TACRO
Efficacy and safety of a 0.1% tacrolimus nasal ointment as a treatment for epistaxis in Hemorrhagic Hereditary Telangiectasia (HHT)
A double blind, randomized, placebo-controlled, multicenter trial

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UPDATE HISTORY

Version	Date	Update reason
01	02/02/2017	First version – CPP & ANSM submission
02	22/03/2017	Second version – Further to ANSM request Addition of a phone call to patient at Day 15, ophthalmic safety data (§1.3.3.), exclusion criteria "women of child bearing potential without reliable contraception", arguments on rationale (§2.2).

03	04/04/2017	Third version – Further to ANSM request Changes in duration: 6 weeks treatment and 6 weeks follow up, inclusion criteria adapted: epistaxis>30 mn for 6 weeks. Addition of blood samples at day 8 & 22 for tacrolimus dosage. Addition of in vivo demonstration for ointment administration.
04	21/06/2017	Fourth version Further to the request of the independent monitoring and safety committee, review of the rules for discontinuation of the study in case of imbalance between the randomization arms §2.3.

CONTENTS

LIST OF ABBREVIATIONS

ALK	Activin-like-receptor-type 1
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (French National Agency for Drug Safety)
AVF	Arteriovenous Fistula
BMP	Body Morphogenetic Proteins
BMPR2	Body Morphogenetic Protein Receptor, type II
CHU	Centre Hospitalier Universitaire (University Teaching Hospital)
CNIL	French Commission for Data Protection and Liberties
CNV	Corneal NeoVascularization
CPP	Comités de Protection des Personnes (French Ethics Committee)
CRF	Case Report Form (Cahier d'observation)
DSMB	Data and Safety Monitoring Board
EC	Endothelial Cells
ENG	Endogline
ENT	Ear, Nose and Throat Specialist
ESS	Epistaxis Severity Score
FKBP	FK-Binding Protein
Flt-1	Fms-like tyrosine kinase
HAS	Haute Autorité de Santé (French National Authority for Health)
HHT	Hereditary Hemorrhagic Telangiectasia
IMER	Information Médicale Evaluation Recherche (Medical Information Research Assessment)
IV	Intra venous
IWRS	Interactive Web Response System
KO	Knock Out
MAPK	Mitogen-activated protein kinases
MCP	Monocyte Chemoattractant Protein
mRNA	messenger Ribonucleic Acid
OLP	Oral Lichen Planus
PAH	Pulmonary Arterial Hypertension
PNDS	Protocoles Nationaux de Diagnostic et de Soins (French National Protocol for Diagnosis and Healthcare)
SAE	Serious Adverse Events
SAS	Statistical Analysis System
SMAD	Mothers Against Dpp homologue 4
SPC	Summary of Product Characteristics
TGF-β	Transforming Growth Factor-β
TNF	Tumor Necrosis Factor
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor.

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Synopsis

Title of the study:
TACRO: Efficacy and safety of a 0.1% tacrolimus nasal ointment as a treatment for epistaxis in Hemorrhagic Hereditary Telangiectasia (HHT) - A double blind, randomized, placebo-controlled, multicenter trial.

Context:
HHT is a rare but ubiquitous hereditary vascular disease, with estimated prevalence of 1/6000. It is related to disequilibrium in the angiogenic balance, resulting from abnormal homeostasis between the factors involved in the activation phase and those involved in the maturation phase of angiogenesis. ENG (Endoglin) and ACVRL1 encoding ALK1 (Activine receptor like kinase 1) genes are responsible for 90% of cases of HHT. These genes both intervene in the signaling pathway of the Transforming growth factor beta (TGFbeta) family in endothelial cells.

The recognized manifestations of HHT are all due to abnormalities in vascular structure. Lesions may be small (telangiectases) or large arteriovenous malformations (AVMs). Telangiectases and AVMs vary widely between individuals and even within the same family. Epistaxes are spontaneous, very variable, recurrent in 90% of patients, and associated with severe anemia in 2-10%. They also significantly reduce quality of life.

Nosebleeds are the most frequent complication in HHT and may occur as often as several times every day. Blood transfusions are sometimes required in 10-30% of patients, but are regularly required (every 2 or 3 weeks) in 2-5% of patients. The incomplete and transient efficacy of surgical therapies has inspired a new search for adjuvant medical treatments which would greatly diminish daily iron loss.

Intra-venous anti-VEGF treatment is efficient on epistaxis[1], but its use is limited to severe forms of the disease, and local administration (nasal spray) recently evaluated in a phase 2 study is not efficient (Dupuis-Girod S et al., in press – clinical trial identifier: NCT02106520).

Improvement in epistaxis has been shown in HHT patients after a liver transplantation. It was hypothesized that the immunosuppressive treatment (FK506) used to prevent rejection may have an anti-angiogenic effect.

Albiñana et al. found that the immunosuppressor FK506 increases the protein and mRNA expression of ENG and ALK1 in cultured endothelial cells, and enhances the TGF-β1/ALK1 signaling pathway and endothelial cell functions such as tubulogenesis and migration. These results suggest that the mechanism of action of FK506 involves a partial correction of endoglin and ALK1 haplosufficiency and may therefore be an interesting drug for use in patients with HHT.

Topical nasal administration of tacrolimus may be an easy local ENT treatment that is non-aggressive and results in little trauma for the patient in relation to other first line treatment possibilities. In addition, tacrolimus ointment is available on the market for the treatement of eczema and can therefore readily be used as it is for nasal administration.

Objectives

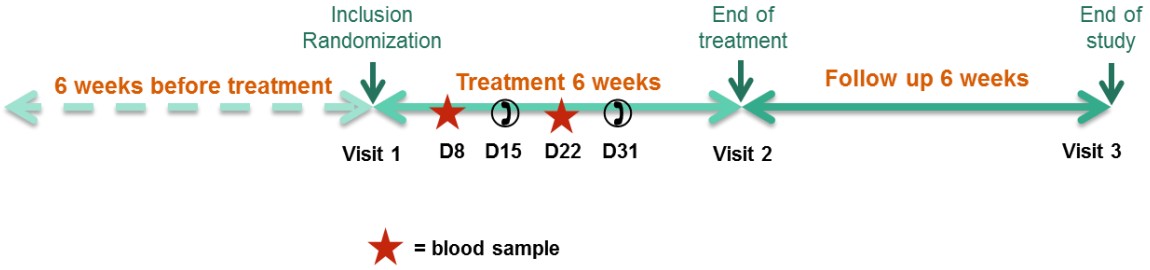
Main objective: To evaluate, at 6 weeks after the end of the treatment, the efficacy on the duration of nosebleeds, of tacrolimus nasal ointment, administered for 6 weeks in patients with HHT complicated by nosebleeds.

Secondary objectives are to evaluate:

1. Tolerance of tacrolimus nasal administration for 6 weeks, throughout the study.
2. Efficacy of the treatment on progress in the
   - clinical parameters:
     - Nosebleed duration
     - Number of nosebleeds
     - Number of transfusions of red blood cells
     - Quality of life
     - ESS = Epistaxis Severity Score
   - biological parameters: hemoglobin and serum ferritin concentrations

   These parameters will be evaluated at the end of the 6 weeks of treatment (V2) and at the end of 6 weeks' follow-up (V3).
3. Systemic absorption after 1, 3 and 6 weeks of nasal administration.

Methodology
This is a phase II multicenter, randomized study carried out in double blind.
Number of patients: 48 patients will be randomized with an active/placebo ratio = 1:1.
For all patients, monitoring will be for 84 days (6 weeks' treatment + 6 weeks' follow-up).



For safety reasons, as no tolerance data are available with a nasal administration, we decided to include patients sequentially. We designed an inclusion scheme in 3 or 4 steps. An independent safety committee will give its rcommandations on the continuation of the study.

Product tested:
The treatment tested is Tacrolimus, manufactured by the laboratories Astellas and marketed under the name of Protopic® (tacrolimus at 0.1%). For the study, the ointment will be used as is.

The comparative treatment, placebo, is the same formulation as the active product but without tacrolimus.

One tube of product is delivered to patients, for administrations twice daily for 6 weeks.

Patients:

Inclusion criteria:

- Age ≥ 18 years.
- Patients who have given their free informed and signed consent.
- Patients affiliated to a social security scheme or similar.
- Patients monitored for clinically confirmed HHT (presence of at least 3 Curaçao criteria) and/or confirmed by molecular biology.
- Patients presenting nosebleeds with total duration ≥ 30 minutes for 6 weeks prior to the time of inclusion justified by completed follow-up grids.

Exclusion criteria:

- Women who are pregnant or nursing (lactating), women of child-bearing potential without reliable contraception.
- Patients not affiliated to a social security scheme.
- Patients who are protected adults under the terms of the law (French Public Health Code).
- Refusal to consent.
- Patients for whom the diagnosis of HHT has not been confirmed clinically and/or by molecular biology.
- Participation in another clinical trial wich may interfere with the proposed trial (judgment of the investigator).
- Patients who have undergone nasal surgery in the 6 weeks prior to inclusion.
- Known hypersensitivity to macrolides in general, to tacrolimus or to any of the excipients.
- Patient with an inherited skin barrier disease such as Netherton's syndrome, lamellar ichtyosis, generalized erythroderma, graft-versus-host skin disease, or suffering from generalized erythroderma. .
- Patient with CYP3A4 inhibitors treatment, e.g. erythromycin, itraconazole, ketoconazole and diltiazem.
- Patients who have incompletely filled in the nosebleed grids in the 6 weeks preceding the treatment. If there is missing data for more than 7 days (10%), the patient cannot be included.
- Patients who do not present nosebleeds with total duration ≥ 30 minutes for 6 weeks prior to the time of inclusion.
- Patients with ongoing immunosuppressive treatment
- Patients with known and symptomatic immune deficiency

Main judgement criterion: The main judgement criterion is the percentage of patients experiencing an improvement in their nosebleeds. An improvement is defined as a 30% reduction in the total duration of

nosebleeds over 6 weeks after treatment, compared with duration of the nosebleeds in the 6 weeks before treatment.

Secondary judgement criteria

1. Adverse events (AE) and Severe Adverse Events (SAE) observed throughout the study (clinical examination, epistaxis grids, ENT examination at each visit before and after the treatment). Additionally, all patients are contacted by phone after 14 and 30 days of treatment in order to collect data on tolerance and observance of the treatment.
2. Clinical efficacy criteria:
   - Nosebleed duration will be evaluated by the nosebleed monitoring grids completed by the patients (Appendix 1). The grids will be collected at inclusion (V1): observation of nosebleeds in the 6 weeks prior to inclusion, at the end of the treatment (V2): observation of nosebleeds in the 6 weeks of treatment, and at the end of the study (V3): observation of nosebleeds in the 6 weeks after the end of treatment.
   - Progress in the number of nosebleeds. This criterion will be evaluated by the nosebleed monitoring grids completed by the patients (Appendix 1) and collected at inclusion (V1): observation of nosebleeds in the 6 weeks prior to inclusion, at the end of treatment (V2): observation of nosebleeds in the 6 weeks of treatment, and at the end of the study (V3): observation of nosebleeds in the 6 weeks after the end of treatment.
   - Comparison of the number of red blood cell transfusions between inclusion (V1) (collected over 6 weeks before treatment), end of treatment (V2) (collected over the 6 weeks of treatment) and end of the study (V3) (collected over 6 weeks after the end of treatment).
   - Progress in the scores obtained in the SF36 quality of life questionnaire completed at inclusion (V1), at the end of treatment (V2) and at the end of the study (V3).
   - Progress in the Epistaxis Severity Score (ESS) using data from the specific questionnaire (Appendix 2) completed at inclusion (V1), at the end of treatment (V2) and at the end of the study (V3).

   Biological efficacy criteria: progress in hemoglobin and serum ferritin concentrations between inclusion (V1) and end of treatment (V2) and the end of the study (V3).
3. Systemic absorption, after 1, 3 and 6 weeks of nasal administration, will be evaluated by blood tacrolimus dosage at the end of treatment.

Benefit/risk ratio:

All the surgical treatments currently on offer are aggressive for the nasal mucosa and present a risk of perforation of the nasal septum.

Patients' participation in this study will not compromise their possibility for future medical or surgical treatment.

The expected adverse events in this study are:

- Skin burning or irritation at the application site (approximately half of the patients). These symptoms are usually mild to moderate and generally go away within one week of using Protopic. Administration could easily be stopped in case of an adverse reaction.
- The risk of systemic adverse events related to tacrolimus is low given the very low doses of tacrolimus administered to the patients. Tacrolimus in blood is monitored and the treatment will be stopped in case of absorption.
- The risk at the blood test may be of the hematoma type at the puncture point or fainting.

If the efficacy of the treatment is shown, the treatment will be proposed to all the patients who have received the placebo.

The benefit/risk ratio for a patient participating in this study is thus perfectly acceptable.

Total maximum duration of the study: 21 months
Inclusion period: 18 months.
Participation duration per patient: 12 weeks

Expected outcomes:
In case of efficacy, a topical nasal administration of tacrolimus could be an easy local ENT treatment that is non-aggressive and results in little trauma for the patient in relation to other first line treatment possibilities. Moreover, a galenic ointment with tacrolimus is available on the market.

