

Rare Disease Clinical Research Network

Brain Vascular Malformation Consortium

Study Title: **Sirolimus for Nosebleeds in HHT: A Phase II pilot study**

Protocol Number: 200421448

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Clinical protocol: This protocol is for research purposes only

Phase: II

Drug: Sirolimus (1, 2 or 5mg tablets)

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Synopsis:

This pilot study is to determine the safety and efficacy of oral sirolimus (blood trough level 6-10ng/ml) in patients with HHT that are experiencing moderate or severe epistaxis. The effect of oral sirolimus on epistaxis will be compared to baseline using the Patient-Reported Outcome of cumulative weekly nose Bleeding Duration (PRO-CB). The PRO-CB association with biomarker variability over the duration of the study will be investigated. In the pilot study subjects will be treated with 2mg of sirolimus once daily to obtain a trough level of 6-10ng/ml for 3 months.

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Number of study sites: ONE

Study site: St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8

Collaborator: (study procedure)

Dr. Cecilia Chaparro, St. Michael's Hospital, Toronto, Ontario, Canada

Collaborators: (sample and data analysis)

Dr. Doug Marchuk, Duke University Medical Center, NC USA

Dr. Helen Kim, University of California, San Francisco

Consortium's Data Management and Coordinating Center (DMCC) at Cincinnati

Children's Hospital Medical Center

Statement of Compliance

The clinical trial will be conducted in compliance with Good Clinical Practice (GCP), the applicable regulatory requirements and according to protocol

All individuals responsible for the design and conduct of this trial have completed Human Subjects Protection Training.

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

Principal Investigator: Dr. Marie E. Faughnan

Signed: _____ Date: _____

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1.0 Introduction and Background

The most common symptom of the hereditary hemorrhagic telangiectasia (HHT) disease is epistaxis (1). HHT is characterized by vascular (blood vessel) malformations, of the skin and mucus membranes of the nose (telangiectasia), gastrointestinal track, brain, lung and liver (1).

HHT is an autosomal dominant disease which is found in approximately 1 in 5000 individuals (1). Epistaxis affects 90% of adults with HHT, negatively affects quality of life (2, 3) and often causes anemia. Recent topical therapeutics trials have been negative (3) and surgical therapies are invasive and offer only temporary benefit at best. Currently there are no highly-effective or approved systemic therapies for HHT-related epistaxis, but this is an area of active research and development. There is considerable in developing and identifying therapies that target the abnormal biology and mechanisms in HHT, including antiangiogenic therapies, such as bevacizumab (1). Bevacizumab, however, is associated with significant toxicity, costly and administered intravenously.

Over the past few years, there has been considerable new evidence of the pathways involved in HHT disease and related potential therapeutic targets, including the mTOR pathway. Evidence suggests that HHT pathogenesis strongly relies on overactivated PI3K-Akt-mTOR and VEGFR2 pathways in endothelial cells. Ruiz et al (4) recently reported that the mTOR inhibitor, sirolimus, and the receptor tyrosine-kinase inhibitor, nintedanib, synergistically fully blocked, and also reversed, retinal AVMs, in the BMP9/10- immunoblocked neonatal mouse model of HHT. Subsequent unpublished preliminary data demonstrated that sirolimus was more effective than nintedanib at blocking anemia and bleeding in inducible ALK1 knockout HHT mice, and similarly effective to combined sirolimus-nintedanib. As such, sirolimus may provide therapeutic benefit for HHT patients (5). Human studies have shown “low-dose” sirolimus to be low risk and effective as a treatment for other vascular anomalies (6)(7).

There is an urgent need for effective therapies for HHT and the chronic bleeding associated with the disease. Preliminary cellular and animal model data have identified sirolimus as a potential new pathway-based therapy in HHT. In addition, sirolimus is an interesting agent, as it is given orally and is available for repurposing. Data from other vascular malformations syndromes suggest that it can be effective in a “low-dose” range, reducing risk of toxicity, but there is only one published case report of sirolimus use in an HHT patient. This phase II pilot study will provide safety data as the primary outcome, and secondarily, efficacy data, outcome measure data and biological exploratory data, to support the planning of a future randomized and placebo-controlled clinical trial of sirolimus for epistaxis in HHT patients.

