

## I. TITLE

Efficacy of a Timolol Gel in the Care for Epistaxis in Patients with Hereditary Hemorrhagic Telangiectasia: A Double-Blinded, Randomized Controlled Trial (ETIC HHT Trial)

## II. SITE INVESTIGATORS

**Washington University Hereditary Hemorrhagic Telangiectasia (HHT) Center of Excellence**

Jay F. Piccirillo, MD, FACS

Murali Chakinala, MD

**Froedtert & Medical College of Wisconsin Center of Excellence**

David Poetker, MD

## III. Trial Registration

Prior to enrollment of the first subject, the trial protocol will be registered in ClinicalTrials.gov.

## IV. ABSTRACT

Hereditary hemorrhagic telangiectasia is an autosomal dominant inherited disorder that progressively manifests with telangiectasias, mucosal bleeding, and possibly solid organ hemorrhage within the first few decades of life. Epistaxis is the most common presentation of the disease, with the vast majority of HHT patients developing recurrent epistaxis by the age of 20. Epistaxis alone has been shown to be the biggest contributor of morbidity and decreased quality of life in HHT patients. While a variety of medications and procedures have been tried to prevent the bleeding in HHT patients with epistaxis, no standard of care exists as each therapy has its own drawbacks. As a result, there is a need to further investigate potential therapies to prevent blood loss and iron deficiency anemia, and to improve the quality of life in HHT patients with moderate to severe epistaxis. Propranolol and timolol, nonselective beta blockers, in a topical gel form, are promising therapies to reduce epistaxis and reduce the likelihood of systemic side effects. The mechanism of action is proposed to be due to indirect shunting of catecholamines towards the alpha-1 receptor and possible direct anti-angiogenic effects. Timolol is an available topical therapy in infantile hemangiomas and may play a role in the prevention and treatment of epistaxis in HHT. Due to propranolol's toxicity to nasal cilia, timolol is the more favorable of the two drugs. Thus, we propose a double-blinded, placebo-controlled, 8-week randomized clinical trial investigating the efficacy of timolol gel in the management of epistaxis in adults with HHT. The Specific Aims are to determine in adults with HHT-associated epistaxis:

1. If topical timolol gel is more effective than placebo in reducing the frequency and severity of epistaxis.
2. If topical timolol gel is more effective than placebo in improving hemoglobin levels.
3. The frequency of adverse events, side effects, and safety profile of topical timolol gel delivered to the nasal mucosa.

The study population will consist of: adults with confirmed clinical (meeting at least 3 of the 4 Curaçao Criteria) or genetic diagnosis of HHT; *Epistaxis Severity Score (ESS)*  $\geq 4$  and 2 or more nosebleeds per week with a cumulative nosebleed duration of at least 5 (or 10) minutes per week; stable nasal hygiene and medical regimen for preceding 1 month; stable epistaxis pattern over the preceding 3 months. We will recruit subjects from the Washington University Hereditary Hemorrhagic Telangiectasia (HHT) Center of Excellence, Froedtert & Medical College of Wisconsin Center of Excellence, and The CureHHT *Participate in Research* website. The intervention will be prepared and dispensed by Advanced Rx Pharmacy, Plymouth Meeting, Pennsylvania. Timolol nasal gel 0.1% will be prepared with a poloxamer gel and 0.5 ml applied to each nostril twice daily. The total daily dose will amount to 2 mg. Placebo gel is prepared with

poloxamers and no active ingredients. Timolol is odorless so the research subjects should not be able to identify the placebo gel from the active gel. The primary outcome will be the difference in the mean pre- to post-intervention change in the *ESS* among the subjects in the two intervention arms. The 95%CI around this effect size will be determined to assess the precision of the observed effect and whether a clinically meaningful difference is plausible given the observed results. A total sample size of 24 patients is required to allow us to detect with 80% power at the 2-sided alpha level of 0.05 a difference of 62% or more in the percent of subjects who experience reduction of severity of bleeds between treatment groups. Considering a 20% drop out rate, we plan to enroll 30 subjects in the study.

## V. STATEMENT OF RESEARCH PROBLEM

### BACKGROUND

Hereditary hemorrhagic telangiectasia (HHT) is an inherited autosomal dominant disorder that leads to abnormal formation of blood vessels throughout the body.(McDonald, Bayrak-Toydemir, and Pyeritz 2011) Patient symptoms primarily consist of bleeding from various mucosal surfaces from telangiectasias (dilated capillaries) across the total body to more severe or life-threatening hemorrhage from arterio-venous malformations (AVMs) in the lung, brain, or liver. The telangiectasias tend to spontaneously rupture, most commonly resulting in nasal or gastrointestinal bleeding. Diagnosis of HHT is currently with the use of the Curaçao Criteria, which involves a combination of epistaxis, telangiectasias, visceral lesions (AVMs), and a family history of a first degree relative with HHT. Symptoms are age-dependent and gradually emerge over time.(Faughnan et al. 2011) By age 20, more than 75% of patients with HHT have developed recurrent epistaxis.(Dheyauldeen, Abdelnoor, and Bachmann-Harildstad 2011) Epistaxis is the leading cause of morbidity and decreased quality of life in these patients.

### TREATMENT

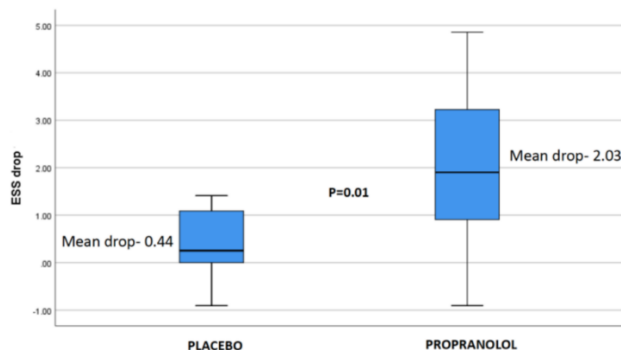
A variety of medical and surgical treatments are available for epistaxis. A recent evidence-based review was performed to provide treatment information.(Halderman et al. 2018) The authors used the Oxford levels of evidence(Group 2011) to grade the methodological quality of each article and the strength of the evidence. A total of 123 abstracts were reviewed covering systemic hormonal therapy, thalidomide, tranexamic acid, and propranolol. Of the 123 abstracts, 18 articles were of sufficient methodological quality to be included. Systemic hormonal therapy delivered as selective estrogen receptor modulators (raloxifene and tamoxifen) and topical estriol was described in 5 articles.(Albinana et al. 2012; Minami and Haji 2016; Whitehead et al. 2016; Yaniv et al. 2009; Yaniv et al. 2011) The level of evidence for systemic hormonal therapy was rated as Grade C and the authors concluded that hormonal therapy has potential benefits of improvement in frequency, severity, and number of epistaxis episodes. Thalidomide has antiangiogenic properties and has been used to treat epistaxis and gastrointestinal bleeding. The review identified 4 articles that described observational studies of the impact of low-dose thalidomide (50-200 mg/d) on frequency and severity of epistaxis.(Fang et al. 2017; Invernizzi et al. 2015; Lebrin et al. 2010; Peng et al. 2015) The aggregate level of evidence of the four studies was Grade C and the authors concluded that improvements in patients' bleeding without serious side effects were observed at the lower doses. Tranexamic acid (TXA) decreases the conversion of plasminogen to plasmin and thus stabilizes blood clots. The authors reviewed 5 articles, 2 of which were double-blinded randomized placebo clinical trials, that examined oral and topical TXA.(Fernandez et al. 2007; Gaillard et al. 2014; Geisthoff et al. 2014; Whitehead et al. 2016; Zaffar et al. 2015) The results of the two clinical trials of oral TXA failed to show a change in hemoglobin level but did show improvements in various epistaxis parameters. The authors concluded that oral TXA is likely associated with a reduction in epistaxis without serious side effects, but additional high-quality studies are needed. The one clinical trial to examine the impact of topical TXA showed no benefit.

## The Use of $\beta$ -Blockers in the Management of HHT-Associated Epistaxis

$\beta$ -blockers have several possible biological mechanisms of action to reduce HHT-associated epistaxis and several studies in humans to suggest a clinically meaningful effect. The  $\beta$ -blockers propranolol and timolol have been studied the most.