Conduct of the study and research sites:

Selection and recruitment modalities: Patients for the study will be recruited and given all the necessary information during a standard ENT consultation or in the Reference Center or Skill center for HHT.
Inclusion and prescription of the treatment: Inclusion and treatment prescription will take place in the skill centers in Montpellier or Clermont-Ferrand or the reference center for HHT in Lyon.
Treatment: The ointment tube is delivered by the pharmacies in the hospital centers involved. Treatment (active or placebo) is self-administered by patients, twice daily in each nostril, for 6 weeks.
Follow-up: Throughout the study, patients will be required to complete epistaxis grids.
Follow-up is scheduled by the center which has carried out the inclusion as follows:

- Tacrolimus dosage in blood at 1, 3 and 6 weeks after the beginning of the treatment.
- Two phones questionnaire on day 15 and 31, 14 and 30 days after the start of the treatment to collect data on the tolerance and observance of the treatment.
- Two follow-up visits: after 6 weeks of treatment and 6 weeks after the end of treatment. There will be a consultation in the skill center or the reference center for HHT, an ENT examination and a blood sample

These consultations and examinations are in addition to usual patient care to ensure follow-up of these patients and the collection of data during the study.

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Favorable decision issed by the Ethics Committee (CPP), on 03/04/2017

Authorization by the Competent Authorities, on 07/04/2017

EUDRACT n°: N° 2017-000085-30

The State of the Matter

1.1 Hereditary Hemorrhagic Telangiectasia (HHT)

1.1.1 Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare but ubiquitous hereditary vascular disease that concerns between 1/6,000 and 1/10,000 patients.
The French HHT National reference center received its label in 2004. With 12 skill centers, it has a cohort of more than 2,000 patients managed both clinically and genetically.

1.1.2 The disease

1.1.2.1 Clinical picture

The diagnosis of Hereditary Hemorrhagic Telangiectasia is based on several criteria, known as the Curaçao criteria[2]:

- The hereditary element. Transmission is dominant autosomal (50% to each child).

- Telangiectasias. These are lesions that are characteristic of the disease and are cutaneous (lips, fingers, face, hands and feet) and mucosal (inside of the lips, tongue, palate, nasal and digestive mucosae).

- Epistaxis (nosebleeds). These are the main form of expression of these telangiectasias, both in terms of their frequency and the handicap that they provoke. Chronic disabling anemia is an unannullable and predominant consequence in these patients.

- Visceral arteriovenous fistulae (AVF). These are vascular lesions whose impact is always aggravated in cases of anemia. Visceral involvement can replace one of the three main external signs in a positive diagnosis. The localization of these AVF can be:

  - pulmonary (6 to 60% of patients [3-9]). The treatment has now been codified and is based on radiological vaso-occlusion. Annulling hemorrhagic ruptures, cerebral complications (abscesses and transitory ischemic attacks) and pulmonary signs (dyspnea, cyanosis and polyglobulitis, consequences of hypoxia) is a major issue.

  - neurological, cerebral or medullary [10,11]. Prevention of these lesions is problematic during the asymptomatic phase. Once their existence becomes evident, the sequellae of the possible treatments are serious. Scanning for these lesions is controversial [12-16] and their presence is evaluated at between 5 and 23% of patients with neurologically asymptomatic HHT [2,17,18].

  - hepatic [19,20]. Their definition is based on several radiological criteria. Their progress leads certain patients to a liver transplant [21-24].

The clinical diagnosis is - certain if at least 3 of the criteria are present, - suspected or possible if 2 of the criteria are present, - unlikely if only 1 of the criteria is present.

Every typical visceral complication can form one of the three criteria required for the diagnosis, thus replacing the nosebleeds, telangiectasias or the hereditary nature[2]. Certain patients can have 4 or 5 signs of the disease, with several forms of visceral involvement.

1.1.2.2 Genetics and physiopathology

There are three genes known to be responsible for HHT:
- Endoglin (*ENG*), responsible for the HHT1 phenotype of the disease.
- Activin-like-receptor-type 1 (*ALK-1*), responsible for the HHT2 phenotype of the disease.
- *SMAD 4*, responsible for a rarer phenotype that associates HHT and chronic juvenile polyposis.

A fourth gene has been localized but not yet identified and is responsible for the HHT3 phenotype.

ENG and ALK1 are responsible for 90% of cases of HHT. These genes both intervene in the signaling pathway of the TGFβ family in endothelial cells.

1.1.3 Nosebleeds

These are the main expression of HHT and are often the most disabling complication of the disease in terms of quality of life and morbidity.

Nosebleeds affect more than 95% of patients. They are spontaneous, repeated, irregular, diurnal and nocturnal; they lead to anemia and are both disabling and socially embarrassing. They are also the motivation for repeated periods of sick leave and even on occasion a classification of disability [25]. The duration of the nosebleeds may be greater than 24 hours per month in certain patients, and may require repeated blood transfusions and hospitalizations. As a result, the anemia may be severe, and the repeated ENT treatments have a risk of complication (perforation of the nasal septum, infections after packing).

Their objective assessment is achieved by means of a grid that contains the number of nosebleeds per month and the duration of the bleeding (Appendix 1: Nosebleed monitoring grid).

Furthermore, a validated scoring index, the Epistaxis Severity Score (ESS), was developed as a standardized measurement of patient-reported epistaxis severity. This score summarizes the severity of epistaxis symptoms along multiple domains, including frequency and intensity of nosebleeds, duration of epistaxis episodes, and the medical consequences of recurrent epistaxis such as anemia and dependence on blood transfusions. An increase in the ESS is significantly correlated to a decline in health-related quality of life, as measured by the Medical Outcomes Study 36-Item Short Form (SF-36).[26]

1.1.4 Treating nosebleeds in HHT

There is currently no surgical treatment that makes it possible to cure nosebleeds definitively. The repetition of ENT treatments is often the source of significant iatrogenic conditions, including the perforation of the nasal septum, resulting in worsening of the nosebleeds. No studies with a “high level of proof” have shown the efficacy of any medical or surgical treatments.
The French national protocol for the diagnosis and care (PNDS) of patients with HHT, drawn up by the reference center(s) that have been labelized with the support of the French national authority for health (HAS), contains the following information and recommendations regarding the treatment of nosebleeds.

The PNDS groups together the various medical and surgical treatments available.

- platelet agents such as ethamsylate are indicated in the treatment of bleeding by means of capillary fragility. Nevertheless, no specific studies have been carried out in the context of HHT;
- other treatments are being discussed or studied:
  - tranexamic acid (antifibrinolytic) has a moderately positive effect on anemia and nosebleeds[27];
  - aminocaproic acid and estrogens. The use of estrogens is limited by the existence of their thromboembolic risk and should only be envisaged in the context of clinical trials.

- As first line treatments the following are proposed:
  - laser photocoagulation,
  - injections of biological glue,
  - injections of sclerosing agents (Ethibloc®, Aetoxisclérol®).
- As second line treatments:
  - selective arterial embolization, either isolated or associated with the previous techniques,
  - arterial ligature of the sphenopalatine and/or ethmoidal arteries,
  - the Saunders surgical technique (suppression of the nasal mucosa), dermoplasty or septodermoplasty with or without graft (amniotic cells, jugal mucosal cells or skin flap),
  - Young’s nasal obstruction (surgical closure of the nasal cavities), either uni- or bi-lateral.

In addition to the treatments already mentioned, regular (several times a day) humidification of the nasal mucosa by the patient by means of an association of pomades and physiological serum makes it possible to partially improve the nosebleeds.

Iron supplementation is recommended for all patients whose repeated nosebleeds result in long term iron deficiency anemia. Patients with poor tolerance of oral iron supplementation may benefit from intravenous iron injections every 3 weeks. Blood transfusions are carried out in accordance with the recommendations of the ANSM.

1.2 Angiogenesis and its regulation

1.2.1 Angiogenesis and HHT

Angiogenesis is the formation of new blood vessels from an existing vascular network. There are two phases in angiogenesis: an activation phase, in which the extracellular matrix is degraded and the endothelial cells migrate and proliferate (*Figure 1*). VEGF is one of the key factors in this activation phase. This phase is followed by a maturation phase, in which the endothelial cells stop migrating and proliferating, the cellular matrix is reconstituted and there is recruitment of mesenchymatous cells which differentiate into pericytes or smooth muscle cells, depending on the type of vessel. Angiogenesis is generally quiescent in adults.

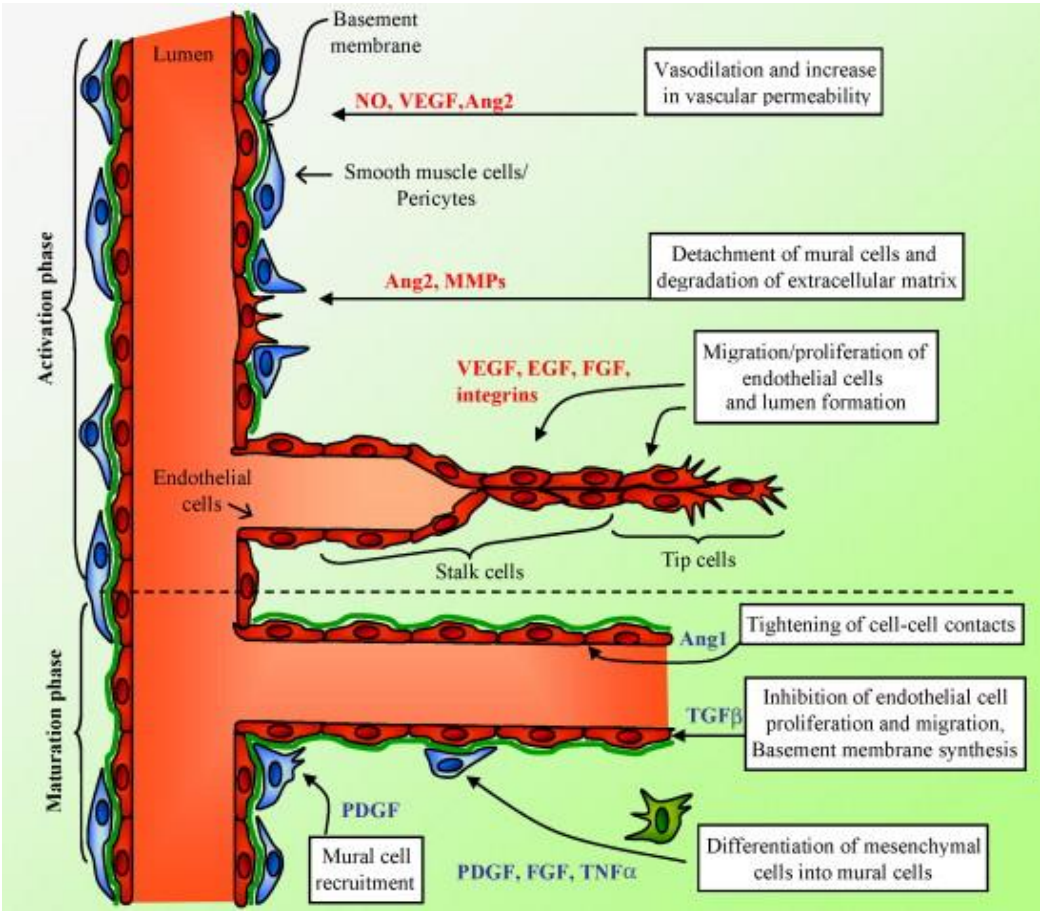

Figure 1: Angiogenesis results from an activation phase and a maturation phase. (Taken from David L. [28])
(NO: nitric oxide, VEGF: vascular endothelial growth factor, Ang2: angiopoietin 2, Ang1: angiopoietin 1, MMPs: matrix metalloproteinases, EGF: epidermal growth factor, FGF: fibroblast growth factor, TGFb: transforming growth factor beta, PDGF: platelet-derived growth factor and TNFa: tumour necrosis factor alpha.)

What is known as angiogenic balance results from homeostasis between the factors involved in the activation phase and those involved in the maturation phase of angiogenesis. The receptor ALK1 plays a key role in inhibiting the proliferation, migration and budding of endothelial cells *in vitro*, as well as neo-angiogenesis *in vivo*[28,29]. The ligand for ALK1, BMP9, may thus be a key factor in the maturation phase

of angiogenesis *(Figure 2)* and its presence in the blood suggests it plays a role in maintaining vascular quiescence in adults[30]. When the BMP9/ALK1/endoglin pathway is disturbed, the quiescence decreases, resulting in the dysregulation of this angiogenic balance, and thus neo-activation of angiogenesis *(Figure 3)*.