2.0 Rationale

Sirolimus has been identified as a potential pathway-based therapy for HHT. Pre-clinical research has suggested that the pathogenesis of HHT is as a result of overactive mTOR and VEGFR2 pathway (4). Sirolimus has been found to work as an mTOR inhibitor to prevent the effects of overactive mTOR that results in arteriovenous malformations in a HHT (4). One clinical trial that used sirolimus to treat vascular anomalies, found that sirolimus was well

tolerated and acted as an effective and safe treatment for most study participants (6). Considerable experience using sirolimus in post-transplant patients and growing experience using sirolimus in patients with vascular anomalies exist. This pilot study will assess the safety and effectiveness of repurpose oral sirolimus, for epistaxis in patients with HHT.

3.0 **Objectives and Purpose**

There is an urgent need for effective therapies for HHT and this sirolimus pilot study will provide safety and outcome measures to guide planning of a future randomized and controlled clinical trial.

The hypothesis

We hypothesize that oral sirolimus (blood trough level 6-10ng/ml) will be a safe and effective therapy for epistaxis in HHT patients.

3.1 Purpose

Aims	Endpoint
Specific Aim 1 To determine the safety of a 6-10ng/ml dose oral sirolimus in patients with HHT, with moderate or severe epistaxis.	Clinical and laboratory adverse event (AE) measures, as per detailed Safety Monitoring:
Specific Aim 2A: To measure the effect of a 6-10ng/ml dose of oral sirolimus on epistaxis in HHT patients, compared to baseline epistaxis	Epistaxis will be measured using the Patient-Reported Outcome of cumulative weekly nose Bleeding Duration (PRO-CB), compared to baseline PRO-CB, obtained from daily epistaxis diary.
Specific Aim 2B: To characterize PRO-CB in HHT patients with moderate to severe epistaxis.	PRO-CB using daily diary throughout the 9 months of the study.
Specific Aim 3: To explore biomarkers variability over time, on/off therapy and association with PRO-CB.	We will collect plasma for biomarkers (specific panel will be determined with the HHT Study team which may include the following: ANG2 sICAM1 PIGF TSP2 sVEGFR2, BMP9 IL6 SDF1 sVCAM1 sVEGFR3, sCD73 sIL6R TGFβ1 VEGF, sENG OPN TGFβ2 VEGF-C, GP130, PDGF-AA, sTGFβR3, VEGF-D, HGF PDGF-BB, TIMP1, sVEGFR1 (Wetzel-Strong et al. Orphanet J Rare Dis (2021) 16:372)

4.0 **Research Plan**

Sirolimus is a potential therapy of interest in HHT, The primary outcome is the reduction of epistaxis (minutes per week), as adults with HHT are almost universally affected by epistaxis and it is known to impair quality of life (3). The study aims to investigate subjects with moderate to severe epistaxis, using sirolimus target trough 6-10 ng/ml for 3 months.

4.2 Study Participants:

The study will include a maximum of 20 enrolled participants with a final target of 10 subjects who entirely or partially complete study drug intervention. Participants will be recruited from the Toronto HHT Center, at St. Michael's Hospital, and through the Rare Diseases Network website (<https://www1.rarediseasesnetwork.org/cms/bvmc/Get-Involved/Studies>).

The primary outcome for the trials will be the reduction of epistaxis severity (minutes of bleeding per week).

4.3 Inclusion and Exclusion Criteria:

4.3.1 Inclusion criteria:

- a) Age \geq 18 years
- b) Clinical HHT diagnosis (8) or genetic diagnosis of HHT
- c) Epistaxis at least 15 min per week.
- d) COVID-19 Vaccine (2 doses)
- e) Ability to give written informed consent, including compliance with the requirements of the study.

