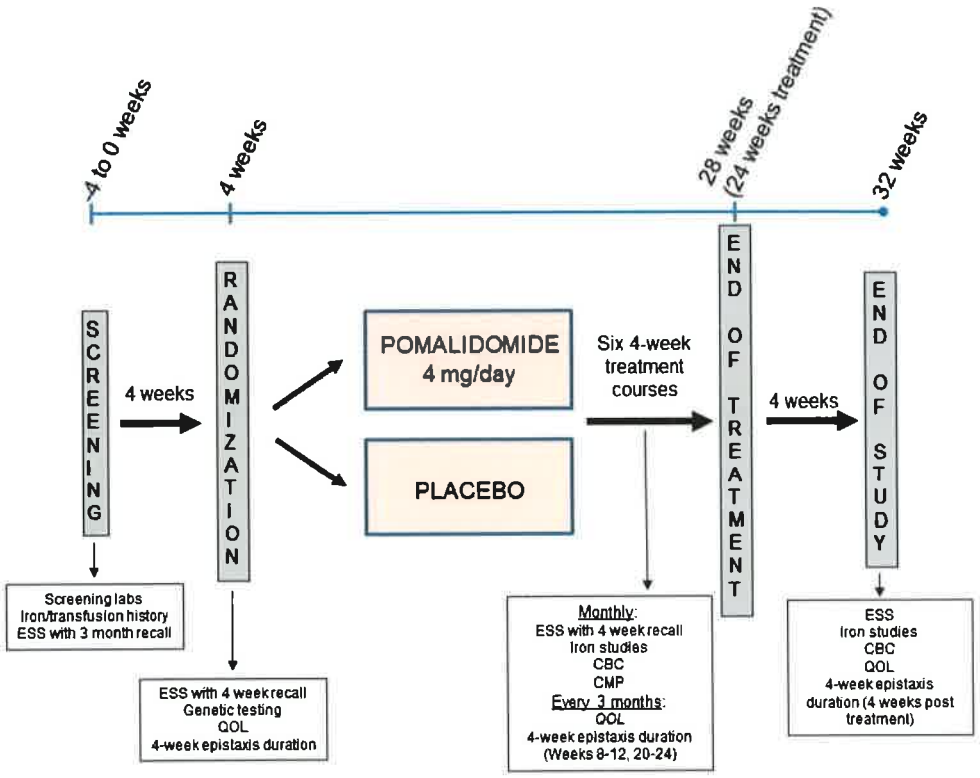

Figure 1: Study Design Schematic. After joining the study, you will be screened for your medical and HHT history, undergo laboratory (iron studies, complete blood count, and complete metabolic panel) testing, and have severity of your nosebleed calculated using the Epistaxis Severity Score (ESS) with 3-month recall (i.e. over the previous three months). If you are found to be eligible, you will be randomized 2:1 to pomalidomide or an identical-appearing placebo. In addition, you will undergo genetic testing for mutations in HHT-related genes to determine whether patients with specific mutations respond better to pomalidomide (genetic testing is optional, and declining to undergo this will not disqualify you from the study), complete quality of life (QOL) surveys, and ESS with 28 day recall. You will come for your study visits once every 4 weeks for 24 weeks, which is six 4-week cycles of therapy. Study drug will be stopped after the 24 week end-of-treatment visit. You will be seen once more 4 weeks after stopping study drug to find out if you continue to show response 4 weeks after stopping study drug. You will also record the duration of each nosebleed event during the 4-week periods between screening and baseline before starting study drug, weeks 8-12 and weeks 20-24 after starting study drug, and 4 weeks after study drug is stopped.

What is involved if you decide to take part in this research study?