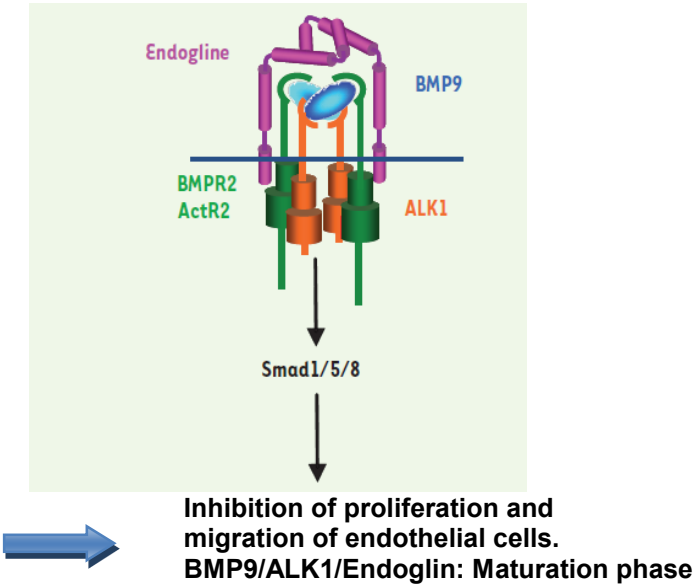

Figure 2: Involvement of the BMP9/ALK1/endoglin pathway in HHT (taken from S. Bailly[31])

BMP9 binds on to a heterocomplex composed of two ALK1 receptors and two type 2 receptors (BMPR2 or ActR2). The type 2 phosphoryl ALK1 receptor in turn phosphorylates the Smad1/5/8 transcription factors. Adding BMP9 results in inhibition of the migration and proliferation of endothelial cells, suggesting that this signaling pathway plays a role in the maturation phase of angiogenesis.

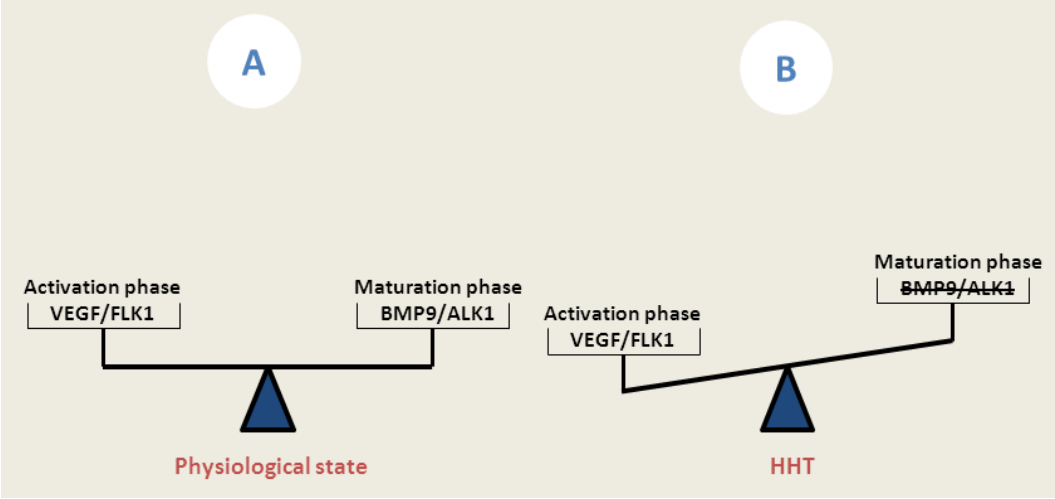

Figure 3: Angiogenic balance in HHT (taken from S. Bailly[31])

***A*. In healthy adults, angiogenic balance is equal between the activation phase and the maturation phase, and the vascular network is quiescent.**

***B*. In HHT patients, the BMP9/ALK1/endoglin signaling pathway is deficient, which results in a decrease in the maturation phase and thus an imbalance in the angiogenic balance in favor of the activation phase (VEGF).**

In HHT, the mechanisms leading to a predisposition to, and the formation of AVMs, the direct connections between arteries and veins, are yet to be determined. One proposed mechanism is defective arteriovenous differentiation, observed in *Eng* and *Alk1* null embryos that develop AVMs [32] but absent in the endothelial-targeted *Eng* (*Eng*-iKOe) and *Alk1* inducible knockout (*Alk1*-iKOe) mice [33]. Moreover, focal regression of capillaries leading to the formation of AVMs has also been postulated in HHT, although supporting data for this model are still lacking. Recently, it was shown that wound injury was necessary for development of AVMs in adult *Alk1*-iKOe [34] and *Eng*1-iKOe mice. In addition, intracerebral injection of an adenovirus expressing VEGF contributed to pathogenesis of cerebral AVMs in several transgenic *Eng* KO mice. Angiogenesis is the *de novo* formation of vessels from the pre-existent vascular tree, in response to a stimulus. This biological process is controlled by pro-angiogenic factors that promote vascular growth and angiostatic factors that induce vascular regression. Physiological angiogenesis occurs during development and in healthy individuals, in wound injury and repair, menstruation, and pregnancy.

1.3 Tacrolimus

Tacrolimus (FK506) is a macrolide antibiotic with immunosuppressive and anti-angiogenic properties.

1.3.1 Mechanism of action

FK506 (tacrolimus), via a dual mechanism of action, is a calcineurin inhibitor that also binds FK-binding protein-12 (FKBP12), a repressor of BMP signaling. FK506 released FKBP12 from the type I receptors activin receptor-like kinase 1 (ALK1), ALK2, and ALK3, and activated both downstream SMAD1/5 and MAPK signaling and ID1 gene regulation in a manner superior to the calcineurin inhibitor cyclosporine and the FKBP12 ligand rapamycin.[35]
Via its binding to a specific cytoplasmic immunophilin (FKBP12), tacrolimus inhibits calcium-dependent signal transduction pathways in cells. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection.

The mechanism of action of tacrolimus in atopic dermatitis is not fully understood.
In vitro, in Langerhans cells isolated from normal human skin, tacrolimus reduced the stimulatory activity towards T cells. Tacrolimus has also been shown to inhibit the release of inflammatory mediators from skin mast cells, basophils and eosinophils.
In animals, tacrolimus ointment suppressed inflammatory reactions in experimental and spontaneous dermatitis models that ressemble human atopic dermatitis. Tacrolimus ointment did not reduce skin thickness and did not cause skin atrophy in animals.
In patients with atopic dermatitis, improved skin lesions during treatment with tacrolimus ointment was associated with reduced Fc receptor expression on Langerhans cells, as well as reducing their hyperstimulatory activity toward T cells. Tacrolimus ointment does not affect collagen synthesis in humans. [36]

1.3.2 Current indications

At present, when administered either intravenously or orally, tacrolimus is used to prevent rejection following organ transplant. Tacrolimus (FK-506) is a strong immunosuppressant neutral macrolide isolated from streptomyces tsukubaensis. It has been used to prevent allograft rejections in the liver, kidney, lungs, and heart. [37,38]

Tacrolimus ointment has been developed in dermatology and provides physicians with an alternative to conventional topical corticosteroid therapy for atopic dermatitis[39].Monotherapy is rapidly effective, resulting in clinical improvements within three days of starting therapy, and produces a progressive increase in efficacy that is sustained throughout long-term treatment. Tacrolimus treats the signs and symptoms of atopic dermatitis, reduces the incidence of flares, and offers the potential for long-term disease control.

1.3.3 Safety: Ointment safety

1.3.3.1 Skin

No major safety concerns have been reported to date. Tacrolimus ointment is generally well-tolerated, the primary adverse events being mild to moderate and transient application-site reactions: skin burning, pruritus and erythema.[36 40]

Approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation, pruritus, and erythema were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment. Increased skin sensitivity and skin tingling were also common skin irritation adverse reactions. Alcohol intolerance (facial flushing) was common. Patients may be at an increased risk of folliculitis, acne, and herpes simplex. [36]

Three published observational studies have assessed the carcinogenic risk on large cohorts of patients:

- The retrospective Arana study (2010)[41] compared the incidence of cancer in the general population and in patients with atopic dermatitis. It focused on a cohort of 4,456,008 patients with no history of cancer from "The Health Improvement Network" database, representative of the population of the United Kingdom. This study showed a higher incidence of skin cancer in atopic patients, but it did not make it possible to establish a link between skin cancer and treatment for atopic dermatitis.

- Hui (2009)[42] studied safety in a retrospective cohort. Of the 11,961 cancer cases reported between 2001 and 2005, no difference was observed for all forms of cancer combined between patients exposed or not exposed to calcineurin inhibitors after adjustment according to age and sex.

- Schneeweiss [43] studied a cohort of 1,252,300 patients, to assess the risk of lymphoma during treatment with tacrolimus, pimecrolimus or corticosteroids. Compared to the general population, these three treatments were associated with an increased risk of occurrence of lymphoma. Compared to patients with untreated

atopic dermatitis, however, the three treatments were not associated with an increased risk of lymphoma.

An open-label multicenter trial in children has been performed to evaluate safety. Skin infections occurred in 26% of patients. A burning sensation with product application, reported by 38% of patients, was transient and of mild-to-moderate severity in most cases. They concluded that Tacrolimus 0.1% ointment was safe, well-tolerated, and efficacious in the treatment of atopic dermatitis in children over the age of six months and adults [44].

Long-term safety was studied in a systematic review of published trials with long term treatments (at least 12 weeks)[45] . Data from 9 trials using tacrolimus were collected i.e. 1370 patients, treatment duration varied from 12 weeks to 5 years. This review supports the long-term safety with no evidence of cutaneous atrophy or cumulative systemic exposure and no reports of lymphoma[45].

1.3.3.2 Mucosae

To evaluate the tolerability of tacrolimus on mucosae (tacrolimus 0.3 mg g(-1) ointment), in the treatment of chronic plaque psoriasis affecting facial and genitofemoral regions, a double-blind, parallel, 6-week study was carried out on 50 patients who were randomized in a 1 : 1 ratio to apply calcitriol or tacrolimus twice daily. The authors concluded that both calcitriol 3 microg g(-1) and tacrolimus 0.3 mg g(-1) are safe and well-tolerated therapeutic agents in the treatment of psoriasis in sensitive areas. Tacrolimus demonstrated a more effective clinical outcome compared with calcitriol. [46]

Tolerability has been evaluated in the treatment of oral lichen planus (OLP). Corrocher reported in the group treated with tacrolimus, nine of 16 patients (56.3%) who had an initial worsening of burning sensation during the first 2 days of treatment. However, it resolved rapidly within 4–5 days as OLP improved[47], Vohra et al reported a transient burning sensation by seven patients (six in the tacrolimus and one in the pimecrolimus group), and two patients complained of dysgeusia following tacrolimus application. No serious adverse effects necessitating stopping treatment were recorded in the two groups.[48]. More recently, Arduino et al published a randomized study treated with tacrolimus or piperolimus. Among them, in the tacrolimus group, two patients reported mucosal burning sensation during the first days of the therapy and one reported a transient sialorrhoea. In the pimecrolimus group, two patients reported xerostomia, two experienced episodes of gastroesophageal reflux and one the recurrence of two lesions of herpes labialis. None of these adverse effects was severe enough to require discontinuation of therapy. There were no statistically significant differences between the two groups in the incidence of adverse effects[49] and Sonthalia et al compared the efficacy of clobetasol propionate (0.05%) ointment or tacrolimus (0.1%) ointment for eight weeks in 40 patients. None of the patients in either group showed any abnormality in hematological or biochemical parameters at eight weeks of treatment and no severe adverse events were reported. The majority of patients in both treatment groups reported good local tolerance to the topical drugs. Three patients in the tacrolimus group (15%) and three in the clobetasol group (15%) complained of a transient burning sensation following the application of the ointment, which lasted for a few seconds to a few minutes and did not necessitate the discontinuation of therapy. No patient

developed any clinically detectable atrophy, pigmentation, telangiectasia, or any type of allergic reaction.[50]

1.3.3.3 Ophtalmic

Tacrolimus ointment can be used by ophtalmic route for ocular diseases treatments, several studies were published:
Barot RK [51] studied effect 0.1% tacrolimus ointment in allergic ocular diseases on 36 patients.
Fukushima A[52] investigated efficacy of topical 0.1% tacrolimus eye drops for allergic ocular diseases on a cohort of 1436 patients.
Chatterjee S[53] in an open-label study enrolled 30 patiens with vernal keratoconjunctivitis, they were treated with 0.03% tacrolimus eye ointment for at least 4 weeks.
Shoughy S[54] studied efficacy and safety of topical tacrolimus 0.01% solution on 62 patients with vernal keratoconjunctivitis.
In all cases the treatment was well tolerated, no serious adverse event was observed, the most common adverse reaction was a transient burning sensation, rare corneal infections were described, one bacterial corneal ulcer and one trachoma.

1.3.4 Pharmacokinetic and systemic absorption

Data from healthy human subjects indicate that there is little or no systemic exposure to tacrolimus following repeated topical application of tacrolimus ointment. As systemic exposure is low with tacrolimus ointment, the high binding of tacrolimus to plasma proteins is not considered to be clinically relevant. The metabolism of tacrolimus by human skin was not detectable. Systemically-available tacrolimus is extensively metabolized in the liver via CYP3A4. Following repeated topical application of the ointment, the average half-life of tacrolimus was estimated to be 75 hours for adults and 65 hours for children.[36]

Several studies in infants[55,56] on the pharmacokinetics of tacrolimus after first and repeated application showed minimal systemic exposure. 92% of blood samples contained tacrolimus concentrations of less than 1 ng per mL and 17% of samples were less than 0.025 ng per mL (lower limit of quantification). These values are minimal compared with an oral dose after a liver transplant. Systemic exposure to tacrolimus increased in proportion to the size of the body surface treated, and decreased with time as the skin lesions healed. There was no evidence of systemic accumulation.