4.3.2 Exclusion criteria:

- a) Allergy/intolerance to the study drug or related agents
- b) Unstable medical illness
- c) Acute infection
- d) Creatinine > ULN (upper limit of normal)
- e) Liver transaminases (AST or ALT) \geq 2x ULN
- f) Women participant who are pregnant or breastfeeding or plan to become pregnant during the duration of the study
- g) Women of childbearing potential not on effective contraception.
- h) Male participants of reproductive potential whose female partners are of childbearing potential and are not planning to use highly effective contraceptive method
- i) Immunocompromised
- j) History of malignancy
- k) Known untreated dyslipidemia (20% above the ULN of total cholesterol and triglycerides)
- l) Specific contra-indications for study drug (detailed in the product monograph)

5.0 Study Design

This pilot study (final n=10) of oral sirolimus (starting dose of 2mg once daily, adjusted to maintain drug blood levels of 6-10 ng/ml, 3-month course) in HHT subjects with moderate-severe recurrent epistaxis. The subjects recruited will have zero or greater than two telangiectases of \geq 2 mm diameter available for excisional biopsy

5.1 Schedule of Events

- i. Screening visit: Confirm eligibility
- ii. Baseline: All subjects will undergo a 3 month baseline period following the screening visit
- iii. Study drug arm: Subjects will be treated with a 3 month course of sirolimus at a starting dose of 2mg once daily. This dose will be adjusted as needed, to maintain drug blood levels of 6-10 ng/ml.
- iv. Follow up: All subjects will undergo a 3 months follow-up period.

5.2 Study Design Discussion

All participants will receive 3-month course of study drug

The collaborating doctor (Dr. Chaparro) will advise on dose adjustment to maintain a drug blood level of 6-10 ng/ml.

A medical history and physical examination will be performed at all clinic visits.

5.2.1 Specific study drug dosing:

Sirolimus starting dose of 2 mg once daily, orally adjusted as need to maintain drug blood levels of 6-10 ng/ ml

The first dose will be given at the week 12 visit and participants will be observed for 30 min

5.3 Study Timelines

The study is expected to take place over a period of 9 months; all subjects will have a screening visit for eligibility review and informed consent. Participants will start with a baseline period of 3 months, treatment period of 3 months (study drug), and a follow-up period of 3 months. Tissue biopsy will occur prior to the start of study drug and at the end of the study drug period

5.3.1 Baseline period:

There will be a 3-month baseline period for accurate measurement of primary outcomes; epistaxis severity in minutes of bleeding per week. Participants will be asked to keep a daily diary of all epistaxis events, recording duration and intensity for each, for the three months baseline period and the duration of the study.

5.3.2 Treatment period

There will be a 3- month treatment period of sirolimus.

5.3.3 Follow-up period

There will be a follow-up period of 3 months post the investigational product period, during which safety and outcome data will be collected.

5.4 Table of Study visit Summary:

*Visit Summary	***Weeks (time Point)	****Blood work (safety) + Biomarkers	Daily Diary (DD)+ Epistaxis severity score (ESS)	Safety and Adverse event Monitoring, Medical history	Tissue biopsy	Pill count
Screening Clinic visit/ ICF	0	Safety	DD+ESS	X	X	
Phone Visit/ baseline period	1,2,4,6,8,1 0		DD	X		
Investigational product assignment/ clinic visit/(day 0)	12	Safety + biomarker	DD+ESS	X		X
**Dose adjustment (as needed)	13	Safety		X		
Phone visit	14,16		DD	X		
Clinic visit (6 weeks investigational product)	18	Safety + biomarker	DD+ESS	X		X
Phone visit	20, 22		DD	X		
Clinic Visit (12 weeks) End of investigational product	24	Safety + biomarker	DD+ESS	X	X	X
Start of Follow-up Period, Phone visit	26, 28, 30, 32, 34		DD	X		
Final Epistaxis daily diary documentation	36	Safety + biomarker	DD+ESS	X		

* Medical History and Physical Examination at all clinical visits..

** a blood sample will be collected for sirolimus blood level, for dose adjustment

*** +/- 7 days, unscheduled clinic visit or safety blood work – will occur if required to assess safety and for women of childbearing potential on effective contraceptive – will occur if required to assess safety and for women of childbearing potential on effective contraceptive.

****safety blood work will include: Electrolytes (Sodium, Potassium, Chloride, total CO₂), Hematology (total blood count-CBC), Renal Function test (urea, creatinine), Liver function (AST, ALT, total Bilirubin), ferritin level, Pregnancy test (BHCG level) and sirolimus blood level, blood glucose level, lipid assessment (total Cholesterol, Triglycerides)

*****Biopsy samples will be collected if the subject have two skin telangiectases of >2mm diameter available for excisional biopsy, prior to the start of study drug and at the end of treatment period.