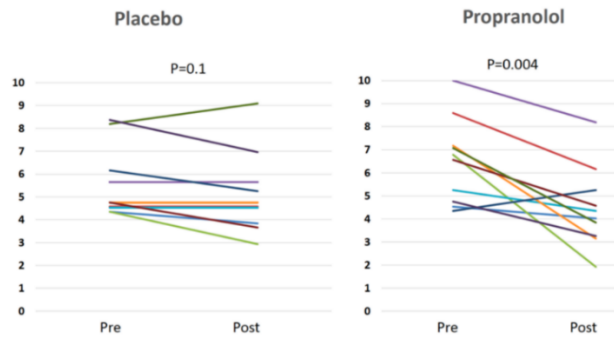
**Propranolol.** The non-selective beta-blocker propranolol is used both topically and systemically to treat superficial and deep infantile hemangiomas, respectively.(Price et al. 2018) While the precise mechanism is unclear, it is likely a combination of vasoconstrictive properties of the drug as well as anti-angiogenic effects(Storch and Hoeger 2010) and decreased migration of endothelial cells in vitro.(Albinana et al. 2012) Infantile hemangiomas and HHT have similar pathophysiologic mechanisms, both showing dysregulated angiogenesis and high levels of tissue VEGF.(Przewratil, Sitkiewicz, and Andrzejewska 2010; Zheng et al. 2013) For these reasons, oral and topical propranolol has been identified as a treatment for HHT-associated epistaxis. The systematic review identified two small studies(Contis et al. 2017; Mei-Zahav et al. 2017) and the aggregate level of evidence was rated as Grade C. The one study of oral propranolol(Contis et al. 2017) included 10 patients in a retrospective case series and 11 patients in a prospective design. In both the retrospective and prospective series, patients reported a significant reduction in epistaxis severity and frequency. Only one patient had to discontinue therapy due to hypotension. In a retrospective case series of topical propranolol by investigators at the National HHT Center in Israel(Mei-Zahav et al. 2017), clinically significant reduction in frequency and severity of epistaxis as measured by the *Epistaxis Severity Scale (ESS)*(Hoag et al. 2010) was reported. In addition, the investigators report improvement in hemoglobin levels. Without a control group, however, it is difficult to conclude that the beneficial outcomes were due to the propranolol or to increased moisture from the gel. The authors of the systematic review(Halderman et al. 2018) concluded about the use of propranolol “Efficacy, or lack thereof, needs to be determined in large, well-designed studies before further use can be promoted”.

**Recent Study.** At the 13<sup>th</sup> HHT International Scientific Conference (June 13-16, 2019), the same National HHT Center in Israel investigation team lead by Dr. Mei-Zahav reported on the results of a Phase II randomized clinical trial followed by an open-label study of topical propranolol gel. The study included 20 subjects equally divided and randomized to propranolol 1.5% in a topical gel vs. topical gel alone for 8 weeks. Approximated data (raw data not yet available) from Mei-Zahav showed that the average within subject decrease in *ESS* in the propranolol group was 2.03 points (SD=1.7) and in the placebo group it was 0.48 points (SD=0.8) for a mean difference of 1.55 points (95% CI: 0.30 to 2.80; Cohen’s  $d = 1.2$ ) in favor of propranolol group (Figure 1).



**Figure 1. Change in *Epistaxis Severity Score* (pre – post) as a Function of Intervention Arm**

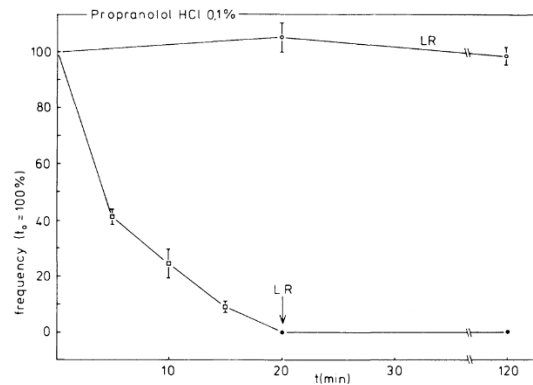
In Figure 2, the spaghetti plot shows individual subject change in *Epistaxis Severity Score* for the subjects in the placebo and propranolol gel arms. Of the 10 patients in the propranolol group, 8 (80%) experienced a clinically meaningful difference while 4 of the 10 (40%) patients in the placebo group experienced a clinically meaningful difference (difference in proportion of 40%; 95% CI -2.3% to 67%).



**Figure 2. Individual Subject Change in Epistaxis Severity Score as a Function of Intervention Arm**

Quality of life, as measured by the SF-12 improved in the propranolol group from  $35 \pm 7$  to  $41 \pm 7$ . There were no cardiovascular adverse effects noted in the trial, and the most common side effect was a burning sensation on application of the gel to the nasal mucosa. The severity was usually mild and resolved within 1-2 weeks in most patients. The other side effect noted was rhinorrhea, which was severe in two patients, resulting in withdrawal of the two patients during the open label period. While 13 out of the 16 patients that received propranolol have continued to use it topically off label, the investigators feel there is a need to modify the drug delivery system and/or the drug preparation to minimize further the side effects.

Intranasal Propranolol is Not Well Tolerated and is Associated with Adverse Effects on Ciliated Epithelium. Several studies demonstrated that intranasal propranolol is not well tolerated and is associated with arrested cilia movement. Van de Donk et al found that doses as low as 0.1% propranolol had a deleterious effect on the cilia of chicken and human tissue. (Merkus et al. 2006) In Figure 3, the effect of propranolol on the ciliary beat frequency over time is shown. As can be seen, propranolol 0.1%, which is considerably lower than the 1.5% dosage used in the Mei-Zahav study, arrested ciliary movement within 20 minutes. The authors concluded that the effect was irreversible since movement did not return within 2 hours after drug was rinsed away.



**Figure 3. The effect of 0.1% propranolol-HCL on the cilia beat frequency of human adenoids. LR – Locke-Ringer solution (control). Reprinted from *The Influence of Drugs on Nasal Ciliary Movement.* (Hermens and Merkus 1987)**

Duchateau et al studied three different propranolol HCL formulations - oral, sublingual, and intranasal in 8 healthy male volunteers. (Duchateau, Zuidema, and Merkus 1986) The 5-mg intranasal dose was administered as a solution of propranolol HCL in 0.2 ml 2% methylcellulose gel, pH 7.4. The authors found that propranolol was rapidly absorbed from the nasal cavity but was not well tolerated as its use was associated with nasal burning immediately after administration. The authors concluded that chronic use of propranolol should be discouraged due to local side effects of stinging sensation in the nose and ciliotoxicity.

**Timolol.** Timolol is a non-selective  $\beta$ -blocker eliminated by the liver and primarily metabolized by CYP2D6. Topical timolol has been used to treat superficial hemangiomas in infants.(Sorrell and Chamlin 2013) Timolol has been shown to have vasoconstriction properties, causes endothelial cell apoptosis, and decreases VEGF expression.(Storch and Hoeger 2010)

In a case report, Olitsky reported on the intranasal use of topical timolol for HHT-associated epistaxis.(Olitsky 2012) The 48-year patient had had multiple procedures and treatments in the past, including nasal cauterization and use of intranasal bevacizumab, but was experiencing 3 to 4 nosebleeds a day. The patient was started on one drop of timolol 0.5% ophthalmic solution in each nostril three times per day. Significant reduction in the frequency and severity of epistaxis was reported in 3 to 4 days, remained after one month, and was not associated with change in blood pressure or heart rate during the treatment.

A prospective study of the impact of timolol ophthalmic solution (0.5%) delivered as a nasal drop into each nostril 3 times daily for 3 months was performed in 12 HHT patients who had previously undergone nasal dermoplasty.(Ichimura et al. 2016) The mean score of bleeding intensity and frequency were markedly reduced after treatment. Two patients who had required transfusions before treatment did not need them afterward, and patients were generally satisfied with the treatment. One patient, a 78-year-old male, developed disequilibrium, hypotension, and bradycardia on the second day of timolol. He then developed heart failure and was removed from the study.

A third study reported on the use of intranasal timolol 0.5% ophthalmological solution in a 59-year-old man with a history of HHT-associated epistaxis but no known cardiac conditions.(Ichimura et al. 2016) He had a significant family history of cardiac disease and developed lightheadedness and sinus bradycardia with right bundle branch block within 3 weeks of starting treatment. The total daily dose of the patient in the case study was 6 mg/day, which is not excessive as the typical oral dose is 10 mg twice daily. The bradycardia and heart blocked stopped with cessation of timolol drops. Through genetic testing, he was subsequently discovered to be an intermediate metabolizer of CYP2D6 enzyme, which was felt to explain the bradycardia. The CYP2D6 gene encodes an enzyme important in the metabolism of many commonly used medications. Variation in CYP2D6 is associated with inter-individual differences in medication response, and genetic testing is used to optimize medication therapy.