If you take part in this study, you will be asked to come to the doctor's office or clinic for your visits. The total time in this study will be for a maximum of 8-9 months, and you will be treated with either pomalidomide or placebo for 6 of those months. A placebo is a pill that looks exactly like pomalidomide but does not contain any active ingredients. You will not know whether you are taking pomalidomide or placebo. However, the study is designed with a 2:1 randomization, meaning that two of every three patients will receive pomalidomide; i.e., you have a 66.6% chance of being randomized to receive pomalidomide. After completing therapy, you will be followed for another 4 weeks to see if your response, if present, continues after study drug is stopped. An outline of the study is shown in Figure 1.

Screening (SC)

If you agree to take part in this study, after you sign this document, you will be asked to begin the screening process to find out if you meet all study entry criteria. If appropriate, the screening visit may be conducted remotely. At the screening visit, all information related to your medical history and current health status will be collected. Please let your study doctor know all of your present and past health history, as well as allergies and any medication you are taking, including over-the-counter medications, vitamins, herbal, homeopathic or holistic. This is important because a possible interaction of pomalidomide with some medications, vitamins, and remedies may still be unknown.

The procedures below will be performed at the screening visit:

- A detailed physical exam
- Medical and disease history
- Review of current medications
- An epistaxis severity score (ESS), which will measure the severity of your nosebleeds over the previous three months.
- Blood counts and tests (complete blood count, blood clotting tests, iron studies, serum chemistries including tests of liver and kidney function)
- Pregnancy test for females of child bearing potential in accordance with the REMS schedule
- Blood sample for storage in a biorepository (blood samples will be used to identify blood markers that predict response to pomalidomide and provide new information about the mechanisms by which HHT causes bleeding)
- Determine need for intravenous iron therapy based on results of iron studies.
- Provide you with instructions for recording duration of nosebleeds (epistaxis duration) between screening and the next baseline/randomization visit.

It is recommended that you use an app on your smartphone to record information on your nosebleed events. This app will securely transfer the information you record directly to the site that coordinates the data for this study. The study team will help you with set-up and can answer any other questions or concern regarding use of the phone app. If you are unable to use the phone app, you will be provided with a paper diary to record your nosebleed events.

Randomization (BL)

The randomization visit will be conducted between 28 and 56 days (approximately) after your screening visit. You will be scheduled for a randomization visit only if you meet all the study entry criteria. The randomization will be 2:1, meaning that you will have two chances out of three to receive the active drug. Neither you, your doctor, nor any of the study personnel will know, or be able to tell whether you are receiving pomalidomide or placebo until the end of the study. If you were to develop a serious side effect during the study, and if your study doctor thinks it is necessary, we will find out whether you were taking pomalidomide or placebo. We will then determine if your side effects could be related to pomalidomide and thereby provide more specific treatment.

At this randomization visit, the following procedures will be performed:

- A physical exam
- Review of current medications and other medical events that may have occurred after the screening visit
- Blood counts and tests (complete blood count, complete metabolic panel, iron studies)
- Pregnancy test for females of child bearing potential in accordance with the REMS schedule
- Blood sample (optional) for storage in a biorepository
- Genetic testing to determine whether you have one of the known genetic mutations associated with HHT. If you have already had genetic testing performed as part of routine clinical care, we will not repeat this testing. If you have previously undergone genetic testing for HHT and are known to have a mutation in SMAD4 gene, you will not be eligible for the study unless you have had a colonoscopy with normal (negative) results or no more than 5 small colonic polyps completely removed within the preceding 18 months. However, if you are enrolled in the study prior to the completion of genetic testing and are later found to have a SMAD4 mutation, you will be allowed to continue in the study.
- Collection of epistaxis duration diary that records duration of each nosebleed event over the previous 28 days
- ESS score with a 28-day recall period.
- Quality of life (QOL) questionnaire, which asks questions about your activities and social/emotional impact due to the severity of your nosebleeds
- Study drug dispensation

Because pomalidomide is regulated by Celgene's POMALYST-REMS (risk evaluation and mitigation strategies) program, it is important that female study subjects of child bearing potential have two negative pregnancy tests before drug initiation. The first pregnancy test would be 10-14 days before study drug order and the second pregnancy test would be within 24 hours before study drug order. Pregnancy testing must occur weekly during the first four weeks of use. For subsequent treatment cycles pregnancy testing will occur once every 4 weeks if menses are regular and once every 2 weeks if menses are irregular.