6.0 Study Investigational Product

Study drug – Sirolimus

Starting dose of 2 mg once daily. Adjusted to maintain drug blood levels of 6-10 ng/ml,

Route – Administered orally

Instructions- Sirolimus can be administered with or without food; however, doses should be administered in a consistent manner. Patients should avoid consuming grapefruit juice while enrolled in the study, as it can interact with the drug mechanism of action.

6.1 Study drug

Six weeks of study drugs will be dispensed at each study drugs visit (and an additional amount for 7 days of study visit window). Investigational product will be stored according the manufacturer's recommendations. The Pharmacy staff will keep a study temperature log for the study drugs. A drug accountability log will be kept by the Pharmacy staff [dispensing information (date and pill number) and drug return information will be recorded].

6.2 Concomitant Medications

Serious drug interactions may occur if GD-sirolimus is co-administration with strong inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or inducers of CYP3A4 (such as rifampin or rifabutin).

Participants who meet the inclusion and exclusion criteria for this study and are now enrolled can continue their usual medication/therapy if applicable. All current medications will be reviewed at screening and reviewed for changes at all safety monitoring visit

7.0 Study Outcomes:

7.1 Primary outcome:

Clinical and laboratory adverse event (AE) measures, as per detailed Safety Monitoring: Study participants will be monitored for typical side effects of the study drug, such as gastrointestinal intolerance, infectious symptoms, cough, rash, tremors, etc. Study participants will be monitored for adverse events with history, physical examination (including blood pressure, heart rate, chest exam, etc.) and laboratory studies (electrolytes, renal function, liver function, routine hematology, lipids, drug levels, etc.). Safety monitoring will occur every two weeks by phone and every 1.5 months with clinic visits during treatment periods, and every two weeks by phone during the baseline and follow-up period. Participants will also have daily access to the Study team as needed for any concerns between assessments.

7.2 Secondary outcomes:

Epistaxis data will be collected by PRO-CB using daily diary throughout the 9 months of the study. We will also collect blood sample for biomarkers (specific panel will be determined with the HHT Study team based on biomarkers pilot study analyses) at 4 time points: 3, 4.5, 6 and 9 months

Biopsy tissue sample and blood sample will be sent to two facilities for further analysis; Duke University, USA under the direction of Dr. Douglas Marchuk PhD and University of California, San Francisco (UCSF), USA under the direction of Dr. Helen Kim. The samples will be in secure storage space in limited access facility until such time as the samples are completely used up or up until study data analysis is completed at which point any remaining samples will be destroyed.

8.0 Data Management

For this pilot study, we plan for 10 participants who complete the 36-week study or at minimum 18 weeks of the study, for the purpose of data analysis.

The following collaborators will be involved in data analysis:

Dr. Doug Marchuk, Duke University Medical Center, NC USA

Dr. Helen Kim University of California, San Francisco (UCSF), USA

Consortium's Data Management and Coordinating Center (DMCC) at Cincinnati Children's Hospital Medical Center

The Data Management and Coordinating Center (DMCC) Cincinnati, USA, will assign all recruited participants with a participant ID. The link between patient identifying information and database participant ID will only be maintained at the recruiting center. Data will be entered through a web-based system (REDCap) into a central Database developed at the DMCC. Transfer of PHI to the DMCC will be limited as feasible. An appropriate data use agreement is in place to allow secure exchange and confidential processing of PHI by DMCC. A detailed table of relevant fields and their data types and ranges were constructed by combining elements that are in use by the HHT community.

8.1 Sample-size estimate and statistical considerations:

We estimated to have a final sample size of 10 participants for the pilot study. Standard descriptive statistics will be used for reporting the primary and secondary outcome.

8.2 Data collection:

At baseline, comprehensive data regarding patient HHT clinical disease will be collected, including all aspects of disease. In addition, co-morbid disease and baseline medications will be recorded.

9.0 Study Assessment and Procedures

The table of events list (5.4) the assessment time periods

9.1 Tissue Biopsy of available telangiectases:

Excisional punch biopsy of one cutaneous telangiectasia will be performed with 3mm punch biopsy for lesions <3mm in diameter, and with a 5mm punch biopsy for larger telangiectases. The biopsy sample will be taken at the start of study prior to treatment and at end of the 3- month study drug treatment period.