## **Conclusion**

The mechanisms of action, published literature, and results of an unpublished study presented at the 13<sup>th</sup> HHT International Scientific Conference suggest a role of  $\beta$ -blockers in the management of HHT-associated epistaxis. The work by Mei-Zahav et al suggest propranolol gel may be an effective treatment for HHT-associated epistaxis. However, intranasal propranolol is not well tolerated and is associated with arrested cilia movement. Topical timolol has advantages over propranolol in that it is well-tolerated and has been shown to not have an effect on nasal mucosa.(Jagdale, Shewale, and Kuchekar 2016) Patients with certain pre-existing heart conditions or metabolizing variants of the liver enzyme CYP2D6 are at increased risk for adverse effects of timolol ophthalmological solution.

Given our understanding of the pathophysiology of HHT-associated epistaxis, mechanism of action, and pharmacokinetics of intranasal timolol, we believe it is now appropriate to conduct a Phase II double-blinded, placebo controlled randomized clinical trial to evaluate the efficacy of intranasal timolol gel. The results of this Phase II study will provide additional information on the benefits and risks of intranasal timolol, which can be used to inform the design of a definitive Phase III study.

## **VI. SPECIFIC AIMS**

The Specific Aims are to determine in adults with HHT-associated epistaxis:

1. If topical timolol gel is more effective than placebo in reducing the frequency and severity of epistaxis.
2. If topical timolol gel is more effective than placebo in improving hemoglobin levels.
3. The frequency of adverse events, side effects, and safety profile of topical timolol gel delivered to the nasal mucosa, and safety profile of topical timolol gel delivered to the nasal mucosa of HHT patients.

## VII. DESIGN PLAN

### Study Type

The study will be a multi-site, double-blind, placebo-controlled randomized clinical trial performed at two tertiary academic medical center HHT Centers of Excellence.

### Blinding

Research participants and the members of the investigative team who will have direct subject interaction will be blinded to treatment assignment. The research statistician, Dr. Kallogjeri, will not be blinded. All subject assessments will be performed without knowledge of treatment.

### Study Population

#### Inclusion Criteria:

- 1) Adults ages 18 and older
- 2) Confirmed clinical (meeting at least 3 of the 4 Curaçao Criteria) or genetic diagnosis of HHT
- 3) *Epistaxis Severity Score (ESS) ≥ 4 and 2* or more nosebleeds per week with a cumulative nosebleed duration of at least 5 minutes per week
- 4) Stable nasal hygiene and medical regimen for preceding 1 month
- 5) Stable epistaxis pattern over the preceding 3 months

#### Exclusion Criteria:

- 1) Contraindications for systemic  $\beta$  adrenergic blocker administration
  - a. Hypersensitivity to  $\beta$  adrenergic blockers
  - b. Asthma or bronchospasm
  - c. Congestive heart failure with LVEF <40%
  - d. Hereditary pulmonary arterial hypertension
  - e. Baseline bradycardia (HR <55 beats per minute)
  - f. Sick Sinus Syndrome
  - g. 2<sup>nd</sup> or 3<sup>rd</sup> degree heart block, left or right bundle branch block, or bifasicular block
  - h. Uncontrolled diabetes mellitus (most recent HbA1c >9%) or diabetic ketoacidosis within last 6 months
  - i. Hypotension (systolic blood pressure < 90)
- 2) Known hypersensitivity to timolol
- 3) Severe peripheral circulatory disturbances (Raynaud phenomenon)
- 4) Known intermediate or poor metabolizer variant of the liver enzyme CYP2D6

- 5) Current use of any of the following known strong CYP2D6 inhibitors: fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin), quinidine, quinine, ritonavir (Norvir), and terbinafine (Lamisil)
- 6) Current use of the following other drugs known to pharmacodynamically interact with timolol: diltiazem, verapamil, digoxin, digitalis, propafenone, disopyramide, clonidine, flecainide, or lidocaine
- 7) Patients currently treated or who plan to initiate treatment with  $\beta$ -blockers
- 8) Use of any anti-angiogenic medication in the last month prior to recruitment, including bevacizumab, pazopanib, thalidomide, or lenalidomide
- 9) Illicit drug use, except marijuana
- 10) Known pheochromocytoma
- 11) Use of anticoagulants, antiplatelet, or fibrinolytic therapies within the last month prior to recruitment, except for low-dose (81 mg or less) of aspirin
- 12) Pregnancy or planned pregnancy in the next 6 months or currently breastfeeding
- 13) Inability to read or understand English
- 14) Inability to complete 8 weeks of therapy for any reason

## Eligibility Determination

To determine potential eligibility for the study, the research team will query the medical record based on the following inclusion/exclusion criteria:

- Age (18 years or older)
- Medication history to assess current use of a  $\beta$ -blocker (exclusion)
- Allergy history to timolol (exclusion)
- Changes in epistaxis care in the last month (exclusion)
- Use of illicit drugs (exclusion)
- History of unresected pheochromocytoma (exclusion)

For those meeting the selection criteria, we will access name, telephone number, age, sex, and date/time of any clinic visits related to HHT and/or epistaxis.

## Recruitment and Consent Process

**Washington University Hereditary Hemorrhagic Telangiectasia (HHT) Center of Excellence.** Adult HHT patients will be recruited from the Washington University Hereditary Hemorrhagic Telangiectasia (HHT) Center of Excellence database and the EPIC electronic medical record. Advertisements describing the study will be posted in the WU Department of Otolaryngology-Head & Neck Surgery clinic and the Division of Pulmonary Medicine. We will attempt to recruit minorities through the assistance of Ms. Sara Kukuljan, Department of Otolaryngology-Head and Neck Surgery Subject Recruitment Coordinator. However, HHT is quite rare in people of African descent and so recruitment of African-Americans with HHT-associated epistaxis is expected to be quite low.

**Froedtert & Medical College of Wisconsin Center of Excellence.** Research subjects will be recruited from HHT patients seeking care from any of the participating physicians at the HHT Center for Advanced Care - Froedtert Hospital.

**CureHHT Website.** Trial information, including inclusion and exclusion criteria, will be posted on CureHHT website *Participate in Research* page [<https://curehht.org/research/participate-in-research/>]

Eligible patients who present to clinic or respond to advertisements will be approached by a research team member to review the informed consent process and thoroughly discuss the research protocol, potential benefits, and risks of the study. The informed consent discussion will take place with the patient and any available family members in person. Any subsequent questions or concerns from the potential participant and any family members will also be addressed at that time. After discussion, the patient will be asked to re-summarize the steps involved in the study to ensure understanding. If interested, written consent will be obtained. Patients will be reminded that study participation is voluntary and will in no way affect their current or future care.

## Variables Under Study

**Assisted Epistaxis Severity Score (aESS).** Assessment of epistaxis severity will be obtained by the validated instrument, the *Epistaxis Severity Score (ESS)*.(Hoag et al. 2010) (Appendix 1) To complete the *ESS*, patients are asked to consider typical symptoms over the previous 3 months. However, with the 8-week duration of our trial, patients will complete the *aESS* in reference to their epistaxis over the past 1 month. The *ESS* contains 6 items – frequency, duration, and intensity of nosebleeds, whether patient has sought medication attention, whether patient is anemic, and whether patient has received a blood transfusion. The overall score ranges from 0 to 10, with severity of nosebleed based on score graded as *None* composite score of 0-1, *Mild* 1-4, *Moderate* 4-7, and *Severe* as 7-10. The minimal important difference noticeable by both patients and clinicians in the *ESS* scoring system is estimated as a change of 0.71.(Yin et al. 2016)

**HHT Endoscopy Score (HES).** The *HHT Endoscopy Score (HES)* is an endoscopy staging score developed as a way to quantify the severity of the patient's nasal telangiectasias as seen on physical exam.(Reh et al. 2014) The *HES* was shown to correlate with the *ESS*. Its parameters are telangiectasia sites, patterns, crusting, location, perforation, density, and relative AVMs. Scoring of the *HES* is illustrated in Appendix 2.

**Epistaxis-Specific Quality-Of-Life Questionnaire (EQQoL).** The *EQQoL* measures 13 items that focus on the impact of epistaxis on the patient's physical, functional, and emotional status and quality of life.(Ingrand et al. 2011) The *EQQoL* was shown to have satisfactory psychometric properties and when combined with the *SF-36* measures both disease-specific and general quality of life. See Appendix 3 for questionnaire.