Further to an administration on mucosae, pharmacokinetic was evaluated in two clinical trials and no systemic absorption was detected[47,49].

1.4 Tacrolimus and HHT

In vitro, Albinana et al.[57] reported the efficacy of tacrolimus (FK506) in increasing ENG and ALK1 protein levels at the surface of endothelial cells; it also increases the expression of ENG and ALK1 mRNA and *ENG* and *ALK1* promoter activity in cultured endothelial cells, and enhances the TGF-β1/ALK1 signaling pathway and endothelial cell functions such as tubulogenesis and migration.

Furthermore, we know that after HHT patients have had a liver transplant for hepatic AVMs and high-output cardiac failure, their epistaxes improve dramatically [58] and mucosal bleeding stops. Their hemoglobin levels normalize and cutaneous and gastrointestinal telangiectases disappear.
This suggests that the immunosuppressive therapy might have had anti-angiogenic effects on the telangiectases [59], and that the mechanism of action of FK506 involves a partial correction of endoglin and ALK1 haploinsufficiency. It may therefore be an interesting drug for use in HHT patients.

It has recently been reported (HHT Meeting, Florida 2015) by Feige et al., in the HHTreat project that aims to identify new drugs that could be of interest in the treatment of HHT patients, that tacrolimus would be a good candidate.

The antiangiogenic effect of tacrolimus has been demonstrated in other vascular diseases. *In vitro*, in pulmonary artery endothelial cells (ECs) from patients with idiopathic pulmonary arterial hypertension (PAH), low-dose FK506 reversed dysfunctional BMPR2 signaling. In mice with conditional Bmpr2 deletion in ECs, low-dose FK506 prevented exaggerated chronic hypoxic PAH associated with the induction of the EC targets of BMP signaling, such as apelin. Low-dose FK506 also reversed severe PAH in rats with medial hypertrophy following monocrotaline and in rats with neointima formation following VEGF receptor blockade and chronic hypoxia. These data indicate that low-dose FK506 could be useful in the treatment of PAH. [35].
More recently, sirolimus (rapamycine), which also binds FK-binding protein-12 (FKBP12), is safe and efficient in the treatment of Blue rubber bleb nevus syndrome, a rare multifocal venous malformation syndrome involving predominantly the skin and gastrointestinal tract[60] or other vascular malformations[61].
A recent study on corneal neovascularization in rabbits compares the antiangiogenic effects of tacrolimus and bevacizumab. They conclude that topical or subconjunctival administration of tacrolimus reduces experimental CNV, shown by the decreased levels of VEGF, macrophages, TNF-α, IL-1β and MCP-1.[62]

2 Justification for the study

2.1 Rationale for the study

To date, no surgical treatment has made it possible to significantly decrease nosebleeds – the most common complication of the disease, responsible for significant morbidity – in the medium to long term in patients with HHT. Moreover, surgical treatments are aggressive for the nasal mucosa and risk perforating the nasal septum.

Intra-venous anti-VEGF treatment is efficient on epistaxis [1], but its use is limited to severe forms of the disease, and local administration (nasal spray) recently evaluated in a phase 2 study is not efficient (NCT02106520)[63].

Improved epistaxes have been observed in HHT patients after a liver transplant. It was hypothesized that the immunosuppressive treatment (FK506) used to prevent rejection may have an anti-angiogenic effect.

A topical nasal administration of tacrolimus could be an easy local ENT treatment that is non-aggressive and results in little trauma for the patient in relation to other first line treatment possibilities. Moreover, a galenic ointment with tacrolimus is available on the market.

2.2 Safety and rationale for the pharmaceutical form, means of administration and doses used

The pharmaceutical form retained for this phase II study is an ointment: Protopic® 0.1%, packaged in tubes of 30 g. This marketed product (market authorization EU/1/02/201/003) is precribed to treat severe atopic dermatitis.
In the study, this ointment can be use as is in the nose.

Nasal administration of tacrolimus ointment and its safety is unknown. Nevertheless data published on mucosae and ophtalmic route are encouraging, tacrolimus ointment is generally well tolerated including long-term treatments. Burning sensation is the most common reaction but it is transient and usally without treatment interruption.

As safety and pharmacokinetics have been extensively studied in dermatitis, we decided to use the same posology, i.e. twice daily.
For a nasal administration, the quantity applied will be about 0.1 g in each nostril; it represents 0.4 g of ointment per day i.e. 0.4 mg of tacrolimus.
In order to show efficiency, the treatment period has to be long enough to heal lesions responsible for epistaxis and to decrease vascularization. The longer period treatment recommended on SmPC has been chosen, that is to say 6 weeks.

The risk of systemic effect is limited because of the low doses prescribed. The administered dose is 0,4 g of ointment per day, that is to say 0,4 mg of tacrolimus per day.
Transplant patients treated with tacrolimus by oral route receive a dose from 0,1 to 0,2 mg / kg / day (i.e. 5 to 10 mg per day for a 50 kg person). The dose on IV route is 0,01 to 0,05 mg/kg/day (i.e. 0,5 to 3 mg per day for a 50 kg person).
Although systemic absorption was not observed after administration on mucosae[47,49], if a systemic absorption occurs, no adverse reactions are expected given the low doses and the good tolerance of tacrolimus per os.

It should be noted that the risk of surdosage is very low in this study, since the application of ointment in the nose can cause discomfort for the patient, it is unlikely that the patient will increase the doses to be administered.

Tacrolimus systemic absorption will be monitored in this study. FK506 dosages in blood are scheduled at Day 8, 22 and 43. Analysis will be centralized in “Hospices Civils de Lyon”.
After transplantation , the optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL[64] and should be maintained below 20 ng/mL.
In the present study, no systemic absorption and effect are expected. However in case of positive dosage, from 5 ng/mL and above, the laboratory will immediately inform the investigator who will ask the patient to stop treatment.
In case of dosage higher than 20 ng/mL, the laboratory will immediately inform the investigator who will ask the patient to stop treatment and the patient will be hospitalized.

The placebo formulation is strictly identical to Protopic: it contains all the ingredients except tacrolimus. The packaging is similar. The posology is also twice daily.

2.3 Rationale for the methodology

The methodology retained for this efficacy (phase II) study is a randomized trial, which is the design presenting the highest level of evidence.

We started to assess parameters by comparing data collected at 3 visits:

- Visit 1: inclusion, data collected for 6 weeks before treatment and during the visit
- Visit 2: end of treatment, data collected during the 6 weeks preceding the visit (i.e. 6 weeks of treatment) and during the visit
- Visit 3: end of study, data collected during the 6 weeks preceding the visit (i.e. 6 weeks following the end of treatment) and during the visit.
- In addition, data are collected on pharmacokinetic at Day 8 and Day 22 (blood sample) and on safety at Day 15 and Day 31 (phone call).

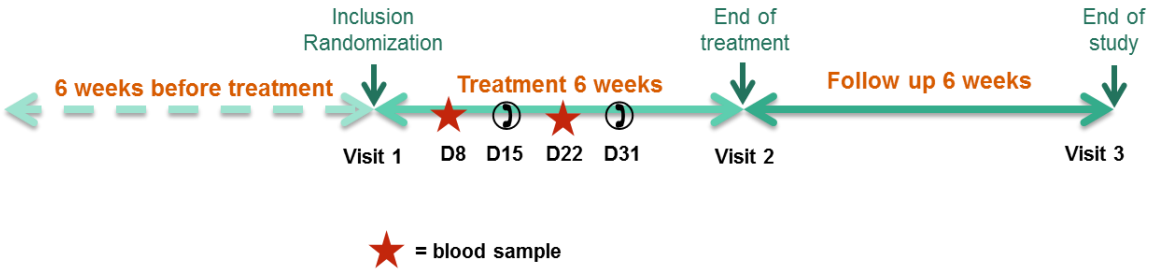

Figure 4 General diagram of the study

For safety reasons, as no tolerance data are available with a nasal administration, we decided to include patients sequentially. We designed an inclusion scheme in 3 or 4 steps. An independent safety committee will give its recommandations on the continuation of the study.

The theoretical inclusion scheme is described as follows. It was established pragmatically based on our sample size.
We consider that a cessation of treatment for at least 8 consecutive days, for safety concern, that is to say adverse reaction due to the ointment, is a major issue.

- **<u>STEP 1</u>- 8 patients will be included in Lyon**.

On day 31 (phone call): information regarding adverse events (AE), severe adverse events (SAE) and observance of the treatment for the first 30 days of treatment are collected for these 8 patients.
Based on these data, a DSMB meeting (#1) will be consulted and will give its recommandations on the continuation of the study according to the following theoretical scheme:

Number of patient who stop treatment for 8 consecutive days		ARM PLACEBO				
		0	1	2	3	4
ARM ACTIV	0	0	1	2	3	4
	1	1	2	3	4	5
	2	2	3	4	5	6
	3	3	4	5	6	7
	4	4	5	6	7	8

The numbers inside the table = total number of events in both arms

	No imbalance between arms
	Imbalance between arms active>placebo
	Imbalance between arms placebo>active
0	+ 16 patients
0	+ 8 patients
0	Stop

If there is no imbalance between arms (difference ≤ 1), the total number of patient who stop treatment at least 8 consecutive days will be consider (semi-blind data transmitted to DSMB):

- < 4 patients in both arms → inclusion of 16 new patients (Step 2A)
- ≥ 4 patients in both arms → inclusion of 8 new patients (Step 2B)

Note: if a large number of patients stopped the treatment for at least 8 consecutive days, the hypothesis will be that the ointment form is not well accepted. Then we consider it is worthwhile to check this point by including 8 additionnal patients.

If there is an imbalance between arms (difference > 1), (unblinded data will be transmitted to DSMB):

- The number of "stops" is higher in the placebo arm
  - If "0" or "1" patients in active arm stop treatment → inclusion of 16 new patients (**Step 2A**)
  - If "2" patients in active arm stop treatment → inclusion of 8 new patients (**Step 2B**)

- The number of "stops" is higher in the active arm
  - If difference between arms is 2 → inclusion of 8 new patients (**Step 2B**)
  - If difference between arms is over 2 → inclusions may be discontinued **(Step 2C).**

The first 8 patients will be included in the Lyon center. Further inclusions will take place in all centers.

For the following steps, we consider the total number of patients who have a cessation of treatment for at least 8 consecutive days for safety concerns. Indeed, if 50% or more of patients are “in failure”, the continuation of the study may be called into question and the analysis on the main judgement criteria will then not be relevant.

- **STEP2 – Following inclusions, all centers**

STEP 2A- **In case of inclusion of 16 new patients**.
For these 16 patients, on day 31 (phone call): information regarding adverse events (AE), severe adverse events (SAE) and observance of the treatment for the first 30 days of treatment are collected. Additionally, safety assessment is carried out on the data collected at the visit after the end of treatment for the first 8 patients.
Based on these data, a DSMB meeting (#2) will be consulted and will give its recommandations on the continuation of the study according to the following theoretical equations:

- If less than 12 of the 24 patients stop treatment for 8 consecutive days due to safety concerns, 24 new patients will be included (**Step 3A**). Total number of patients included: 8 + 16 + 24 = 48.
- If 12 or more patients stop treatment for at least 8 consecutive days due to safety concerns, depending on the group imbalance, the DSMB may request the lifting of the blind and inclusions may be discontinued (**Step 3B**). Total number of patients included: 8 + 16 = 24.

STEP 2B- In case of inclusion of 8 new patients.
For these 8 patients, on day 31 (phone call): information regarding adverse events (AE), severe adverse events (SAE) and observance of the treatment for the first 30 days of treatment are collected. Additionally, safety assessment is carried out on data collected at the visit after the end of treatment for the first 8 patients.
Based on these data, a DSMB meeting (#2) will be consulted and will give its recommandations on the continuation of the study according to the following theoretical equations:

- If less than 8 patients stop treatment for 8 consecutive days due to safety concerns, 16 new patients will be included (**Step 3C**).
- If 8 or more patients stop treatment for at least 8 consecutive days due to safety concerns, depending on the group imbalance, the DSMB may request the lifting of the blind and inclusions may be discontinued (**Step 3D**). Total number of patients included: 8 + 8 = 16.

- **STEP3 – Following inclusions, all centers**

STEP 3A- Inclusion of 24 new patients, total number of patients included = 48

STEP 3C- In case of inclusion of 16 new patients.
For these 16 patients, on day 31 (phone call): information regarding adverse events (AE), severe adverse events (SAE) and observance of the treatment for the first 30 days of treatment are collected. Additionally, safety assessment is carried out on data collected at the visit after the end of treatment for the first 16 patients.
Based on these data, a DSMB meeting (#3) will be consulted and will give its recommandations on the continuation of the study according to the following theoretical equations:

- If less than 16 patients stop treatment for 8 consecutive days due to safety concerns, 16 new patients will be included (**Step 4A**).
- If 16 or more patients stop treatment for at least 8 consecutive days due to safety concerns, depending on the group imbalance, the DSMB may request the lifting of the blind and inclusions may be discontinued (**Step 4B**). Total number of patients included: 8 + 8 + 16 = 32.