Biopsy will be performed, using standard aseptic technique, and after local injection with lidocaine-epinephrine. We have local experience using this technique and it has been low-risk. Tissue will be fixed in 10% buffered formalin or frozen below 80 degrees Celsius or colder and stained for analysis. Section slides will be prepared, using standard techniques. Tissue will also be stained for angiogenesis, pathway and inflammatory markers (VEGF, Endoglin, ALK1, etc.).

9.2 Serum and plasma collection:

Blood will be drawn for safety measures at each clinic visit and for dose adjustment (see Table of Study Events 5.4). Biomarker samples will be collected at screening, 3, 4.5, 6 and 9 months. Serum/plasma levels will be measured for inflammatory, angiogenic, and BMP9-ALK1-endoglin-Smad1/5/9 pathway markers (9).

10.0 Data and Safety Monitoring

The Study protocol will be reviewed and approved by the Research Ethics Board at St. Michael's Hospital (REB). Participants will be enrolled after the study protocol, consent form and study materials are approved by the REB. Study drug monitoring will occur at each clinic visit and telephone contact. The study team can be reached daily. All current medications will be reviewed at screening and reviewed for changes at all safety monitoring visit.

The study staff will be responsible for documenting and reporting adverse events or serious adverse events. Safety monitoring will occur every 2 weeks by phone during the baseline, study drug treatment and follow-up period. Additionally, safety monitoring will occur at each clinic visits every 6 weeks. Participants will also have daily access to the study team as needed for any concerns between assessments.

10.1 Study drug and adverse event monitoring:

Study participants will be monitored for very common side effects of sirolimus (occur in 10% or more of patients) (10) include:

- a) Abnormal wound healing
- b) Stomach pain, upset and other digestive symptoms, such as diarrhea, nausea, constipation, vomiting
- c) Headache, abnormal vision, shaking (tremor) and some weakness could occur
- d) Acne
- e) Insomnia
- f) Joint, bone or back pain, Swelling of the hands, feet, ankles, or lower legs
- g) Urinary tract infection

Common side effects (occur in less than 9% of patients) include:

- h) Infection (sinusitis, gastroenteritis, influenza, upper respiratory, COVID etc.)
- i) Abnormal bleeding (menstrual, other) or bruising may occur
- j) Dizziness upon standing, feeling anxious and fever or chills may occur
- k) Fluid accumulation/retention
- l) Increased heart rate or heart palpitations
- m) Mouth ulcers or cold sores
- n) Ovarian Cysts
- o) Shortness of breath
- p) Swollen abdomen

Common side effects (occur in less than 1% of patients) include:

- q) Skin cancer (melanoma)

- r) Pancreatitis (inflammation of the pancreas)
- s) Rash and severe allergic reaction including skin reaction may occur

* Women of childbearing potential (pre-menopausal female who are able to become pregnant by any means), will be monitored for pregnancy during follow-up phone visits and at each clinic visit (every six weeks, as a part of the safety lab). Women with a pregnancy lab result for beta hCG Quantitation of > 24 IU/L will be immediately discontinued from study participation and we will seek the participant's permission to monitor the pregnancy and outcome.

Concomitant medications will be monitored; Sirolimus should not be taken with strong inducers and inhibitors of CYP3A or P-glycoprotein (ketoconazole, voriconazole, itraconazole, telithromycin, clarithromycin, or rifampicin, rifabutin)
Pneumonitis (inflammation of the lung tissue) and hyperlipidemia (lipids in the blood) can occur.

Participants are recommended to stop taking study drug and seek immediate medical attention if you develop signs of severe allergic reaction which may include: Chest tightness, Dizziness, Faintness, Rapid heartbeat, Shortness of breath, Skin reaction, Swollen face, lips, or tongue and Wheezing and to contact their doctor immediately if they notice a lump in the neck, armpits, collarbone region, or groin, or unintended weight loss, new moles or any changes in the size, shape, or colour of moles they already have, to monitor for skin cancer.

Vaccination information: Immunosuppressants may affect response to vaccination. Therefore, during treatment with GD-sirolimus, vaccination may be less effective. The use of live vaccines should be avoided”.