**Short Form (SF-36).** The *Medical Outcomes Short Form-36 (SF-36)* was developed for use in clinical practice and research to measure general physical functional and quality of life.(Ware and Sherbourne 1992) The *SF-36* includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. See Appendix 4 for questionnaire.

**Patient Satisfaction with Treatment.** The *Treatment Satisfaction Questionnaire for Medication Version II (TSQMII)* was is an 11-question questionnaire adapted and validated from the *TSQM v. I* in order to more precisely collect information (fewer questions and more consistent wording) regarding four general topics of patient satisfaction with treatment: effectiveness, side effects, convenience, and overall satisfaction. (See Appendix 5 questionnaire)(Atkinson et al. 2005; Atkinson et al. 2004)



**Clinical Global Impression Scale (CGI).** The overall response to treatment will be measured with the *Clinical Global Impression (CGI)* scale. The *CGI* Scale measures response to treatment for a number of disorders and has good internal consistency and validity. (Dunlop, Gray, and Rapaport 2017) Upon completion of the study, subjects will be asked to answer the following question: "Overall, how would you rate your response to treatment?" Response options are: *Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, Much Worse, and Very Much Worse.*

**Epistaxis, Transfusion, and Compliance (ETC) Logs.** Patients will be asked to use the Cure HHT app from the online app store if they have a mobile device capable of this feature. It will include a daily reminder to track epistaxis frequency and severity, energy levels, if they received a blood transfusion and/or iron transfusion, and if they took their medication. If the patient answers yes to the transfusion, he or she will be prompted to describe the details of the transfusion, including quantity of units received. The app can directly share the information with the study team at the patient's request.

If patients are not able to use the app for any reason, a text message and/or email will be sent to the patient each evening via the REDCap™ (Research Electronic Database) website that will ask questions about the frequency and severity of epistaxis and energy level that replicates the Cure HHT app. The REDCap™ survey will assess for compliance by asking if the research subject has used the assigned treatment that day. Once each week, the survey will ask the subject if he or she received a blood transfusion that week. REDCap™ is a password-protected site that will keep the information confidential.

## **Methods**

Demographic information, including age, gender, and race, will be collected from each enrolled patient. Data will be collected regarding the duration of each patient's epistaxis history, previous treatments, and estimation of the average number of nosebleeds per day; HHT treatment history; co-morbid conditions, such as hypertension, inhalant allergies, and other blood dyscrasias; risk factors, such as cigarette smoking, use of CPAP, and use of supplemental oxygen; and medications associated with increased bleeding.

At the initial visit, research subjects will complete the informed consent process, *SF-36, ESS*, baseline electrocardiogram (ECG), CYP2D6 enzyme allele, blood pressure (BP), and heart rate (HR). ECGs are to be read by Dr. Murali Chakinala. Subjects will undergo a directed otolaryngology physical exam by Dr. Piccirillo that will include nasal endoscopy to describe nasal mucosa telangiectasias. Dr. Piccirillo will rate the nasal mucosa telangiectasias using the *HES*. Patients will be scheduled for phlebotomy to obtain a blood specimen to measure hemoglobin levels prior to beginning therapy. Baseline daily iron supplementation will also be recorded and it will be recommended to the patient not to alter their daily supplementation of iron or other treatments, unless indicated by a change in epistaxis frequency.

Upon demonstration that patient does not have the CYP2D6 allele associated with a low or intermediate metabolizer of timolol and successful completion of questionnaires, physical examination, and laboratory tests, subjects will be randomized to receive either timolol gel or placebo.

**Pharmaceutical Preparation.** The intervention will be prepared and dispensed by Advanced Rx Pharmacy, Plymouth Meeting, Pennsylvania. Timolol nasal gel 0.1% will be prepared with a poloxamer gel (combination of poloxamer 188 and 407; pH adjusted to 4.5-6.5) and 0.5 ml applied to each nostril twice daily. The total daily dose would amount to 2 mg. Placebo gel is prepared with poloxamers and no active ingredients. Timolol is odorless so the research subjects should not be able to identify the placebo gel from the active gel.

Subjects will be instructed to apply 0.5 ml to the nasal mucosa of each nostril twice daily via 20 mL syringes. The gel will be dispensed in an amber vial with an adapter to which the syringe can attach in order to draw out the medication for each dose. Patients will be supplied with one syringe per day for a total of 56 syringes. They will be given alcohol wipes to clean the syringe between the morning and evening gel application. When the syringes are distributed, the research assistants will make sure that the patient understands how to apply correctly the medication to the nasal cavity.

BP and HR measurements will be obtained by the subject weekly at home with the use of the blood pressure monitor given to them at the beginning of the study and blood pressures will be reported via the use of REDCap™. Subjects will also be instructed to report any local or systemic side effects throughout the duration of the study. Telephone calls with the study team at the end of Week 1 and again at Week 4 will be arranged.

After 8 weeks of intervention, subjects will be asked to return to clinic and the physician will perform nasal endoscopy and complete the *HES* scale. Subjects will have blood pressure and heart rate measurements. Subjects will complete the *SF-36*, *ESS*, *CGI*, *EQQoL*, and the *TSQMII* questionnaires. To assess the quality of the blind, subjects will be asked which arm of the study they thought they were randomized. Subjects will also be asked whether they would recommend the treatment to a friend or family member if they suffered with HHT-associated epistaxis. A follow-up blood draw to measure hemoglobin and hematocrit will be completed.

It will be emphasized to the patient not to change their current nasal hygiene regimen (e.g., nasal saline spray) or other chronic treatments (e.g., tranexamic acid).

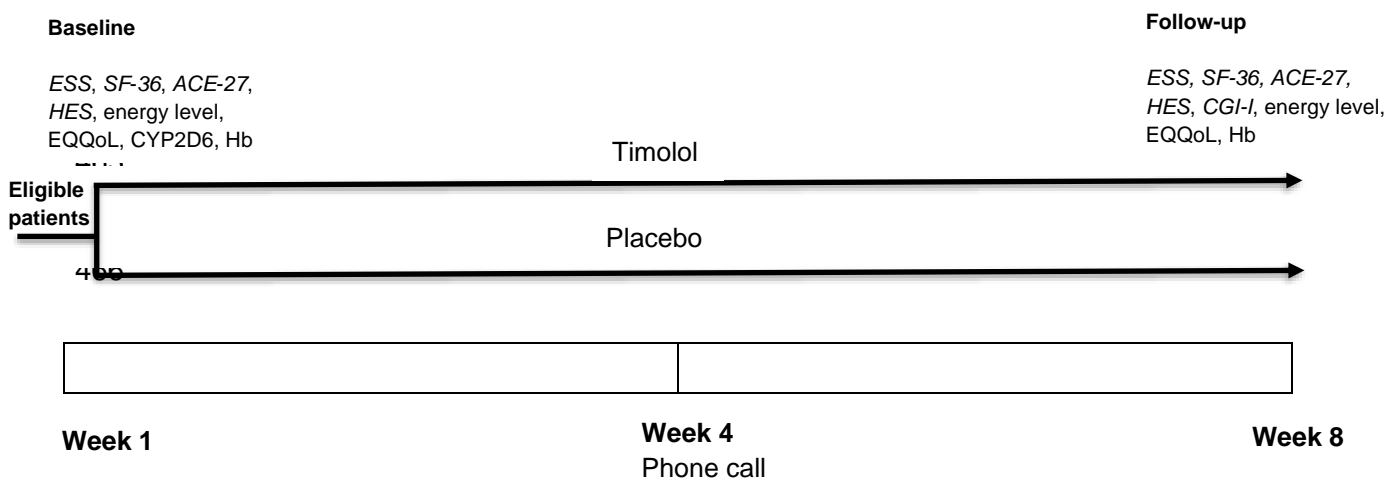
**Primary Outcome:**

- 1) Mean change in Epistaxis Severity Score (ESS) between baseline and follow-up.

**Secondary Outcomes:**

- 1) Clinical Global Impression – Improvement (CGI-I) Score
- 2) Mean change in hemoglobin
- 3) Change in intensity of telangiectasias in the nasal mucosa as determined by the HHT endoscopic scale (HES)

**Summary of Project Design**



## VIII. SAMPLE SIZE AND PLANNED STATISTICAL ANALYSIS

### Sample Size

Sample size estimate for the proposed study were derived from the single study (Ichimura et al. 2016) of within subject change in severity of epistaxis associated with timolol ophthalmic solution (0.5%) as a nasal drop. In that study, 9 of the 11 subjects (82%) experienced a reduction in the severity of bleeds as measured on a 5-point Likert scale. We hypothesize a similar response (82%) in our proposed study among subjects randomized to receive timolol gel and a 20% response rate among subjects randomized to placebo gel, corresponding to a difference of 62%.