- **STEP4 – Following inclusions, all centers**

STEP 4A- Inclusion of 16 new patients, total number of patients included = 48

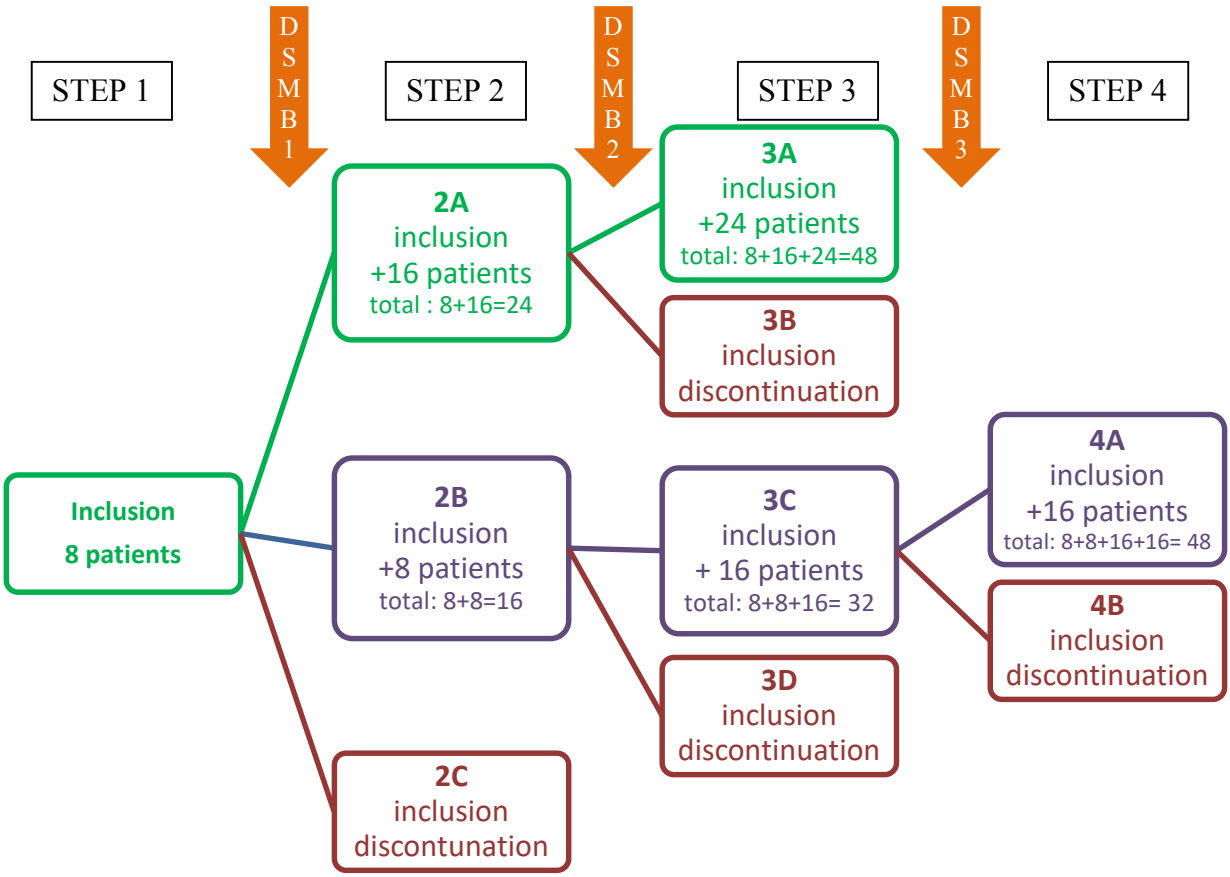

Figure 5: Inclusions flow chart

3 Objectives

3.1 Main objective

To evaluate, at 6 weeks after the end of the treatment, the efficacy of tacrolimus nasal ointment on the duration of nosebleeds when administered for 6 weeks in patients with HHT complicated by nosebleeds.

3.2 Secondary objectives

The secondary objectives are to evaluate:

4. Tolerance of tacrolimus nasal administration for 6 weeks, throughout the study.

5. Efficacy of the treatment on progress in the
   - clinical parameters:
     - Nosebleed duration,
     - Number of nosebleeds,
     - Number of transfusions of red blood cells.
     - Quality of life
     - ESS = Epistaxis Severity Score
   - biological parameters: hemoglobin and serum ferritin concentrations

   These parameters will be evaluated at the end of the 6 weeks of treatment (V2) and at the end of 6 weeks of follow-up (V3).

6. Systemic absorption after nasal administration.

4 Methodology

4.1 Outline of the experiment

This is a multicenter, randomized study carried out in double blind. For all patients, monitoring will be for 12 weeks (6 weeks' treatment + 6 weeks' follow-up).

4.1.1 Monitoring the patients

The tacrolimus ointment will be delivered at the centers participating in the study during the first visit after verifying the inclusion criteria. A phone call is scheduled on day 31, i.e. 30 days after the beginning of the treatment, to monitor the safety of the treatment. Patients will have two medical visits: at the end of the treatment and after 6 weeks of follow-up.

A scientific committee and an independent monitoring committee will be set up (see paragraph 12.1 & 12.2).

A specific management procedure is envisaged for each expected complication (see paragraph 7.3).

4.1.2 Patient selection

Patients in the HHT network will thus be informed of the study in progress during a standard ENT consultation or in the Reference Center or Skill Center.
Patients will be included (the consent form will be signed) on the day of the treatment is prescribed.
Subjects will be attributed a number in relation to their chronological inclusion.

4.1.3 Duration of the study

The duration of the inclusion period will be maximum 18 months.

The duration of participation per patient will be 12 weeks (6 weeks' treatment + 6 weeks' of follow-up).

The total duration of the study will thus be maximum 21 months.

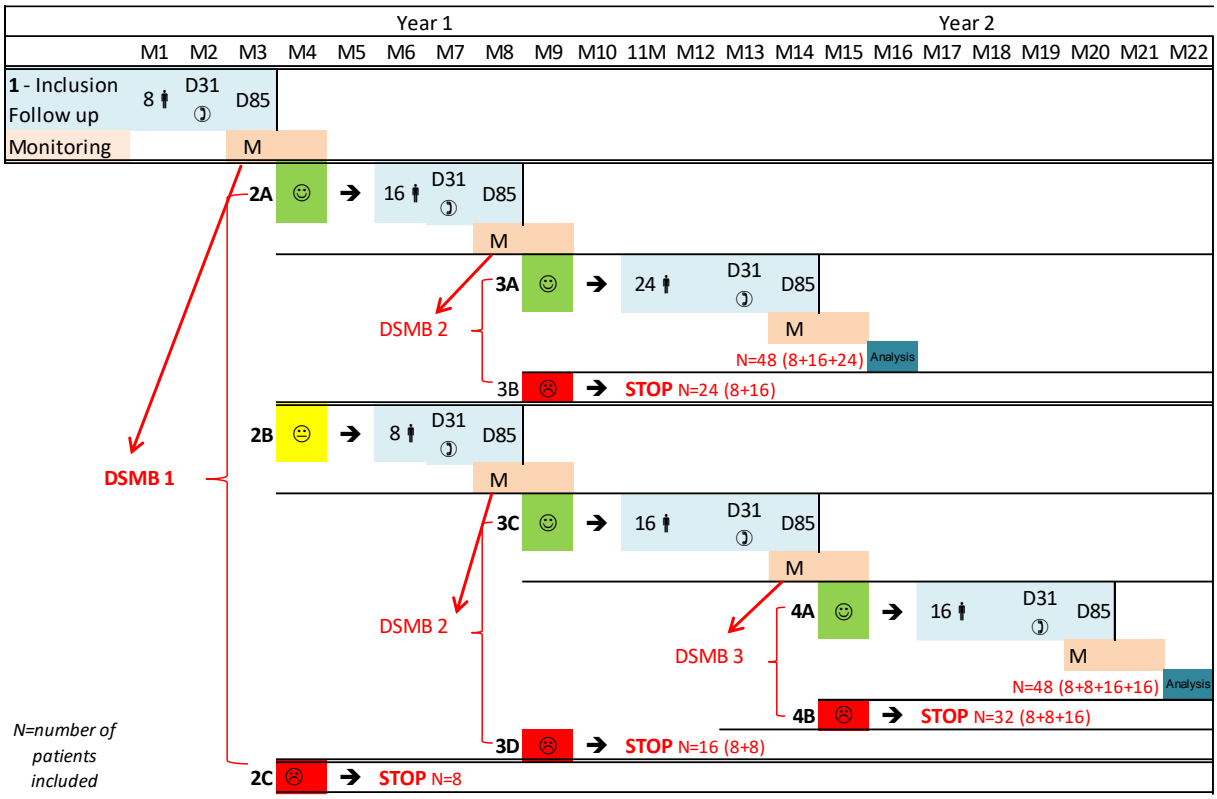

Figure 6: Schedule

4.2 Patients

4.2.1 Recruitment and feasibility

Aspects to ensure the feasibility of the project

- Network coordinated by the reference center (over 2000 patients followed regularly). The cohort of patients followed for HHT in the Lyon reference center is around 1,000 patients. At the national level, more than 2,000 patient files are currently included in the database. Of these patients, at least 25% present with nosebleeds that justify ENT management.
- The complication targeted by the treatment (epistaxis) is frequent, present in 95% of patients over the age of 50.
- Previous studies conducted by the Reference center, including Metafore published in 2012,[1] Ellipse published in 2014[65] and Alegori published in 2016[63].
- The support of the patients' association (AMRO) and the high expectations of the patients.

4.2.2 Number of patients

We intend to randomize 48 patients.

4.2.3 Modalities for recruitment, inclusion and follow-up

Recruiting and informing the patients of the study in progress will take place during a standard ENT consultation or in the Reference Center or Skill Center for HHT.

Patients will be included on the day the treatment is prescribed.

The treatment is self-administered by patients, twice daily, for 6 weeks.

The follow-up period will be scheduled as follows:

- at each consultation, an ENT examination and a clinical examination including measurement of heart rate and blood pressure will be performed

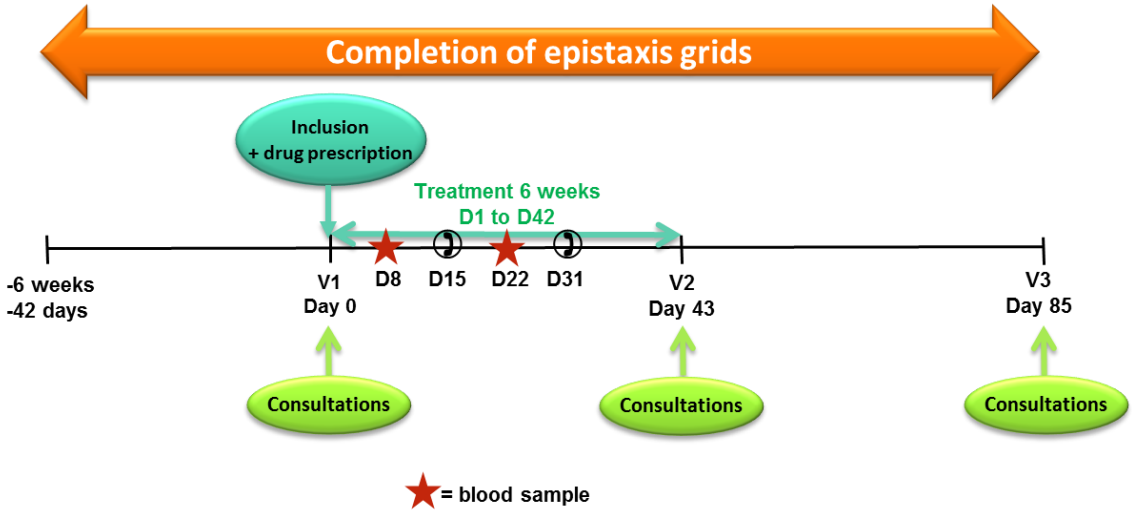

Figure 7: Diagram of the running of the study

4.2.4 Inclusion criteria

- Age ≥ 18 years.
- Patients who have given their free, informed and signed consent.
- Patients affiliated to a social security scheme or similar.
- Patients monitored for clinically confirmed HHT (presence of at least 3 Curaçao criteria) and/or confirmed by molecular biology.
- Patient presenting nosebleeds with total duration > 30 minutes for 6 weeks prior to the time of inclusion justified by completed follow-up grids.

4.2.5 Exclusion criteria

- Women who are pregnant or nursing (lactating), women of child-bearing potential without reliable contraception.
- Patients not affiliated to a social security scheme.
- Patients who are protected adults under the terms of the law (French Public Health Code).
- Refusal to consent.
- Patients for whom the diagnosis of HHT has not been confirmed clinically and/or by molecular biology.
- Participation in another clinical trial wich may interfere with the proposed trial (judgment of the investigator).