You will only receive one bottle of study drug that has enough supply for only one cycle of treatment, which is 28 days (4 weeks). You will take your assigned treatment (pomalidomide/placebo) at a dose of 4 mg/day (one capsule), every day with water on an empty stomach. Study drug capsules should be swallowed whole, and should not be broken, chewed or opened. You should not eat food for at least 2 hours before or after you take study drug. If you miss a dose of study drug, it should be taken as

soon as possible on the same day. If you missed it for the entire day, it should not be made up the next day. If you take more than the prescribed dose of study drug, please seek emergency medical care if needed, and contact study staff immediately.

If you have any side effects, you should immediately inform your study doctor. Your doctor will evaluate your symptoms and decide whether it would be appropriate to continue with study drug, reduce your daily dose, or discontinue study drug. You should not make these decisions by yourself, as it may not be safe for you to change dosage or stop study drug without consulting with your study doctor.

You should never share your medication with another person. You need to return all unused medication to your study doctor at the end of treatment or if you discontinue study medication before the study ends.

Treatment Visits (C1-C6)

The treatment study visits will occur every 4 weeks, at the end of each cycle. There will be a total of 6 treatment cycles, starting from the baseline visit. Study drug for the next cycle of treatment will be given during your monthly study visits. For every treatment cycle, female subjects of child bearing potential must have a negative pregnancy test to receive study drug.

For scheduling convenience, you have a window of up to 5 days after your last study drug dose to schedule your next visit and get study drug for the next treatment cycle. It is acceptable to have a gap (where you do not take study drug) of up to 5 days in between your treatment cycles. This will not affect your treatment response. If appropriate, study visits at the end of treatment cycles 1, 2, 3, 4 and 5 may be conducted remotely. The visit at the end of treatment cycle 6 must be in-person. At each of the treatment visits (C1-C6), you will be asked to bring the bottles (even if they are empty) so that your study nurse/coordinator can count the pills and record your drug intake. In case of remote visits, you will be instructed to bring the bottles at the next in-person visit. Alternatively, your study nurse/coordinator may request you to ship the empty bottle/bottle with remaining study drug to the study site.

The following procedures will be performed at each treatment visit:

- Limited physical exam (Detailed physical exam at end of cycles 3 and 6)
- Review of current medications and other medical events that may have occurred since the previous study visit
- Blood counts and tests
- Pregnancy test for females of child bearing potential in accordance with the REMS schedule
- ESS score with 28-day recall
- Blood sample (optional) for storage in a biorepository (end of cycles 3 and 6 only)
- Quality of life questionnaire (end of cycles 3 and 6 only)
- Collection of epistaxis duration diary (end of cycles 3 and 6 only)
- Study drug return and dispensation (no more study drug will be given at the end of cycle 6 visit, which marks completion of all 6 treatment cycles)

End of Study Visit (EOS)

The last study visit will be 4 weeks after completing the 6th treatment cycle visit (C6) and this may also be completed remotely. The main reason for this visit is to monitor your nosebleeds and determine whether the effects of pomalidomide on your nosebleeds continues even after the drug is stopped. The following procedures will be performed:

- A detailed physical exam
- Review of current medications and other medical events that may have occurred since the last study visit
- Blood counts and tests
- Blood sample (optional) for storage in a biorepository
- ESS score with a 4-week recall
- Quality of life questionnaires
- Collection of epistaxis duration diary

Study Drug Discontinuation and Early Termination Visit (ET)

If there are any safety concerns your study doctor may ask you to temporarily stop study medication; when it is found to be safe you may be asked to restart study drug. You will continue with study visits on the same schedule even when you are not taking study medication.