A power analysis was performed using Fisher's exact test in G-Power 3.1.2. We estimate that a total sample size of 24 patients (ie., 12 in each arm) is needed to allow us to detect with 80% power at the 2-sided alpha level of 0.05 a difference of 62% or more in the percent of subjects who experience reduction of severity of bleeds between treatment groups. Considering a 20% drop out rate, we plan to enroll 30 subjects in the study.

### Statistical Analysis

Standard descriptive statistics will be used to describe distribution of baseline characteristics in each of the study groups. The effect of the intervention will be measured as the difference in the within-subject change (baseline – 8-week follow-up) in *ESS* scores between the two treatment groups calculated as shown below.

#### 1) Within subject difference with each treatment group

$$\Delta ESS_{\text{Timolol}} = (ESS_{\text{Timolol\_base}} - ESS_{\text{Timolol\_8-Week}})$$

$$\Delta ESS_{\text{Control}} = (ESS_{\text{Timolol\_base}} - ESS_{\text{Timolol\_8-Week}})$$

#### 2) Between treatment difference

$$\Delta ESS_{\text{Timolol}} - \Delta ESS_{\text{Control}}$$

The 95%CI around this effect size will be determined to assess the precision of the observed effect and whether a clinically meaningful difference is plausible given the observed results.

An independent sample t-test will be used to compare the change in scores between the two study groups. If potential confounding factors are identified, a mixed model analysis will be employed to compare the change in the scores between the two study groups after controlling for potential confounding factors.

Appropriate analyses will be performed for the secondary outcome measures.

## IX. EXEMPTION FROM IND REQUIREMENTS

The use of timolol in topical nasal gel is a change in the approved route of administration. An exemption from IND requirements will be requested as the proposed use of timolol in this study fulfills all of the criteria for exemption.

- 1) Timolol is lawfully marketed in the United States.

- 2) This study is not intended to be reported to the FDA in support of a new indication or significant change in labeling.
- 3) This study is not intended to support a significant change in the advertising for the drug.
- 4) The study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of timolol.
- 5) The study will be conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- 6) The study is not intended to promote or commercialize timolol.

## X. ASSESSMENT OF TREATMENT SAFETY

### Treatment Safety

Treatment safety information comes from three different sources. First, a study was conducted to assess the properties of 1% (10 mg) topical intranasal timolol gel and to optimize controlled release *in situ* nasal delivery.(Jagdale, Shewale, and Kuchekar 2016) The authors studied timolol and Poloxamer 407 polymer interaction and were able to show that there was no chemical reaction between timolol and the polymer.(Nieminen et al. 2007; Volotinen et al. 2011) The authors also demonstrated no histological changes to nasal mucosa after the study. The authors concluded that the combination of timolol with Poloxamer 407 was associated with adequate gelation temperature, mucoadhesive strength, and *in situ* controlled release of timolol. They concluded that timolol gel is safe for nasal administration. Second, Olitsky studied intranasal delivery of one drop of timolol 0.5% as ophthalmic solution to each nostril three times daily for a total daily dose of 1.5 mg in one adult patient with HHT-associated epistaxis.(Olitsky 2012) The drug was well tolerated with no change in blood pressure or heart rate; no other side effects were reported. Third, timolol 0.5% ophthalmic drops administered intranasally has been associated with systemic side effects, especially in patients with CYP2D6 enzyme variants.(Epperla, Brilliant, and Vidaillet 2014) Ocular administration of timolol has been associated with systemic adverse effects, including bradycardia.(Canpolat et al. 2013; Nieminen et al. 2007; Volotinen et al. 2011) (See Appendix 6 – Adverse Reactions). Among the various symptoms of systematically absorbed ophthalmic timolol, change in heart rate is the most frequent and is more likely with the 0.5% aqueous rather than the 0.1% hydrogel formulation.(Nieminen et al. 2007) Since the pharmacokinetics of timolol are dependent on the CYP2D6 polymorphic enzyme, the individual patient phenotype for this enzyme will dictate plasma concentrations and frequency of adverse events. Four major phenotypes of CYP2D6 metabolizers have been identified: *Poor*, *Intermediate*, *Extensive*, and *Ultrarapid*.(Ingelman-Sundberg and Rodriguez-Antona 2005; Sikka et al. 2005; Volotinen et al. 2011) In one study, it was found that *Poor* metabolizers had a 2.5-fold higher plasma concentration than *Extensive* metabolizers after application of timolol 0.5% aqueous eye drops.(Nieminen et al. 2007). Timolol eye drops delivered intranasally was associated with greater  $\beta$ -blockade in *Poor* metabolizers as compared with *Extensive* metabolizers. Thus, the metabolism of systematically absorbed timolol is clearly related to the phenotype of the individual for the CYP2D6 enzyme.

### Frequency of Different CYP2D6 Alleles in the Population

The frequency of different CYP2D6 alleles and thus the ability to metabolize timolol was studied in population of 104,509 de-identified patient samples from across the United States between February 2015 and March 2016.(Del Tredici et al. 2018) The frequency distribution of various phenotypes of CYP2D6 alleles was observed to be: ultra-rapid metabolizers (2.2%), normal metabolizers (81%), intermediate

metabolizers (11%), and poor metabolizers (6%). Therefore, an estimated total of 17% or 5 subjects otherwise eligible for the study would be expected to be at increased risk of side effects due to timolol compared to the normal metabolizers and therefore will be excluded.

While ophthalmic solution is readily absorbed into the blood stream, CYP2D6 genetic testing is not commonly done for open-angle glaucoma patients prior to initiation of timolol therapy. To prevent cardiovascular side effects, it is recommended that glaucoma patients be screened for coexisting conditions and consideration of genetic phenotypic CYP2D6 status testing if readily available.(Maenpaa and Pelkonen 2016)

In this study, all eligible patients will undergo CYP2D6 testing, ECG, BP, and HR readings at initial visit. Patients with a CYP2D6 allele that is associated with an intermediate or poor metabolizer or an ECG that demonstrates conduction abnormalities, such as second-degree and third-degree AV block and/or clinically significant bradycardia will be excluded from the study. Enrolled patients will be given a blood pressure monitor by the study team and taught how to use it at their baseline visit. They will be instructed to take and report weekly BP and HR to the study team in addition to local or systemic side effects. Patients will be called at the end of Week 1 and Week 4 of the study to answer any questions or concerns they may have as well as to ask if they have experienced any side effects. During these phone calls, patients will be asked whether they have changed their daily iron supplementation or blood transfusion pattern from baseline. If patients have an increase in nosebleeds for any reason, they will be asked to contact the study team or report to the emergency department, depending on the severity.

Any of the following will be considered an indication to stop the study:

- 1) Asymptomatic systolic BP drop to less than 80 mmHg or a drop of 20% from baseline systolic BP
- 2) Symptomatic blood pressure drop
- 3) A drop of HR to less than 50/min
- 4) Any clinical signs of heart block
- 5) Grade >2 local or systemic side effects, such as local irritation or an allergic reaction to the medication
- 6) Patient's request or physician's determination of continuing the study to be no longer safe

In the event of a Serious Adverse Event determined by the PI to necessitate the breaking of the blind, the intervention assignment will be revealed by Dr. Kallogjeri to the medical staff doctor caring for the patient. In the event Dr. Kallogjeri is unable to be reached in a time needed, to assure the safety of the subject, the blind can be broken by Sara Kukuljan, RN or Dr. Piccirillo and information will be shared with the medical staff assuming care for the research subject.

## **XI. Data and Safety Monitoring**

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations, this study will have a monitoring board comprised of Dr. Piccirillo, Dr. Chakinala, Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. The monitoring board will meet to review data at least every 6 months. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

## **XII. Ethical considerations**

While patients will be randomly selected to receive timolol, an FDA-approved drug, the efficacy and safety, including local and/or systemic reactions, are largely unknown when applied in topical gel form. Patients will be informed in the informed consent process that they may or may not personally benefit from the study and that the data obtained from the study will be used to inform the future care of HHT patients with epistaxis. There will be phone assistance available 24/7 during the study period to report any possible adverse reactions. To reduce the risk of breach of confidentiality, all data forms with identifying information will be kept in locked cabinets and only members of the study team will have access to secured files. There are no financial conflicts of interest.