- Patients who have undergone nasal surgery in the 6 weeks prior to inclusion.
- Known hypersensitivity to macrolides in general, to tacrolimus or to any of the excipients.
- Patient with an inherited skin barrier disease such as Netherton's syndrome, lamellar ichtyosis, generalized erythroderma, graft-versus-host skin disease, or suffering from generalized erythroderma.
- Patient with CYP3A4 inhibotors treatment, e.g. erythromycin, itraconazole, ketoconazole and diltiazem.
- Patients who have incompletely filled in the nosebleed grids in the 6 weeks preceding the treatment. If there is missing data for more than 7 days (10%), the patient cannot be included.
- Patients who do not present nosebleeds with a total duration of > 30 minutes for 6 weeks prior to the time of inclusion.
- Patients with ongoing immunosuppressive treatment
- Patients with known and symptomatic immune deficiency.

4.3 Assessment criteria for the study product

4.3.1 Main judgement criterion

The main judgement criterion is the percentage of patients experiencing an improvement in their nosebleeds. An improvement is defined as a 30% reduction in the total duration of nosebleeds over 6 weeks after treatment, compared with the duration of the nosebleeds in the 6 weeks before the treatment.

4.3.2 Secondary judgement criteria

1. Adverse Events (AE) and Severe Adverse Events (SAE) observed throughout the study (clinical examination, epistaxis grids, ENT examination at each visit before and after the treatment). Additionally, all patients are contacted by phone after 15 and 30 days of treatment in order to collect data on tolerance and observance of the treatment.
2. Clinical efficacy criteria:
   - Nosebleed duration will be evaluated by the nosebleed monitoring grids completed by the patient (Appendix 1), collected at inclusion (V1): observation of the nosebleeds in the 6 weeks prior to inclusion, at the end of the treatment (V2): observation of the nosebleeds in the 6 weeks during treatment, and at the end of the study (V3): observation of the nosebleeds in the 6 weeks after the end of the treatment.
   - Progress in the number of nosebleeds. This criterion will be evaluated by the nosebleed monitoring grids completed by the patient (Appendix 1) collected at inclusion (V1): observation of the nosebleeds in the 6 weeks prior to inclusion, at the end of the treatment (V2): observation of the nosebleeds in the 6 weeks during treatment, and at the end of the study (V3): observation of the nosebleeds in the 6 weeks after the end of the treatment.
   - Comparison of the number of red blood cell transfusions between inclusion (V1) (collected over 6 weeks before treatment), the end of the treatment (V2) (collected over 6 weeks of treatment) and at the end of the study (V3) (collected over 6 weeks after the end of the treatment).
   - Progress in the scores obtained in the SF36 quality of life questionnaire

completed at inclusion (V1), at the end of the treatment (V2) and at the end of the study (V3).

- Progress in the ESS (Epistaxis Severity Score) using data from the specific questionnaire (Appendix 2) completed at inclusion (V1), at the end of the treatment (V2) and at the end of the study (V3).

Biological efficacy criteria: progress in hemoglobin and serum ferritin concentrations between inclusion (V1) and the end of the treatment (V2) and at the end of the study (V3).

3. Systemic absorption, after 1, 3 and 6 weeks of nasal administration, will be evaluated by a tacrolimus dosage in the blood at the end of the treatment.

   Blood samples on EDTA are sent to the laboratory for a centralized analysis. A specific procedure is established to maintain the blind: the analysis results will not be transmitted as the study is ongoing, but may be provided on request at the end. Investigator will be informed in case of dosage above 5 ng/mL.

If convenient, patients can connect to the Clinsight platform (Ennov Clinical), with a personal identification number, and complete on-line questionnaires (ESS and SF36) and epistaxis grids. Otherwise they will complete a paper form.

4.4 Randomization, blinding and lifting the blind

The randomization process will be centralized. Allocation of a randomization arm to a patient included will be made by IWRS (Interactive Web Response System), on the basis of a unique randomization list for all investigation centers.

The lists of randomization will be pre-established, by the “Pole IMER” at the Hospices Civils de Lyon – Clinical Research Unit.

Clinsight (Ennov clinical) software will be used to manage this study.
During the inclusion visit, after verifying the inclusion criteria, the investigator connects to the platform to include the patients in the eCRF. This will assign an identification number. When inclusion is validated, the patient is randomized and a treatment code is allocated by the system. The treatment is then dispensed by the pharmacy at the Hospital Center.

This will be a double blind study in which neither the patient nor the investigator will be aware of the nature of the treatment administered so as to annul any bias in the follow-up and measurements.

Tubes of Tacrolimus 0.1% or placebo will be identical and will have appropriate labeling.

Should a serious adverse event occur, the main investigator, the co-investigators or the sponsor may request that the Anti-Poison Center in Lyon lift the blind 24h/24h (the phone number is written on the clinical trial participation card). The written detailed procedures for lifting the blind will be given to the investigators and the Anti-Poison Center in Lyon.

All requests for unblinding must be justified. Most often, study drug discontinuation and knowledge of the possible treatment assignments are enough to treat a study patient who presents with an emergency condition. When the investigator asks for unblinding, he/she must provide patient identifying information, the date, and the reason for unblinding. The investigator will be informed of the details of the drug treatment.

4.5 Modalities for premature termination of the treatment and withdrawal from the study

If the treatment is prematurely or temporary stopped by the patient:

- Due to complications linked to the product: intolerance or discomfort, the patient will not be replaced and will be followed-up as initially planned for the study.
- Due to intercurrent events such as high temperature, rhinitis, etc. the patient may start ointment administrations again when the event turns out favorably and will be followed-up as initially planned for the study.
- Due to reasons other than the onset of complications linked to the drug, such as for logistical reasons (for example, a patient's work-related trips), the patient will not be replaced and will be followed-up as initially planned for the study.

If a visit following treatment is not attended by the patient and cannot be rescheduled, this visit will be considered as absent and the next post-treatment follow-up visit will be scheduled according to the original timetable initially devised for this patient. There is no maximum number of post-treatment follow-up visits missed after which the patient will be withdrawn from the study, particularly in the case of complications.

4.6 Rules for definitive termination

4.6.1 A research person terminates his or her participation in the study

A patient's participation in the study will be terminated should the patient withdraw his or her consent. Patients may withdraw their consent at any time in the course of the study. Their withdrawal from the research does not in any way change their relationship with the investigating doctor, who will propose medical follow-up that is adapted to their clinical condition.

Patients will also stop the study treatment if they undergo nasal surgery or other procedures (such as local hemostatic matrix), as this may modify interpretation of the results. However, their follow-up will be maintained.

4.6.2 Termination of all or part of the research

The research may be terminated either temporarily or definitively:

- by decision of the main investigator, the sponsor or the Competent Authority;
- in case of knowledge of data that could compromise the study for reasons concerning the safety of the patients;
- in case of publication of new scientific data that bring the research into question.

5 Description, supply and management of the drugs

5.1 General modalities of preparation and administration

Marketed Protopic® 0.1% tubes of 30 g are used for this study. For the placebo, the manufacturing and filling is managed by an external pharmaceutical laboratory with GMP agreement. The placebo formulation is similar to the active ointment; it contains all the ingredients except the active one: tacrolimus. The product is provided in strictly identical tubes. The same masked label is placed on both batches in order to respect the blind.

The ointment is self-administered by patient, twice daily, for 6 weeks.

5.2 Treatment tested

The treatment tested is tacrolimus, manufactured by the laboratories Astellas and commercialized as Protopic® (tube of 30 g) at 0.1% of tacrolimus.

5.2.1 Modalities for the preparation

Commercialized tubes (30 g) of Protopic® 0.1% are used. Tubes are completely masked by a specific label. This process will be carried out by Unither pharmaceuticals, a Contract Manufacturing Organization located in Bordeaux (France).
An additional label is attached with suitable information regarding the clinical trial, including the treatment code allocated. This labeling will be carried out by the Pharmacy at the Hospices Civils de Lyon. The tubes will be weighed before delivery to the patient.

5.2.2 Storage and conservation

The shelf life of the product is two years.
Tubes should be stored at room temperature, not above 25°C.

5.2.3 Return and destruction

After the end of the administration period, the tubes will be returned to the pharmacy at the hospital center and will once again be weighed “after administration” so as to determine the exact quantity administered. The tubes will be conserved for the monitoring visits and destroyed in accordance with the procedures in force after sponsor authorization.

5.3 Placebo

The comparative treatment is the same formulation as the active product but without tacrolimus.

5.3.1 Modalities for preparing

This product is manufactured for this study by Unither pharmaceuticals, a Contract Manufacturing Organization located in Bordeaux (France). The ointment is packed in strictly identical tubes to those of Protopic®, and covered by the masking label.
An additional label is attached with suitable informations regarding the clinical trial, including the treatment code allocated. This labeling will be carried out by the pharmacy at the Hospices Civils de Lyon. The tubes will be weighed before delivery to the patients.

5.3.2 Storage and conservation of the placebo

The shelf life of the product is two years.
A certificate is provided by Unither pharmaceuticals, according to stability study results.
The tubes should be stored at room temperature, not above 25°C.

5.3.3 Return and destruction

After the end of the administration period, the tubes will be returned to the pharmacy and will once again be weighed “after administration” so as to determine the exact quantity administered. The tubes will be conserved for the monitoring visits and destroyed in accordance with the procedures in force after authorization.

5.4 Associated treatments

No other experimental drug for nosebleeds may be used during the study. If nasal surgery becomes necessary during the study, the patient will be withdrawn from the study.

Systemically available tacrolimus is metabolized via hepatic Cytochrome P450 3A4 (CYP3A4).The possibility of interactions cannot be ruled out and patients with ongoing treatment of CYP3A4 inhibitors (e.g. erythromycin, itraconazole, ketoconazole and diltiazem) will not be included in the study.

All other concomitant treatments necessary for management of the patient will be authorized during the study and will be documented in the study’s data collection sheets. Recommendations will be given to patients in case of administration of another nasal treatment (see paragraph 6.2.1).

5.5 Drug circuit

5.5.1 Supply

Protopic® 0.1% tubes are ordered by the subcontractor: Unither pharmaceuticals, to carry out the blinding operation.

For the manufacture of the placebo, all operations are managed by the subcontractor: Unither pharmaceuticals, supply of raw materials, manufacturing, filling, masking, and analytic control.

Tubes of Protopic® and placebo are sent to the Central Pharmacy at the Hospices Civils de Lyon. They will be labeled, released and stored on their premises.

The pharmacies in the centers participating in the study are supplied by the Central Pharmacy at the Hospices Civils de Lyon.

5.5.2 Dispensing the study products by the hospital pharmacy in the centers participating in the study

The doctor investigator prescribes Protopic® 0.1% or placebo on the specific prescription sheet for the study. The information provided by the doctor will be:

- date of the prescription;
- surname, forenames and date of birth of the patient using a patient sticker;

- The patient's identification number.
- The treatment code.

The original of the prescription will be taken to the hospital pharmacy of the Hospital Center. The product allocated is then dispensed.

Before delivery, the tube is weighed. It will be weighed again after its return to calculate the total quantity administered. These data processed by the pharmacies will be available if necessary.

One tube is delivered to each patient; a specific leaflet is included with recommendations and application modalities.

All the traceability of the treatments used will be consigned to the prescription register specific to the trial at the HOSPITAL PHARMACY at the Hospital Center.

5.6 Ointment tubes: presentation and supplier

The primary packaging is a laminate tube with an inner lining of low-density-polyethylene fitted with a polypropylene screw cap.

Protopic® 0.1% is manufactured by Astellas pharma.

The placebo formulation is manufactured by Unither Pharmaceuticals.

6 Practical running of the study

6.1 General organization and study sites

Patients will be recruited and informed during a standard consultation with the ENT doctor or doctor responsible in the reference center or skill center for HHT. Patients will be informed of the study and the need to complete nosebleed grids for ENT monitoring for the 6 weeks prior to the start of the treatment (Appendix 1: Nosebleed monitoring grid, a grid completed daily by patients).

The inclusion of the patients will take place when they come for a consultation for prescription of the treatment.

The treatment will be self-administered by the patient, twice daily, for 6 weeks.

Two follow-up visits are organized, at the end of the 6 weeks of treatment, and 6 weeks after the end of the treatment, with medical consultations in the department responsible for coordinating HHT (Reference or skill center) and in the ENT department of each center.

FK-506 dosage in blood are scheduled on Day 8, 22 and 43.

A phone call is scheduled on day 15 and 31 (i.e. 14 and 30 days after the beginning of the treatment) in order to collect information regarding tolerance and observance.