If you have been asked to permanently stop taking study drug for safety reasons or if you choose to stop due to personal reasons, you will be asked to complete the study visit associated with your current treatment cycle and come in for one last study visit (EOS visit as described above) 4 weeks later.

If you choose to withdraw consent from study participation prior to completion, study drug will be stopped and you will be asked to come in for an early termination visit and return all unused study drug at this visit. In addition, the following procedures will be performed:

- A detailed physical exam
- Review of current medications and other medical events that may have occurred
- Blood counts and tests
- Pregnancy test for females of child bearing potential if study medication was taken after the last pregnancy test that was performed
- Blood sample (optional) for storage in a biorepository
- ESS score with 28-day recall
- Quality of life questionnaires
- Collection of epistaxis duration diary if dispensed for the previous visit

Restricted Medications

While you are participating in this research study, you will not be able to take certain medications, such as:

- Octreotide (Sandostatin)

- Bevacizumab (Avastin) or within six weeks prior to starting the study
- Pazopanib (Votrient) or within six weeks prior to starting the study
- You may not initiate treatment with epsilon aminocaproic acid (Amicar) or tranexamic acid (cyclokapron) during the study. However, if you were taking one of these drugs at the time of screening you may continue to take it at the same dose during the study but may not change the dose during pomalidomide treatment.
- You may not initiate treatment with nasal sprays of epsilon aminocaproic acid (Amicar), tranexamic acid (cyclokapron) or timolol (blocadren) or propanolol (Inderal). However, if you were taking either of these drugs at the time of screening you may continue to take the drug during the study but may not change the dose during pomalidomide treatment.
- Erythropoetic agents may increase the risk of blood clots and should be avoided.
- Certain drugs such as ciprofloxacin may increase pomalidomide levels and should be avoided. Fluvoxamine, and fluvoxamine with ketoconazole taken together with pomalidomide may increase levels of pomalidomide and should be avoided.
- Certain drugs such as carbamazepine may cause your body to break down pomalidomide more quickly and thus reduce its therapeutic effect and should not be taken during this study.
- Oral contraceptives which contain combination of estrogens and/or progestins may affect the activity of HHT and also increase thrombotic risk and should be avoided. A Mirena IUD has minimal thrombotic risk and is acceptable.
- Nasal estriol is allowed if you were using this agent before starting the study and do not change the dose during the study. You may not initiate treatment with nasal estriol during the study.

Your doctor and research nurse will review all your medications with you before you start the study. Please ask your nurse or doctor if you are concerned about any medication you are currently taking before you start the study.

Genetic Testing

Blood or saliva samples to test whether there are alterations in the HHT-related genes are requested. This would be a one-time sample collection at the Randomization (BL) visit. It is not mandatory to undergo genetic testing to participate in this study although the results of this testing may assist in predicting which patients will respond to pomalidomide in the future.

If you have had prior genetic testing for the three well-established HHT genes (ENG, ACVRL1 and SMAD4) and if those results would be made available for this study, we will not need any further samples for genetic testing. If you have not had genetic testing and agree to provide samples, genetic testing will be performed at Ambry Genetics using the HHTNEXT panel that includes ENG, ACVRL1 and SMAD4 as well as 3 additional genes (EPHB4, GDF2, and RASA1) that may also be related to HHT. Results of the genetic tests will be shared with you. There is no additional cost for testing six genes rather than the standard three genes given that the HHTNEXT panel is designed to assess all six of the genes.

Since genetic testing may help to identify certain individuals with a higher likelihood of responding to pomalidomide in the future, we encourage all study participants to provide samples for genetic testing, though this is not required for participation in the study. Please check the appropriate box below if you are willing (or not willing) to provide samples for genetic testing.