### XIII. REFERENCES

- Albinana, V., L. Recio-Poveda, R. Zarrabeitia, C. Bernabeu, and L.M. Botella. 2012. Propranolol as antiangiogenic candidate for the therapy of hereditary haemorrhagic telangiectasia. *Thromb Haemost* 108: 41-53.
- Atkinson, M.J., R. Kumar, J.C. Cappelleri, and S.L. Hass. 2005. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health* 8 Suppl 1: S9-S24.
- Atkinson, M.J., A. Sinha, S.L. Hass, S.S. Colman, R.N. Kumar, M. Brod, and C.R. Rowland. 2004. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2: 12.
- Canpolat, U., K.M. Gurses, K. Aytemir, and A. Oto. 2013. Severe bradycardia and syncope due to topical ophthalmic timolol. *Herz* 38: 556-7.
- Contis, A., N. Gensous, J.F. Viallard, C. Goizet, C. Leaute-Labreze, and P. Duffau. 2017. Efficacy and safety of propranolol for epistaxis in hereditary haemorrhagic telangiectasia: retrospective, then prospective study, in a total of 21 patients. *Clin Otolaryngol* 42: 911-7.
- Del Tredici, A.L., A. Malhotra, M. Dedek, F. Espin, D. Roach, G.D. Zhu, J. Volland, and T.A. Moreno. 2018. Frequency of CYP2D6 Alleles Including Structural Variants in the United States. *Front Pharmacol* 9: 305.
- Dheyauldeen, S., M. Abdelnoor, and G. Bachmann-Harildstad. 2011. The natural history of epistaxis in patients with hereditary hemorrhagic telangiectasia in the Norwegian population: a cross-sectional study. *Am J Rhinol Allergy* 25: 214-8.
- Duchateau, G.S., J. Zuidema, and F.W. Merkus. 1986. Bioavailability of propranolol after oral, sublingual, and intranasal administration. *Pharm Res* 3: 108-11.
- Dunlop, B.W., J. Gray, and M.H. Rapaport. 2017. Transdiagnostic Clinical Global Impression Scoring for Routine Clinical Settings. *Behav Sci (Basel)* 7.
- Epperla, N., M.H. Brilliant, and H. Vidaillet. 2014. Topical timolol for treatment of epistaxis in hereditary haemorrhagic telangiectasia associated with bradycardia: a look at CYP2D6 metabolising variants. *BMJ Case Rep* 2014.
- Fang, J., X. Chen, B. Zhu, H. Ye, W. Zhang, J. Guan, and K. Su. 2017. Thalidomide for Epistaxis in Patients with Hereditary Hemorrhagic Telangiectasia: A Preliminary Study. *Otolaryngol Head Neck Surg* 157: 217-21.
- Faughnan, M.E., V.A. Palda, G. Garcia-Tsao, U.W. Geithoff, J. McDonald, D.D. Proctor, J. Spears, D.H. Brown, E. Buscarini, M.S. Chesnutt, V. Cottin, A. Ganguly, J.R. Gossage, A.E. Guttmacher,

- R.H. Hyland, S.J. Kennedy, J. Korzenik, J.J. Mager, A.P. Ozanne, J.F. Piccirillo, D. Picus, H. Plauchu, M.E. Porteous, R.E. Pyeritz, D.A. Ross, C. Sabba, K. Swanson, P. Terry, M.C. Wallace, C.J. Westermann, R.I. White, L.H. Young, R. Zarrabeitia, and H.H.T.F.I.-G.W. Group. 2011. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet* 48: 73-87.
- Fernandez, L.A., E.M. Garrido-Martin, F. Sanz-Rodriguez, J.R. Ramirez, C. Morales-Angulo, R. Zarrabeitia, A. Perez-Molino, C. Bernabeu, and L.M. Botella. 2007. Therapeutic action of tranexamic acid in hereditary haemorrhagic telangiectasia (HHT): regulation of ALK-1/endothelin pathway in endothelial cells. *Thromb Haemost* 97: 254-62.
  - Gaillard, S., S. Dupuis-Girod, F. Boutitie, S. Riviere, S. Moriniere, P.Y. Hatron, G. Manfredi, P. Kaminsky, A.L. Capitaine, P. Roy, F. Gueyffier, H. Plauchu, and A.S. Group. 2014. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. *J Thromb Haemost* 12: 1494-502.
  - Geisthoff, U.W., U.T. Seyfert, M. Kubler, B. Bieg, P.K. Plinkert, and J. Konig. 2014. Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid - a double-blind placebo-controlled cross-over phase IIIB study. *Thromb Res* 134: 565-71.
  - Group, O.C.E.-B.M.L.o.E.W. 2011. The Oxford 2011 Levels of Evidence. Available at <http://www.cebm.net/ocebml-levels-of-evidence/>.
  - Halderman, A.A., M.W. Ryan, C. Clark, R. Sindwani, D.D. Reh, D.M. Poetker, R. Invernizzi, and B.F. Marple. 2018. Medical treatment of epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review. *Int Forum Allergy Rhinol* 8: 713-28.
  - Hermens, W.A., and F.W. Merkus. 1987. The influence of drugs on nasal ciliary movement. *Pharm Res* 4: 445-9.
  - Hoag, J.B., P. Terry, S. Mitchell, D. Reh, and C.A. Merlo. 2010. An epistaxis severity score for hereditary hemorrhagic telangiectasia. *Laryngoscope* 120: 838-43.
  - Ichimura, K., H. Kikuchi, S. Imayoshi, and M.S. Dias. 2016. Topical application of timolol decreases the severity and frequency of epistaxis in patients who have previously undergone nasal dermoplasty for hereditary hemorrhagic telangiectasia. *Auris Nasus Larynx* 43: 429-32.
  - Ingelman-Sundberg, M., and C. Rodriguez-Antona. 2005. Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy. *Philos Trans R Soc Lond B Biol Sci* 360: 1563-70.
  - Ingrand, I., P. Ingrand, B. Gilbert-Dussardier, G. Defosse, V. Jouhet, V. Migeot, X. Dufour, and J.M. Klossek. 2011. Altered quality of life in Rendu-Osler-Weber disease related to recurrent epistaxis. *Rhinology* 49: 155-62.
  - Invernizzi, R., F. Quaglia, C. Klersy, F. Pagella, F. Ornati, F. Chu, E. Matti, G. Spinozzi, S. Plumitallo, P. Grignani, C. Olivieri, R. Bastia, F. Bellistri, C. Danesino, M. Benazzo, and C.L. Balduini. 2015. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. *Lancet Haematol* 2: e465-73.
  - Jagdale, S., N. Shewale, and B.S. Kuchekar. 2016. Optimization of Thermoreversible In Situ Nasal Gel of Timolol Maleate. *Scientifica (Cairo)* 2016: 6401267.
  - Lebrin, F., S. Srun, K. Raymond, S. Martin, S. van den Brink, C. Freitas, C. Breant, T. Mathivet, B. Larrivee, J.L. Thomas, H.M. Arthur, C.J. Westermann, F. Disch, J.J. Mager, R.J. Snijder, A.