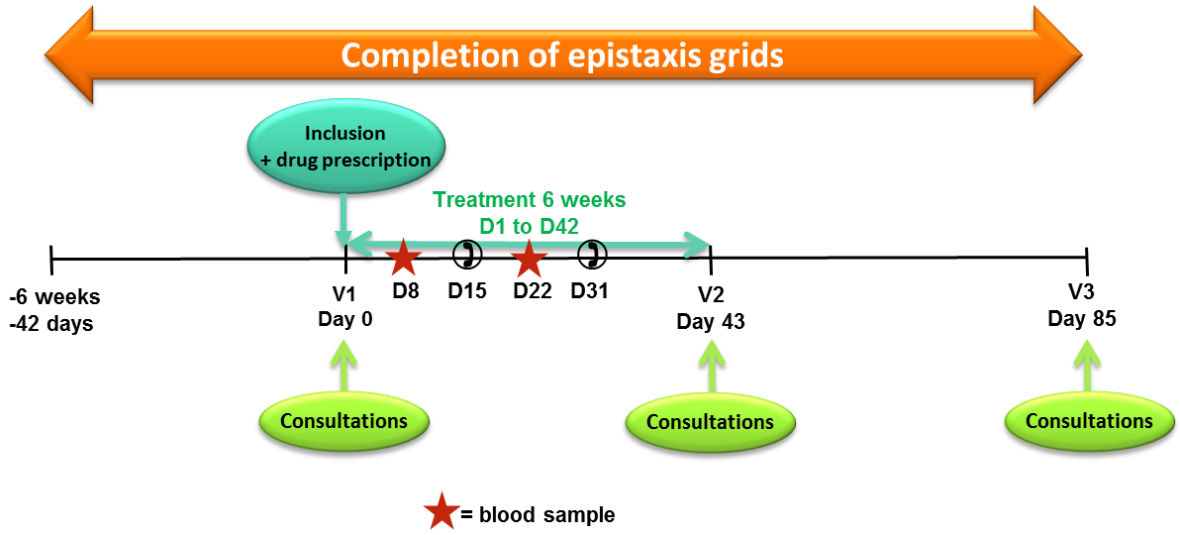

Figure 8: Diagram of the running of the study

6.2 Inclusion visit (V1)

Patients will be seen at a consultation for the treatment by a doctor and a clinical research assistant from the center if possible.

At this visit:

- The investigator will once again inform the patients about the study.
- The nosebleed grids completed by the patient in the 6 weeks prior to the treatment will be collected (Appendix 1: Nosebleed monitoring grid).
- The inclusion and exclusion criteria will be verified and the consent form will be signed. The investigator connects to the platform, includes the patient and an identification number will be assigned to the patient.
- The patient will undergo a clinical examination, including blood pressure and heart rate.
- A urinary pregnancy test will be performed for all female patients of child-bearing age. The investigator will inform these patients that there is no data available in pregnant women and they must use an effective contraceptive method (combined hormonal contraceptive, implant, intra-uterine device). The use of any other means, such as condom, will be left to the judgment of the investigator; the patient will have to give her commitment which will be recorded in the medical file.
- The number of red blood cell transfusions in the 6 weeks prior to administration of the treatment will be noted (as noted by the patient on the nosebleed grids).
- Any concomitant treatments will be noted.

If all the criteria are validated:

- The examination will be completed by a set of biological blood samples (2 x 5 mL tubes) for hemoglobinemia and serum ferritin.

- An ENT examination will be carried out (Appendix 3: Monitoring ENT examination).
- The ESS questionnaire is completed by patient (Appendix 2).
- An SF36 quality of life questionnaire will be given to the patient for completion.
- The nosebleed grids will be given to the patient for ENT monitoring during the 6 weeks of treatment (Appendix 1: Nosebleed monitoring grid). Specific boxes are provided to mark the two daily administrations, in order to verify observance of the treatment. If convenient for the patient a connexion code can be provided to allow them to complete these grids online on eCRF.
- Drug dispensation: The prescription for the drug will be made, and the product will be delivered by the pharmacist at the hospital. Patients are carefully instructed how to apply the medication throught an in vivo demonstration and a written description is provided with the product in which the modalities of application are reported.
- A clinical trial participation card will be given to the patient. It will include phone numbers if needed and in case of emergency. Recommendations are given in case of the onset adverse events.
- A specific prescription will be given to the patient for the dosage of FK506 in blood, one week and three weeks after the beginning of the treatment (i.e. on Day 8 and Day 22). Blood sample will be taken in a laboratory selected by the patient; the latter will send the tube in the biological laboratory for a centralized analysis.

If the criteria are not validated, the patient may be asked to return at a later date if the inclusion criteria can be normalized.

6.2.1 Ointment administration

The ointment is self-administered by the patient twice daily.
About 0.1 g of product should be administered in each nostril. The tube is gently squeezed to extract an amount roughly equivalent to the size of the head of a cotton swab.

The ointment is introduced into each nostril with a finger or a cotton swab. Patients can choose the most convenient way for them to administer the product. The product is extended inside the nostril with a cotton swab or/and by external pressure on the nostril.

Should other nasal product be used, such as physiologic serum or gelositin for example, we recommend that the other product not be applied simultaneously but at a different time, for example two hours before or after the tested product.

6.2.2 Recommendations

Patients will receive recommendations on how to contact the doctor in case of the onset of adverse events.

A burning sensation is frequently observed at the administration site; usually this sensation is acceptable and disappears after a few days of administration.

In case of an adverse event probably due to the product: skin irritation, an unacceptable burning sensation, pruritus, and erythema, at the application site:

- The patient must stop the treatment.
- He or she must inform the investigator as soon as possible.
- Based on symptoms, a medical consultation can be carried out by a general practitioner, a specialist or an investigator involved in the study.
- The treatment can be reintroduced, or not, after clinical normalization.
- It is up to the investigator to make the decision in the interest of the patient, on the basis of the balance between the risk of a new event and the risk of aggravation of the disease.

The modalities for managing nosebleeds will be given to the patients to inform all doctors of the treatment of the nosebleeds specific to this disease.

6.3 Phone calls on day 15, 14 days after the beginning of the treatment (up to day 18 tolerated)

Patients will be contacted by phone, 14 days after the beginning of the treatment, to collect intermediate data regarding tolerance and observance.

The following data will be collected:

- Treatment observance: any interruption to the treatment interruption will be noted precisely (date, duration), as will the reason for the interruption.
- Occurrence of adverse events: nature, date of onset, and whether or not a symptomatic treatment was given.
- Any change in the concomitant treatments.
- The date of the blood sample planned at day 8 (FK506 dosage).

6.4 Phone calls on day 31, 30 days after the beginning of the treatment (up to day 37 tolerated)

Patients will be contacted by phone, 30 days after the beginning of the treatment, to collect intermediate data regarding tolerance and observance.

The following data will be collected:

- Treatment observance: any interruption to the treatment interruption will be noted precisely (date, duration), as will the reason for the interruption.
- Occurrence of adverse events: nature, date of onset, and whether or not a symptomatic treatment was given.
- Any change in the concomitant treatments.
- The date of the blood sample planned at day 22 (FK506 dosage).

6.5 Visit at the end of the treatment, V2 = at day 43 (up to day 50 tolerated)

The patients will be seen in consultation, in the Reference center or skill center for HHT.

The following examinations/consultations will take place:

- Clinical examination including blood pressure and heart rate.
- Collection of the nosebleed grids completed by the patients during the 6 weeks of treatment (Appendix 1: Nosebleed monitoring grid), if not completed on line. These grids include monitoring of treatment administrations.
- The ESS questionnaire is completed by patient (Appendix 2).
- New nosebleed grids will be given to the patients for ENT monitoring during the next 6 weeks (Appendix 1: Nosebleed monitoring grid), if not completed online.
- The number of red blood cell transfusions received by the patient in the last 6 weeks will be noted.
- Patients will return the product, it will be transmitted to the hospital pharmacy.
- A set of biological blood samples (2 x 5 mL tubes) is collected: hemoglobinemia and serum ferritin.
- A blood sample is collected (4 mL on EDTA) for tacrolimus dosage.
- An SF36 quality of life questionnaire will be given to patients for completion.
- Monitoring and collection of any adverse events.
- Concomitant treatments will be noted.

6.6 Visit after 6 weeks follow-up, V3 = at day 85 (up to day 100 tolerated)

The patients will be seen in consultation, in the Reference center or skill center for HHT.

The following examinations/consultations will take place:

- Clinical examination including blood pressure and heart rate.
- Collection of the nosebleed grids completed by the patients during the 6 weeks' follow-up after the treatment (Appendix 1: Nosebleed monitoring grid), if not completed online.
- The ESS questionnaire is completed by the patient (Appendix 2).
- The number of red blood cell transfusions received by the patient in the last 6 weeks will be noted (as noted by the patient on the nosebleed grids).
- A set of biological blood samples (2 x 5 mL tubes) is collected: hemoglobinemia and serum ferritin.
- An SF36 quality of life questionnaire will be given to patients for completion.
- Monitoring and collection of any adverse events.

- Concomitant treatments will be noted.

6.7 Synopsis of the study per patient

	Inclusion V1 J0	Blood sample D8 (to 10)	Phone Call D15 (to 18)	Blood sample D22 (to 24)	Phone Call D31 (to 37)	**V2 D43 (to 50)**	**V3 D85 (to 100)**
Inclusion / exclusion criteria	**x**						
Epistaxis grids surrender	**x**		**x**		**x**	**x**	
Epistaxis grids collection	**x**					**x**	**x**
Consent Form signature	**x**						
Pregnancy Test	**x**						
Clinical examination (HR, BP)	**x**					**x**	**x**
ENT examination	**x**					**x**	**x**
Hémoglobinemia, serum ferrritin	**x**					**x**	**x**
FK 506 dosage		**x**		**x**		**x**	
Treatment : protopic/placebo dispensation	**x**						
Product return						**x**	
Blood Cell transfusions collection	**x**					**x**	**x**
ESS questionnaire	**x**					**x**	**x**
SF36 Quality of life questionnaire	**x**					**x**	**x**
Concomitant treatment collection	**x**		**x**		**x**	**x**	**x**
Adverse events collection	**x**		**x**		**x**	**x**	**x**

Legend: D = dayV = visit

Table 1: Synopsis of the study per patient

7 Intercurrent events

7.1 Definitions

7.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.1.2 Serious adverse event (SAE)

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (t*he term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event ; it does not refer to an event which hypothetically might have caused death if it were more severe)*
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically significant event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.
The term “severe” is a measure of intensity, thus a severe adverse event is not necessarily serious. For example, “nausea of several hours” duration may be severe but may not be clinically serious.
For “TACRO” study, any tacrolimus blood concentration resulting > 5ng/ml and any sign of infection under treatment should be considered as medically significant event and reported immediately by the investigator to the sponsor as a SAE.

7.1.3 Intensity

The intensity of the event will be graded according to the following classification:

- Mild (grade 1): Discomfort noticed but no disruption of normal daily activity
- Moderate (grade 2): Discomfort sufficient to reduce or affect normal daily activity
- Severe (grade 3): Incapacitating with inability to work or perform normal daily activity
- Life-threatening (grade 4): Substantial risk of dying at time of event
- Death: (grade 5)

7.1.4 Adverse reaction

An adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

7.1.5 Reference document for the experimental drug

Reference document for the experimental drug n°1: Summary of Product Characteristics (SPC) for PROTOPIC 0.1% (tacrolimus).

7.2 Responsabilities of the investigator

7.2.1 Adverse Events reporting

All **adverse events (AE)** regardless of seriousness or relationship to Investigational Product that occurred **after the informed consent up to 30 days after the last study drug administration** are to be recorded in the AE pages of the Case Report Form (CRF). After this delay only fatal AE and adverse event related to the IMP must be recorded.
Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all adverse events and his opinion as to whether the adverse event can be related to the study drugs and/or to concomitant drugs.
All events that meet one or more criteria of seriousness will be reported as Serious Adverse Event.

7.2.2 General AE/SAE reporting rules:

Any episode of any grade of toxicities, related to a Serious Adverse Event must be reported as “Adverse Event” in the appropriate CRF pages.
Adverse events (serious or not) will not be recorded after the start of a new out-of-study treatment or after disease progression.
Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the study or before study drug was given are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the study (eg surgery was performed earlier than planned).
All adverse events which meet grade 3, 4 and 5 criteria must be reported immediately to the sponsor.

7.2.3 SAE declaration

All defined **Serious Adverse Events (SAEs)** occurred **after the informed consent up to 30 days after the last study drug administration**, whether or not ascribed to the study, will be recorded in the Serious Adverse Event pages. After this delay only fatal SAE and SAE related to the IMP must be recorded.
Serious Adverse Event (serious or not) will not be recorded after the start of a new out-of-study treatment or after disease progression (fatal event excluded)
All Serious Adverse Events must also be reported on the Adverse Event page of the CRF.
In a case of Serious Adverse event The Investigator must immediately:

- **SEND, by fax, the SAE pages to**

SAFETY DESK:
FAX: +33 (0) 4 72 11 51 90

All SAE forms must be dated and signed by the responsible Investigator or one of his/her authorized staff Members.

- Attach the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical study are properly mentioned on any copy of source document. For laboratory results, include the laboratory normal ranges.
- Follow up of any Serious Adverse Event that is fatal or life threatening should be provided within one calendar week.

For serious adverse events, the following must be assessed: relationship to test substance, action taken, and outcome to date. The relatedness with concomitant treatment must also be evaluated. The Causality is initially assessed by the investigator. For serious adverse events, causality can be one of two possibilities:

- **Unrelated**
- **Related**

7.2.4 Follow up of Adverse Events and Serious Adverse events

- Any SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported should be sent to the SAFETY DESK as soon as information becomes available.
- All adverse events must be documented and the outcome must be followed up until the return to normal or consolidation of the patient's condition.