☐ Yes, I agree to provide samples ☐ No, I do not agree to provide samples

Biorepository

We request biorepository blood samples from all patients as part of this research study; however, contribution of biorepository samples is not required for participation in this study. Samples will be drawn at the same time as required study labs and will not require an additional blood draw. Samples will be sent to the laboratory of Dr. Keith McCrae, the lead Principal Investigator (PI) for this study, where they will be stored in a locked -80° freezer. Patient names will be removed from all tubes and they will be given a unique study ID and barcode. Samples will be used to:

1) determine whether any substances in blood or blood cells predict or correlate with responses to pomalidomide.
2) better define abnormalities in the blood that may contribute to the symptoms of HHT.

Upon written request and review by the lead PI, portions of some of these samples may be shared anonymously with qualified HHT investigators who wish to explore new pathways to HHT therapy. Providing samples for the biorepository and future research is therefore very valuable to finding out how pomalidomide works to treat HHT and understanding HHT in general. Therefore, we encourage all study participants to donate blood for these studies at the specified times, though this is not required for participation in the study. Please check the appropriate box below if you are willing (or not willing) to provide blood samples for the biorepository.

☐ Yes, I agree to provide samples ☐ No, I do not agree to provide samples

Can I stop providing samples for the biorepository?

If you agreed to provide samples and change your mind, you may stop providing samples for the biorepository at any time. You can stop providing samples by contacting your study team contact listed in part 2 of this consent.

Can I withdraw my samples?

If you change your mind and do not want us to store and use your specimens for future research, you should contact the study team contact listed in Part 2 of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, if the specimens have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized specimens, there will be no way to link the specimens back to you. We will not contact you to ask your permission or otherwise inform you before we do this. If we do this, we would not be able to remove your specimens to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens.

ALTERNATIVES

What are the alternatives to participation in the research study?

If you do not wish to participate in this study, the following alternative treatments are available:

- Getting treatment or care for your HHT without being in this study
- Getting no treatment for your HHT
- Participating in another HHT clinical trial, if available

What are the risks of participating in the research study?

Pomalidomide has been studied in healthy volunteers and in subjects with cancer of the blood and other organs of the body as well as in subjects with other diseases. There is always a risk involved in taking any drugs, but you will be carefully monitored for all problems and you should report any symptoms you experience even if you do not think it is related to the study drug. As with any other experimental treatment there may be side effects or risks that are unknown or cannot be predicted at this time. Should you have any questions at any time you should contact the study doctor.

The following is a list of the most serious side effects that have been listed by Celgene (the pharmaceutical company who makes the drug) to be possibly related to pomalidomide. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask your study doctor. The study doctor may give you medicines to help lessen the side effects. Some side effects go away soon after you stop the study drug. In some cases, side effects can be serious, can last a long time, and could even be life-threatening. Everyone taking part in the study will be watched carefully for any side effects and you should report any changes to your health or in the way you feel to your study doctor.

Almost all of these effects have been seen in patients with multiple myeloma, a type of bone marrow cancer, for which the use of pomalidomide is approved by the FDA. Patients with multiple myeloma have usually been treated with chemotherapy before taking pomalidomide, and therefore may have compromised bone marrow function (ability to produce blood cells) before pomalidomide treatment. Moreover, these side effects relating to blood cell counts (platelets, red blood cells, and white blood cells) have been reported in previous myeloma clinical trials, and in many cases may be associated with multiple myeloma itself rather than pomalidomide treatment. Therefore, it is hard to estimate the frequency of blood cell related side effects in patients with HHT who have a healthy bone marrow, but it is likely that they are less common.

Very Common events (≥10):

- muscle cramps
- tiredness
- swelling including arms and legs,
- a decrease in platelets, the cells that help your blood to clot and could lead to bleeding
- changes in bowel habits, particularly constipation
- a decrease in red blood cells (the cells carrying oxygen to your body) that can lead to fatigue
- decreased appetite
- a low number of white blood cells that could result in infection such pneumonia

- rash and itching

Common (1-<10%):

- infection
- dizziness
- vomiting
- sore throat
- changes in sensation such as numbness or tingling in your hands or feet (neuropathy)
- blood clots in legs or lungs
- difficulty in passing urine

Other Important Side Effects

- Cancers (including acute myeloid leukemia [AML], cancer of the adrenal gland, cancer of the urinary bladder, kidney cancer, myelodysplastic syndrome [MDS], skin cancer, and thyroid cancer) have occurred in patients taking pomalidomide for multiple myeloma, but their association with the pomalidomide is uncertain.
- Inflammation of your lungs.