- Eichmann, and C.L. Mummery. 2010. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. *Nat Med* 16: 420-8.
- Maenpaa, J., and O. Pelkonen. 2016. Cardiac safety of ophthalmic timolol. *Expert Opin Drug Saf* 15: 1549-61.
  - McDonald, J., P. Bayrak-Toydemir, and R.E. Pyeritz. 2011. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. *Genet Med* 13: 607-16.
  - Mei-Zahav, M., H. Blau, E. Bruckheimer, E. Zur, and N. Goldschmidt. 2017. Topical propranolol improves epistaxis in patients with hereditary hemorrhagic telangiectasia - a preliminary report. *J Otolaryngol Head Neck Surg* 46: 58.
  - Merkus, P., F.A. Ebbens, B. Muller, and W.J. Fokkens. 2006. Influence of anatomy and head position on intranasal drug deposition. *European Archives of Oto-rhino-laryngology* 263: 827-32.
  - Minami, K., and T. Haji. 2016. Intranasal topical estrogen in the management of epistaxis in hereditary hemorrhagic telangiectasia. *Acta Otolaryngol* 136: 528-31.
  - Nieminen, T., T. Lehtimäki, J. Maenpaa, A. Ropo, H. Uusitalo, and M. Kahonen. 2007. Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. *Scand J Clin Lab Invest* 67: 237-45.
  - Olitsky, S.E. 2012. Topical timolol for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *Am J Otolaryngol* 33: 375-6.
  - Peng, H.L., Y.F. Yi, S.K. Zhou, S.S. Xie, and G.S. Zhang. 2015. Thalidomide Effects in Patients with Hereditary Hemorrhagic Telangiectasia During Therapeutic Treatment and in Fli-EGFP Transgenic Zebrafish Model. *Chin Med J (Engl)* 128: 3050-4.
  - Price, A., S. Rai, R.W.J. McLeod, J.C. Birchall, and H.A. Elhassan. 2018. Topical propranolol for infantile haemangiomas: a systematic review. *J Eur Acad Dermatol Venereol* 32: 2083-9.
  - Przewratil, P., A. Sitkiewicz, and E. Andrzejewska. 2010. Local serum levels of vascular endothelial growth factor in infantile hemangioma: intriguing mechanism of endothelial growth. *Cytokine* 49: 141-7.
  - Reh, D.D., L.X. Yin, K. Laaeq, and C.A. Merlo. 2014. A new endoscopic staging system for hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol* 4: 635-9.
  - Sikka, R., B. Magauran, A. Ulrich, and M. Shannon. 2005. Bench to bedside: Pharmacogenomics, adverse drug interactions, and the cytochrome P450 system. *Acad Emerg Med* 12: 1227-35.
  - Sorrell, J., and S.L. Chamlin. 2013. Topical timolol 0.5% gel-forming solution for small deep facial infantile hemangiomas. *Pediatr Dermatol* 30: 592-4.
  - Storch, C.H., and P.H. Hoeger. 2010. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol* 163: 269-74.
  - Volotinen, M., J. Hakkola, O. Pelkonen, H. Vapaatalo, and J. Maenpaa. 2011. Metabolism of ophthalmic timolol: new aspects of an old drug. *Basic Clin Pharmacol Toxicol* 108: 297-303.
  - Ware, J.E., and C.D. Sherbourne. 1992. The MOS 36 Item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med. Care* 30: 473-83.
  - Whitehead, K.J., N.B. Sautter, J.P. McWilliams, M.M. Chakinala, C.A. Merlo, M.H. Johnson, M. James, E.M. Everett, M.S. Clancy, M.E. Faughnan, S.P. Oh, S.E. Olitsky, R.E. Pyeritz, and J.R. Gossage. 2016. Effect of Topical Intranasal Therapy on Epistaxis Frequency in Patients With Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial. *JAMA* 316: 943-51.



- 0 • Yaniv, E., M. Preis, T. Hadar, J. Shvero, and M. Haddad. 2009. Antiestrogen therapy for hereditary  
1 hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *Laryngoscope* 119: 284-  
2 8.
- 3 • Yaniv, E., M. Preis, J. Shevro, B. Nageris, and T. Hadar. 2011. Anti-estrogen therapy for hereditary  
4 hemorrhagic telangiectasia - a long-term clinical trial. *Rhinology* 49: 214-6.
- 5 • Yin, L.X., D.D. Reh, J.B. Hoag, S.E. Mitchell, S.C. Mathai, G.M. Robinson, and C.A. Merlo. 2016.  
6 The minimal important difference of the epistaxis severity score in hereditary hemorrhagic  
7 telangiectasia. *Laryngoscope* 126: 1029-32.
- 8 • Zaffar, N., T. Ravichakaravathy, M.E. Faughnan, and N. Shehata. 2015. The use of anti-fibrinolytic  
9 agents in patients with HHT: a retrospective survey. *Ann Hematol* 94: 145-52.
- 0 • Zheng, J.W., L. Zhang, Q. Zhou, H.M. Mai, Y.A. Wang, X.D. Fan, Z.P. Qin, X.K. Wang, and Y.F.  
1 Zhao. 2013. A practical guide to treatment of infantile hemangiomas of the head and neck. *Int J Clin*  
2 *Exp Med* 6: 851-60.  
3  
4

## XIV. APPENDICES

### Appendix 1

#### Epistaxis Severity Score Questionnaire:

1. How often do TYPICALLY have nose bleeding?

- Less than monthly
- Once per month
- Once per week
- Several per week
- Once per day
- Several per day

2. How long do your TYPICAL nose bleeding episodes 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?

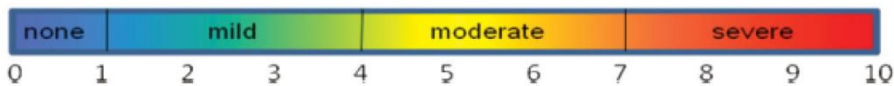
- No
- Yes

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

- No
- Yes

Raw Epistaxis Severity Score

Normalized Epistaxis Severity Score



#### Scoring Guide:

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			
6	No	0	x	0.31 (0.31 Den)	
	Yes	1			
TOTAL =				Denominator (Sum Den)	Raw Score

$$\text{Normalized HHT-ESS} = \left[ \frac{\text{Raw Score}}{\text{Denominator (2.71)}} \right] \times 10$$



7 **Appendix 2.**

8 Scoring of the *HHT Endoscopic Scoring System (HES)*.

9

	Endoscopic staging system score			
	0	1	2	3
Sites	1	2-3	4-5	≥6
Patterns	Punctuate	Interconnected	AVMs	
Crusting	None	Mild	Moderate/severe	
Location	Anterior septum	Inferior turbinate	Middle turbinate	Posterior septum
Perforation	No	Yes		
Density	>10 mm	5-10 mm	2-4 mm	<1 mm
Relative AVMs	None	<25%	25-50%	>50%

0  
1  
2

3  
4  
5  
6  
7

### Appendix 3. Epistaxis-Specific Quality-of-Life Questionnaire (EQQoL)

#### Epistaxis-Specific Quality-of-Life Questionnaire (EQQoL)

Patient ID \_\_\_\_\_ Date \_\_\_\_\_

Please fill out the following survey that measures the burden of your nose bleeds upon your life.

- 1 = All the time
- 2 = Usually (About 90% of the time)
- 3 = Frequently (About 70% of the time)
- 4 = Sometimes (About 50% of the time)
- 5 = Occasionally (About 30% of the time)
- 6 = Rarely (Less than 10% of the time)
- 7 = Very rarely or never

1) Have you ever felt bothered by having a blocked-up nose?	1	2	3	4	5	6	7
2) Have you felt restricted by the weather or had to avoid going outdoors because of your nose bleeds?	1	2	3	4	5	6	7
3) Have you felt frustrated because your nose bleeds have stopped you doing what you wanted?	1	2	3	4	5	6	7
4) Have you been bothered by the presence of crusts in your nose?	1	2	3	4	5	6	7
5) Have you ever been afraid you could not stop a nose bleed?	1	2	3	4	5	6	7
6) Have you been tired or breathless because of your nose bleeds?	1	2	3	4	5	6	7
7) Have you taken any precautions to prevent your nose bleeds?	1	2	3	4	5	6	7
8) Have you ever spent a bad night because of your nose bleeds?	1	2	3	4	5	6	7
9) Have you ever been anxious because you have nose bleeds?	1	2	3	4	5	6	7
10) Do your nose bleeds restrict your relationships with friends or family?	1	2	3	4	5	6	7
11) Have your nose bleeds created problems with your work?	1	2	3	4	5	6	7
12) Have your nose bleeds restricted your leisure activities?	1	2	3	4	5	6	7
13) Have your nose bleeds restricted your mental activities?	1	2	3	4	5	6	7

0  
1  
2  
3 **Appendix 4.**

4 **SF-36:** Accessible at [https://www.rand.org/health-care/surveys\\_tools/mos/36-item-short-form/survey-](https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html)  
5 [instrument.html](https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html)



Patient ID \_\_\_\_\_ Date \_\_\_\_\_



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RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

# 36- Item Short Form Survey Instrument (SF-36)

## RAND 36-Item Health Survey 1.0 Questionnaire Items

9 **Choose one option for each questionnaire item.**

0  
1 1. In general, would you say your health is:

- 2  1 - Excellent
- 3  2 - Very good
- 4  3 - Good
- 5  4 - Fair
- 6  5 - Poor
- 

7  
8  
9 2. **Compared to one year ago**, how would you rate your health in general **now**?