10.3 Reporting timeline for adverse events

Adverse events will be reported to Health Canada, the St. Michael's hospital REB and the safety monitoring board.

- i. All reportable Serious Adverse events will be reported by the Investigator within the reporting timelines as per the REB and Health Canada specific guidelines. Including all events that are considered: life-threatening/disabling, results in death of subject, unexpected/unanticipated and other reportable serious adverse events.
- ii. Suspected reportable adverse event will be reported to the safety monitoring board.

11.0 Definition and Standards

11.1 Adverse Event

The International Conference on Harmonization (ICH) Tripartite Guideline define an Adverse Event (AE) as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

11.2 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out (ICH guidelines).

11.3 Serious Adverse Event (SAE)

Reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening (an event in which the patient was at risk of death at the time of the event), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH guidelines).

11.4 Unexpected Adverse Event

The nature or severity of which is not consistent with risk information described in the protocol.

11.5 Expected Adverse Event

An event identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participating in the study

11.5.1 Expected AE: Underlying disease

- a) Clinically significant abnormal lab findings associated with HHT underlying disease.
- b) Medical or surgical procedure associated with HHT underlying diseases.
- c) Symptoms associated with HHT underlying disease.

11.5.2 Expected AE: Drug

- a) Known risk/Discomforts associated with study Drug.

12.0 Potential challenges and alternative approaches

If we demonstrate poor safety profile of the 6-10ng/ml dose of oral sirolimus, then no further clinical trials of this dose oral sirolimus for treatment of epistaxis in HHT will likely be planned. There may not be an observed effect of this dose oral sirolimus on epistaxis as via PRO-CB based on the number of participants in the study.

13.0 Withdrawal (Stopping) Criteria and Procedures

Subjects may withdraw from the study at any time at his/her own request.

Subjects can be withdrawn from the study by the investigator at any time for any reason and due to the following safety or compliance:

- If continuation in the study appears to be medically harmful
 - Due to evidence of Serious Adverse Events
 - -Adverse Events/Adverse Drug Reaction (unexpected/expected) that are unfavourable and could lead to possible serious adverse events at the discretions of the study investigator
- If it is later discovered that the subject does not meet the eligibility requirements

- If the subject does not follow the instructions for investigational product or follow-up visits
- If the subject becomes pregnant

If a subject is withdrawn from the study or if the study ends early, we will ask subjects to return all leftover study drugs and complete the early termination study visit.

Continued collection and use of data after withdrawal

If a subject withdraw, or are withdrawn from the study, data collected up to that time will still be used. No more data will be collected unless it is necessary to follow up on an adverse event that is not resolved at the time of withdrawal.

Continued use of samples after withdrawal

If a subject decides to leave the study, the subject can request withdrawal of their samples from the research by contacting the study team. The study team will keep and use any research results obtained prior to withdrawal of consent (data from samples that have been analyzed). No further analysis will be done on any remaining samples and the sample will be destroyed.

14.0 Human Subject Recruitment

The study will be conducted in accordance with ICH Good Clinical Practice (GCP). This will include REB and Health Canada approval to conduct the study and written informed consent from each subject.

Subjects will be recruited as follows:

- 1) All subjects with a confirmed diagnosis of HHT and moderate to severe epistaxis will be approached for participation in clinic.
- 2) Participants will learn about the study through the website:

<https://www1.rarediseasesnetwork.org/cms/bvmc/Get-Involved/Studies>

If they're interested, they can contact the research coordinator for pre-screening for eligibility.

Ten subjects will be recruited. Subjects may or may not benefit directly from inclusion in this study. Knowledge from this study may help doctors better understand treatment for HHT or help determine who is more likely to benefit from the sirolimus treatment. It may also help future patients. However, we hope that at the end of this study, researchers may be in a better position to propose clinical trials that may help reduce vascular malformations in individuals with HHT.

14.1 Risk, Warnings and Precautions:

Related to study drug: Please see Product Monograph GD ® -Sirolimus

(Sirolimus Oral Solution and Tablets) GenMed, a division of Pfizer Canada, April 8, 2021

14.2 Warnings related to test

- a) Blood sample collection: When blood samples are taken from a vein. Discomfort or pain may occur. Participants may feel faint or experience bruising, irritation or redness at the site.