If you have any questions or if you do not understand any of the side effects, please ask your study doctor.

Additional Important Precautions

- We do not know if pomalidomide has any effect on you being able to have a child in the future. Please speak with your doctor about family planning options for the future.
- You must agree to abstain from donating blood or sperm while taking study drug (even if you temporarily stop your medication) and for at least 4 weeks after the last dose.
- No one other than you should handle the study drug capsules. This is especially important for females who are able to become pregnant and males who are able to father a child.

Pregnancy Risks

Pomalidomide is related to thalidomide. Thalidomide is known to cause human birth defects. Pomalidomide is therefore considered to have the potential to cause birth defects in humans.

If you are capable of giving birth to or fathering a child, you and your sexual partner should use adequate birth control measures while you are in the study. These measures may include abstinence, IUD, diaphragm, condoms, cervical cap or documentation of medical sterilization. Oral contraceptives that are estrogen/progestin based, are not an acceptable contraceptive method for this study because they may have a treatment effect on HHT and confound the research study. Discuss with your study doctor which birth control measures are acceptable.

Females must not become pregnant while taking pomalidomide. In order to participate in this study you must register into and follow the requirements of the POMALYST REMS™ program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will receive counseling which will be given by both your study doctor and a REMS certified pharmacist before receiving drug at every treatment cycle. You must also follow the pregnancy testing and birth control requirements of the program that are appropriate for

you and take surveys regarding your compliance with the POMALYST REMS™ program. Two pregnancy tests will be required for females with the potential to become pregnant before initiating pomalidomide therapy. The first test will be 10-14 days before and the second test will be within 24 hours before study drug order. Pregnancy testing in females of child bearing potential must also occur weekly during the first four weeks of use. For subsequent treatment cycles, in females of child bearing potential with regular menses, pregnancy tests will need to be repeated once every four weeks, in between cycles of pomalidomide therapy. For women with irregular menses, pregnancy tests will be conducted twice each treatment cycle.

If you are unwilling to do this, we ask that you not participate in this study. If you or your partner become pregnant while taking part in this study you must notify the study doctor immediately.

Risks of Genetic Research

Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. While the chance that someone could access and misuse your information is believed to currently be very small, it is possible that the risk may increase in the future as people find new ways to access information.

The Genetic Information Nondiscrimination Act (GINA) is a federal law designated to protect you from health insurance and employment discrimination based on genetic information. It is illegal for health insurance providers and most employers to ask for genetic information to make decisions about a person's eligibility or coverage or to make employment decisions. The law will not stop health insurance companies from using genetic information to decide whether to pay claims and also does not apply to life insurance, disability insurance or long-term care insurance.

The tests performed as part of this study will be specific for genes that are known to be related to HHT. If required and if you agree, there will be a total of 6 genes that are going to be tested in this study: ENG, ACVRL1, SMAD4, EPHB4, GDF2, and RASA1. Results from the genetic test will be provided to you. Irrespective of whether you have a positive or negative result from the genetic testing, in accordance with GINA, results from the genetic tests will not be shared with your health insurance providers, employers or any other external agency. Samples collected for genetic testing will not be shared with anyone else and will not be used for any research purpose other than what has been stated above.