- 0  1 - Much better now than one year ago
- 1  2 - Somewhat better now than one year ago
- 2  3 - About the same
- 3  4 - Somewhat worse now than one year ago
- 4  5 - Much worse now than one year ago



6 The following items are about activities you might do during a typical day. Does  
7 **your health now limit you** in these activities? If so, how much?  
8

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. <b>Vigorous activities</b> , such as running, lifting heavy objects, participating in strenuous sports	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
4. <b>Moderate activities</b> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
5. Lifting or carrying groceries	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
6. Climbing <b>several</b> flights of stairs	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
7. Climbing <b>one</b> flight of stairs	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
8. Bending, kneeling, or stooping	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
9. Walking <b>more than a mile</b>	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
10. Walking <b>several blocks</b>	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
11. Walking <b>one block</b>	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
12. Bathing or dressing yourself	1	2	3

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During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

- |   | 843<br>844 | Yes                   | No                    |
|---|------------|-----------------------|-----------------------|
| 13. Cut down the <b>amount of time</b> you spent on work or other activities                          | 845        | <input type="radio"/> | <input type="radio"/> |
|   | 846        | 1                     | 2                     |
|   | 847        |                       |                       |
| 14. <b>Accomplished less</b> than you would like  | 848        | <input type="radio"/> | <input type="radio"/> |
|   | 849        | 1                     | 2                     |
|   | 850        |                       |                       |
| 15. Were limited in the <b>kind</b> of work or other activities                                       | 851        | <input type="radio"/> | <input type="radio"/> |
|   | 852        | 1                     | 2                     |
| 16. Had <b>difficulty</b> performing the work or other activities (for example, it took extra effort) |            | <input type="radio"/> | <input type="radio"/> |
|   |            | 1                     | 2                     |

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

- |  | Yes                     | No                      |
|--|-------------------------|-------------------------|
| 17. Cut down the <b>amount of time</b> you spent on work or other activities | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 18. <b>Accomplished less</b> than you would like                             | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 19. Didn't do work or other activities as <b>carefully</b> as usual          | <input type="radio"/> 1 | <input type="radio"/> 2 |

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely



8 21. How much **bodily** pain have you had during the **past 4 weeks**?

- 9  1 - None
  - 0  2 - Very mild
  - 1  3 - Mild
  - 2  4 - Moderate
  - 3  5 - Severe
  - 4  6 - Very severe
- 

6 22. During the **past 4 weeks**, how much did **pain** interfere with your  
7 normal work (including both work outside the home and housework)?

- 9  1 - Not at all
  - 0  2 - A little bit
  - 1  3 - Moderately
  - 2  4 - Quite a bit
  - 3  5 - Extremely
-



9  
0  
5 - None of the time

---

911 How TRUE or FALSE is **each** of the following statements for you.

912

- |  | Definitely true         | Mostly true             | Don't know              | Mostly false            | Definitely false        |
|--|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| 33. I seem to get sick a little easier than other people | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 34. I am as healthy as anybody I know                    | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 35. I expect my health to get worse                      | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 36. My health is excellent                               | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |

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## ABOUT

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**Appendix 5.**  
***Treatment Satisfaction Questionnaire for Medication Version II***  
***(TSQMII)***

**Patient ID** \_\_\_\_\_ **Date** \_\_\_\_\_

- 1) How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
  - 1 Extremely Dissatisfied
  - 2 Very Dissatisfied
  - 3 Dissatisfied
  - 4 Somewhat Satisfied
  - 5 Satisfied
  - 6 Very Satisfied
  - 7 Extremely Satisfied
  
- 2) How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
  - 1 Extremely Dissatisfied
  - 2 Very Dissatisfied
  - 3 Dissatisfied
  - 4 Somewhat Satisfied
  - 5 Satisfied
  - 6 Very Satisfied
  - 7 Extremely Satisfied
  
- 3) As a result of taking this medication, do you experience any side effects at all?
  - 1 Yes
  - 0 No
  
- 4) How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?
  - 1 Extremely Dissatisfied
  - 2 Very Dissatisfied
  - 3 Somewhat Dissatisfied
  - 4 Slightly Dissatisfied
  - 5 Not at all Dissatisfied
  
- 5) How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?
  - 1 Extremely Dissatisfied
  - 2 Very Dissatisfied
  - 3 Somewhat Dissatisfied
  - 4 Slightly Dissatisfied
  - 5 Not at all Dissatisfied
  
- 6) How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?
  - 1 Extremely Dissatisfied
  - 2 Very Dissatisfied
  - 3 Somewhat Dissatisfied

- 999 4 Slightly Dissatisfied  
000 5 Not at all Dissatisfied  
001
- 002 7) How satisfied or dissatisfied are you with how easy the medication is to use?  
003 1 Extremely Dissatisfied  
004 2 Very Dissatisfied  
005 3 Dissatisfied  
006 4 Somewhat Satisfied  
007 5 Satisfied  
008 6 Very Satisfied  
009 7 Extremely Satisfied  
010
- 011 8) How satisfied or dissatisfied are you with how easy it is to plan when you will use the  
012 medication each time?  
013 1 Extremely Dissatisfied  
014 2 Very Dissatisfied  
015 3 Dissatisfied  
016 4 Somewhat Satisfied  
017 5 Satisfied  
018 6 Very Satisfied  
019 7 Extremely Satisfied  
020
- 021 9) How satisfied or dissatisfied are you by how often you are expected to use/take the medication?  
022 1 Extremely Dissatisfied  
023 2 Very Dissatisfied  
024 3 Dissatisfied  
025 4 Somewhat Satisfied  
026 5 Satisfied  
027 6 Very Satisfied  
028 7 Extremely Satisfied  
029
- 030 10) How satisfied are you that the good things about this medication outweigh the bad things?  
031 1 Extremely Dissatisfied  
032 2 Very Dissatisfied  
033 3 Dissatisfied  
034 4 Somewhat Satisfied  
035 5 Satisfied  
036 S24 Atkinson et al.  
037 6 Very Satisfied  
038 7 Extremely Satisfied  
039
- 040 11) Taking all things into account, how satisfied or dissatisfied are you with this medication?  
041 1 Extremely Dissatisfied  
042 2 Very Dissatisfied  
043 3 Dissatisfied  
044 4 Somewhat Satisfied  
045 5 Satisfied  
046 6 Very Satisfied  
047 7 Extremely Satisfied  
048



**ADVERSE REACTIONS**

From NDA 18086/S-076

Reference ID: 3969708

Pages 9, 10

Obtained from:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/018086s076lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018086s076lbl.pdf)

Accessed: July 23, 2019

**TIMOPTIC® 0.25% and 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)**

The most frequently reported adverse experiences of timolol ophthalmic solution (approximately one in eight patients) have been burning and stinging of the eye upon instillation.

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

- A. **BODY AS A WHOLE.** Headache, asthenia/fatigue, and chest pain.
- B. **CARDIOVASCULAR.** Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
- C. **DIGESTIVE.** Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
- D. **IMMUNOLOGIC.** Systemic lupus erythematosus.
- E. **NERVOUS SYSTEM/PSYCHIATRIC.** Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
- F. **SKIN.** Alopecia and psoriasiform rash or exacerbation of psoriasis.
- G. **HYPERSENSITIVITY.** Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
- H. **RESPIRATORY.** Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
- I. **ENDOCRINE.** Masked symptoms of hypoglycemia in diabetic patients.
- J. **SPECIAL SENSES.** Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery; and tinnitus.
- K. **UROGENITAL.** Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.



1           **Efficacy of Timolol in a Novel Intranasal Thermosensitive Gel for Hereditary**  
2           **Hemorrhagic Telangiectasia-Associated Epistaxis: A Randomized Clinical Trial**

3  
4  
5           The following protocol modifications occurred during the duration of our study:

- 6  
7           1) The study was a single institution randomized clinical trial. The planned second  
8           institution, Froedtert & Medical College of Wisconsin HHT Center of Excellence,  
9           could not acquire IRB approval for a medication delivered via courier delivery  
10          services.  
11          2) The HHT Endoscopy Score (HES) was removed from the study once the COVID-19  
12          pandemic limited in-person visits.  
13          3) The *Treatment Satisfaction Questionnaire for Medication Version II (TSQMI)* was  
14          removed from the study due to possible participant burden with excess  
15          questionnaires.  
16          4) The CYP2D6 genetic testing was removed from the study after receiving ambiguous  
17          results of the first 5 participants with unclear phenotypes.  
18          5) A participant was enrolled who did not meet the screening criterion *Epistaxis Severity*  
19          *Score* of 4 but did meet the weekly frequency and duration criteria.  
20  
21  
22