- b) Biopsy: The needle with the freezing may causes a stinging or burning sensation. The freezing can cause nausea. Allergic reaction is unlikely. Bruising may occur, which could last for 2 weeks. There is a small risk of a local skin infection. There is likely to be a small scar at the site of the biopsy. It is much less common to have a raised itchy scar, which could be injected with cortisone to help it flatten. After 7-10 days the (1-2) stitches will be removed.

14.3 Written informed consent

Written informed consent will be obtained from each participant before any study procedure or assessment is conducted. The study will be explained, the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. After all the participant's questions are answered and as much time is give as required by the participant, he/she will be asked to sign and date the informed consent.

14.4 Process of consenting

The study participants will be approached in clinic or by phone (with previous permission given to call). The study coordinator will explain the information in the written informed consent to the participant. The participants will be asked several times if they understood details of the study and if there are questions. The participants will be offered time to read, consider and discuss the study, including taking the consent home for additional time to consider participation. A Qualified Medical Personnel will be available for any medically related questions or concerns. After all questions are answered the participant will be asked if they agreed to participate in this study. The participant will sign and date the informed consent form and a copy will be given to the participant.

14.5 Quality assurance

For the research subject's protection and to ensure compliance with GCP and applicable regulatory requirements, quality assurance assessment and or audits of the site records may be conducted by, Health Canada, National Institute of Health (NIH)). In the event of the assessment or audit direct access to all relevant study documents will be required from the investigator and institution.

14.6 Study Governance

14.6.1 Data safety monitoring plan

The Principal Investigator has appointed a Data Safety Monitoring Board (DSMB), comprising of two physicians and a statistician. The DSMB will convene every six months to review safety data. The DSMB will also convene if necessary to review increased safety events. The DSMB will review the protocol prior to the start of the study. The purpose of the DSMB is to review the protocol and conduct of the study and

provide guidance to the study investigator. The DSMB is a group of experts with relevant knowledge in patient care, the disease (HHT) and in clinical research trial conduct and methodology. The DSMB members will serve in an individual capacity and provide their expertise and recommendations in the conduct of the study.

14.6.2 Study Monitoring

The study Principal Investigator and team will monitor the study according to applicable GCP standards and ICH guidelines to ensure the completeness, correctness, and consistency of the data and to assess whether the study is executed according to this protocol and monitoring plan. Safety monitoring will occur every two weeks and severe adverse events will be reported in compliance with the Unity Health Toronto Research Ethics Board and Health Canada.

14.6.2 Study data storage and retention

Electronic files will be stored securely on hospital or institutional networks.

Based on Health Canada regulations, the principal investigator will keep all study data and personal identifying information collected for study purposes securely stored for at least 15 years

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16.0 Appendices

16.1 Epistaxis Severity Score (ESS) for Hereditary Hemorrhagic Telangiectasia

The purpose of these questions is to calculate a severity score of epistaxis (nose bleeding) for patients with Hereditary Hemorrhagic Telangiectasia.

Please answer each of the following questions as they pertain to your TYPICAL symptoms **WITHIN THE LAST 3 MONTHS** for nose bleeding. Please answer all questions.

HHT-ESS

1. How often do you TYPICALLY have nose bleeding?

- ☐ Less than once per month
- ☐ Once per month

- ☐ Once per week
- ☐ Several per week
- ☐ Once per day
- ☐ Several per day

2. How long does your TYPICAL nose bleeding last?

- ☐ < 1 minute
- ☐ 1-5 minutes
- ☐ 6-15 minutes
- ☐ 16-30 minutes
- ☐ > 30 minutes

3. How would you describe your TYPICAL nose bleeding intensity?

- ☐ Not Typically Gushing or Pouring
- ☐ Typically Gushing or Pouring

4. Have you sought medical attention for your nose bleeding?

- ☐ No
- ☐ Yes

5. Are you anemic (low blood counts) currently?

- ☐ No
- ☐ Yes
- ☐ I don't know

6. Have you received a red blood cell transfusion SPECIFICALLY for nose bleeding?

- ☐ No

[illegible]

dd/mm/yyyy											
dd/mm/yyyy											
dd/mm/yyyy											
dd/mm/yyyy											

16.3 Wallet Card