Risks of Blood Draw

The insertion of the needle to draw blood can be painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problem; however they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Confidentiality Risks

There is a potential risk of loss of confidentiality of your data. Every effort will be made to keep your information confidential, through the use of the following safeguards:

- Information collected about you will be stored in a password protected database at the data coordinating center (Research Triangle Institute) that is accessible only by the research team.
- The database is 21CFR part 11 compliant, meaning it meets all the regulatory and safety standards recommended by the FDA.

If you decide to be in this study, the study team will obtain information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and address. This information will be kept for the length of the study. After that time it will be destroyed or de-identified, meaning we will replace your identifying information with a code that does not directly identify you.

Unknown Risks

There may be risks or side effects related to the study drug that are unknown at this time. You will be notified of any significant new findings that become known that may affect your willingness to continue in the study.

RESEARCH BENEFITS

What are possible benefits of participating in the research?

You may or may not benefit from participating in this study since we cannot predict whether pomalidomide will reduce your bleeding. Your participation in this study may aid our understanding of and lead to new treatments for HHT.

RESEARCH COSTS

Are there any costs to you if you participate in this study?

Study drug will be provided to you at no cost while you are participating on this study. Some of the services you will receive during this research study are considered to be conventional routine clinical services that you would have received even if you were not participating in the research study. You or your insurance company will be responsible for payment of any standard of care tests or procedures that would normally be part of the treatment of your hereditary hemorrhagic telangiectasia, such as blood counts, serum chemistries that measure kidney and liver function and iron studies. The study will pay for all other non-standard of care treatments and procedures including any research sample collections, and the exam on research visits.

Genetic Testing

If you have not been previously genetically tested for HHT, genetic testing of HHT-related genes will be performed by Ambry Genetics (Aliso Viejo, CA). If you have non-federal insurance, your primary insurance will be billed for cost of the genetic tests. For patients who are covered by a government-funded insurance plan, the HHTNEXT panel will be performed at Ambry Genetics with costs covered by the study and your insurance will not be billed.

The costs of genetic testing is usually covered by private insurers. However, if the insurer refuses to cover these costs, or if you have federal insurance coverage such as Medicare, the study will cover the costs of genetic testing.

Are there any payments to you if you participate in this study?

You will receive a stipend of $10.00 for each completed study visit to help cover some of your travel costs. There are a total of 9 visits for this study (Screening, Randomization, 6 Treatment visits and a final end of study visit). Therefore, you would get a total of $90.00 for the entire study if you complete all 9 study visits.

What are your rights as a research participant?

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. Leaving the study at any time will not affect your regular treatment or medical care. If you wish to withdraw, you should notify your study doctor that you no longer want to participate in this study. In addition, your study doctor may decide to end your participation in this study at any time after he/she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

US National Institutes of Health (NIH) Clinical Trial Database

A description of this clinical trial will be available on https://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Please refer to the clinical trial registration number NCT03910244 to get more information about this research study.

Confidentiality

What will happen to your information that is collected for this research?

Cleveland Clinic may share your study information, without anyone knowing that it is related to you specifically, with others or use it for research projects not listed in this form. Your blood samples or data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your blood samples or data, we will no longer be able to identify and destroy them.

Study results may be shared in medical journals, at scientific meetings, and in other mediums without your identifying information. Your records will be confidential and your identity will not be shared in medical journals, at scientific meetings, and in other mediums without your express consent.

POMALYST REMS Program

Pomalidomide has to be dispensed in accordance with the POMALYST REMS program. All recipients of pomalidomide will have to be registered in Celgene's POMLAYST REMS program and will be counseled by a REMS-certified pharmacist on the risks of fetal exposure, blood clots and reduced blood counts. Therefore, to be compliant with the mandatory REMS program, we will need to provide your contact information to Celgene and their pharmacists.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

If you have any questions about what this notice means and would like to speak to someone, you may call your study team listed in the contact section in Part 2 of this form or the Cleveland Clinic Institutional Review Board (216-444-2924). If you would like to read more about Certificate of Confidentiality, the NIH has a website you can visit online at: https://grants.nih.gov/policy/humansubjects/coc.htm.