7.3 Sponsor's responsibilities

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to study drug, to the Health Authorities in each country in accordance with the law of March 5, 2012 international and local regulations, Ethics Committees, Clinical Trial Eudravigilance database and to the Investigators.
The expectedness of an adverse reaction will be determined by the Sponsor according to the Summary Product Characteristics of PROTOPIC 0,1%®.
The sponsor will report all safety information from the trial in the Annual Safety Reports and will notify the reports to the Health Authorities and Ethics Committees in accordance with international and local regulations.

7.4 Specific management of complications

7.4.1 Nosebleeds

Patients will have access to the standard management techniques for nosebleeds in HHT. ENT monitoring will be ensured before the start of administration, after 6 weeks of treatment and 6 weeks after the end of the treatment so as to note any modification to the nasal mucosa during the treatment (Appendix 3: ENT monitoring examination).
The modalities for the management of nosebleeds will be given to the patients, as described in the "PNDS" (Protocole National de Diagnostic et de Soin), so that they may inform any doctor of the treatment modalities for the nosebleeds specific to this

pathology. Emergency document (see Appendix 4), accessible on the internet http://www.favamulti.fr/wp-content/uploads/2016/05/37_RO-Epistaxis.pdf, is given to the patients.

7.4.2 Perforation of the nasal septum

ENT monitoring will take place at each visit so as to note any modification to the nasal mucosa. Should there be any perforation of the nasal septum, the ENT monitoring will be prolonged until the perforation closes, as it generally does spontaneously.

7.4.3 Other complications associated with adverse events linked to topical tacrolimus

Common complications linked to topical administration described in the Summary of Product Characteristics are burning skin, pruritus, skin erythema, skin tingling, folliculitis, acne, herpes simplex, hyperesthesia (increased skin sensitivity, especially to hot and cold) and alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage).

In case of the onset of a severe reaction, patients should stop product administration immediately. They must inform the investigator of the study as soon as possible and, if necessary, consult a doctor.

Adapted management of the complication will be administered.

7.4.4 Tacrolimus systemic absorption

Tacrolimus systemic absorption will be monitored in this study. FK506 dosages in blood are scheduled at Day 8, 22 and 43. Analysis will be centralized in “Hospices Civils de Lyon”.
After transplantation , the optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL[64] and should be maintained below 20 ng/mL.
In the present study, no systemic absorption and effect are expected. However in case of positive dosage, from 5 ng/mL and above, the laboratory will immediately inform the investigator who will ask the patient to stop treatment.
In case of dosage higher than 20 ng/mL, the laboratory will immediately inform the investigator who will ask the patient to stop treatment and the patient will be hospitalized.
Any sign of infection due to immunosuppressive action should be reported immediately to the sponsor as SAE.

8 Data management

8.1 Electronic case report forms

All the information required by the protocol must be provided on the eCRF and an explanation is given for any missing data. All clinical or paraclinical data have to be transferred to the electronic case report forms as soon as they are obtained. The form

at the end of each visit must be dated and signed by the investigator thus indicating his or her approval of the data in the case report forms.

The database (items defined on the basis of the electronic case report forms) will be put together in collaboration with the Clinical Research Unit at the Pole IMER (Dr F. Chapuis).

8.2 Source documents

The source documents are the original documents, the data and dossiers from which the data concerning the patients will be reported in an electronic case report forms (Clinsight). These data include, amongst other things, the results of examinations, monitoring of the patient at the hospital and/or medical notes, self-monitoring forms, dispensation notes and medical correspondence.
The investigator must undertake to authorize direct access to the source data for the study during control visits, audits or inspections.

8.3 Archiving

The following documents concerning this research will be archived in the appropriate premises and locked in accordance with Good Clinical Practices for a period of 15 years following the end of the research by those responsible for the study:

- the original version of the consent forms signed by the participants,
- the protocol and its appendices and any amendments made to the protocol,
- electronic case report forms,
- all the other documents and letters concerning the research.

8.4 Electronic data management

The Clinical Research Unit at the Pole IMER will develop an electronic Case Report Form to collect data for the study.
The study data will be computerized in conformity with the law concerning electronic data, files and civil liberties (law 78-17 of January 6, 1978 modified by law 2004-801 of August 6, 2004). Data access will be restricted.

Electronic report forms will be available for each participating center. Electronic case report forms will be filled in via internet by the investigator. A user guide and online training will be available to investigators.
The investigator is responsible for the accuracy, quality and relevance of all data captured. As such, any changes in value must be validated in the eCRF. Data changes will be drawn in an audit trail.
Patients' eCRF will be printed at the end of the study and will be archived by the investigator.

When entering data, the system will immediately run consistency checks.
Coherence controls will also be carried out using SAS software.

9 Statistics

9.1 Number of participants

We hypothesize that 60 % of patients will be improved in the treatment group against 15 % in the placebo group. It is therefore necessary to include 22 patients in each group to reach an 80% power with a 5% alpha (bilateral), leading to 44 patients overall (Fisher exact test).
Taking into account early withdrawal and patients who may be lost to follow-up, we are going to include 24 patients in each group, that is to say, a total of 48 patients.

9.2 Statistical analysis plan

The following section includes the main elements of the statistical analysis plan. This plan may be revised to take into account any amendments to the protocol and to make changes in order to adapt to the occurrence of unexpected events in the course of the study and which may have an impact on the analysis of the data.
These possible revisions will be carried out before the database is frozen.

At the end of the study, the data analysis will be carried out by the Clinical Research Unit at the Pole IMER (Department of Dr François Chapuis, Hospices Civils de Lyon), who will have the randomization codes.

In case of scattered numbers of ointments across patients, the analyses would be repeated with an adjustment for the number of ointments or would be broken into subgroup analysis.

9.2.1 Analysis populations

9.2.1.1 “Efficacy” population in intention to treat

This population will be composed of all the randomized patients. If patients stop the study treatment, their follow-up will be maintained in order to obtain the epistaxis grids.

9.2.1.2 “Efficacy” population per protocol

This population will be composed of all the patients who have received all the treatments set out in the protocol. A treatment will be considered complete if the patient received at least a total of 60 administrations out of 84 (twice a day for 42 days) envisaged by the protocol.

9.2.1.3 “Safety” population

This population will be composed of all the patients who have received at least one ointment.

9.2.2 Statistical methods

9.2.2.1 Populations

All the populations in the study will be presented with their numbers.

9.2.2.2 Deviation from the protocol

Any deviation from the protocol that may have an impact on the results of the study will be listed.

9.2.2.3 Initial characteristics

All the initial characteristics of the patients will be summarized by means of descriptive statistics (number, average, standard deviation, median, minimum and maximum for the quantitative variables and numbers and percentages for the qualitative variables).

9.2.2.4 Analysis of the main judgement criterion

The percentage of patients experiencing improvement in their nosebleeds will be computed in each group. An improvement is defined as a 30% reduction in the total duration of nosebleeds over 6 weeks after treatment, compared with the duration of the nosebleeds in the 6 weeks before the treatment.
The percentage of the two groups will be compared using a Fisher exact test, and the analysis will be performed on the intention to treat population.
Patients who stopped the treatment but who have epistaxis grids will be analyzed using their data. Patients who withdraw from the study before completing the follow-up will be considered as failures.
A descriptive listing will present for each patient: the duration of nosebleeds before treatment, during treatment, after treatment, the treatment group, the number of consecutive days of treatment, the total number of days of treatment.

9.2.2.5 Analysis of the secondary judgement criteria

All AE and SAE will be coded with MedDRA. Each adverse event observed between inclusion and the end of follow-up will be listed by frequency in each group. Then, the percentage of patients with at least one adverse event, or at least one severe adverse event will be computed and compared between the 2 groups. A list and verbatim of severe adverse events will be provided. All analyses will be performed on the safety population.

Efficacy criteria:

- The total duration of nosebleeds will be presented in each group for the 3 periods (6 weeks before treatment, 6 weeks of treatment, 6 weeks' follow-up after treatment). The relative evolution in duration of nosebleeds will be computed by subtracting the baseline value from the V2 value (end of treatment) and the V3 value (end of study). The delta from inclusion (V3/V1 & V2/V1) in total duration will be compared between the 2 groups using student t-tests (or

Mann-Withney tests in case of non normality). Mixed models will be produced to compare evolution between the groups.

- The number of nosebleeds will be presented in each group for the 3 periods (6 weeks before treatment, 6 weeks of treatment and 6 weeks' follow up after the end of treatment). The relative evolution in duration of nosebleeds will be computed by subtracting the baseline value from the V2 value (end of treatment) and the V3 value (end of study). The delta (V3/V1 & V2/V1) in number will be compared between the 2 groups using student t-tests (or Mann-Withney tests in case of non normality). Mixed models will be produced to compare evolution between the groups.
- The number of red blood cell transfusions will be presented in each group for the 3 periods (6 weeks before treatment, 6 weeks of treatment, 6 weeks' follow-up after treatment). The relative evolution in the number of red blood cell transfusions will be computed by subtracting the baseline value from the V2 value (end of treatment) and the V3 value (end of study). The delta (V3/V1 & V2/V1) in number of red blood cell transfusions will be compared between groups using student t-tests (or Mann-Withney tests in case of non normality). Mixed models will be produced to compare the evolution between groups.
- The physical component and mental component of the SF36 and its domains will be presented in each group at inclusion, at the end of the treatment and at the end of the study. The relative evolution in SF36 (overall and per item) will be computed by subtracting the baseline value from the V2 value (end of the treatment) and the V3 value (end of the study). The delta (V3/V1 & V2/V1) in components and in each SF36 domain will be compared between groups using student t-tests (or Mann-Withney tests in case of non normality). Mixed models will be produced to compare evolution between the groups.
- The ESS will be presented for each group at inclusion, at the end of the treatment, and at the end of the study. The relative evolution in ESS will be computed by subtracting the baseline value from the V2 value (end of treatment) and the V3 value (end of study). The delta (V3/V1 & V2/V1) in ESS will be compared between groups using student t-tests (or Mann-Withney tests in case of non normality). Mixed models will be produced to compare evolution between the groups.
- The biological values (hemoglobin and serum ferritin) will be presented in each group at inclusion, the end of the treatment and the end of the study. The relative evolution in hemoglobin and ferritine levels will be computed by subtracting the baseline value from the V2 value (end of treatment) and the V3 value (end of study). The delta (V3/V1 & V2/V1) in biological measures will be compared between groups using student t-tests (or Mann-Withney tests in case of non normality). Mixed models will be produced to compare the evolution.

Systemic tacrolimusTacrolimus systemic absorption: the percentage of patients who present with systemic absorption of KK506 will be calculated. If tacrolimus is detected in the blood the level of exposure will be listed.

9.2.2.6 Handling of missing values/censoring/discontinuations

Follow-up of patients will be pursued regardless of the situation, except if the patient withdraws his or her consent. In the case of nasal surgery during the study period or any other treatment that is a substitute to the studied treatment, the patient will be followed up but his or her results will be considered as a failure.

The main judgement criterion is based on grids that are filled in daily. Patients are used to these grids and fill them in carefully; the daily durations are summarized over 6 weeks. However if one day is missing, the value will be replaced by an average of the 4 values before and the 4 values after the missing value. This strategy will be applied up to 7 missing values over 6 weeks (i.e. 10%).
If more than 7 days and less than 21 days (included) are missing, a daily average will be computed from the data available (from the 6-week period evaluated) and will be multiplied by 42 to obtain the overall estimated duration.

If a patient is lost to follow-up or refuses to communicate his nosebleed grids or has more than 21 days missing on his grids, the result for the concerned patient will be considered as a failure.

10 Quality assurance

The Clinical research associate mandated by the sponsor is responsible for inspecting the case report forms in conformity with the monitoring schedule for the study, throughout the study, verifying that the protocol is being respected, as well as the totality and the conformity of the source documents, the coherence of the data and that the regulations governing good clinical practices are being respected. The Clinical research associate mandated must have access to the medical files of the patients and other files in relation to the study needed to verify the data entered in the study's electronic case report forms.
The controls of presence, verisimilitude, and coherence will be carried out electronically in accordance with the rules defined in advance. Requests for information will be generated when possible errors are detected.

The health authorities and/or an independent auditor mandated by the sponsor may audit any investigation site, or the sponsor, throughout the duration of the study or after the end of the study so as to control how the study is being conducted and the quality of the data. The investigator must provide direct access to the source documents, and the sponsor to the regulatory documents.

11 Ethical and regulatory aspects

The study will be conducted in conformity with the protocol, the guidelines from the French and European Good Clinical Practices, the Helsinki declaration in its most recent version (Seoul 2008), as well as the recommendations of the ICH (International Conference on Harmonization), and in conformity with the law covering research involving the human person in the French Public Health Code (Law 2012-300 of March 5, 2012).

11.1 Qualification of the research and patient information

In accordance with Law n°2012-300 of March 5, 2012 of the French Public Health Code, this is considered as research involving the human person. The study effectively concerns a drug, called tacrolimus. This drug is not generally used locally in nosebleeds in patients with HHT, but is instead administered topically in the treatment of dermatitis.

11.1.1 Information sheet

Patients may only participate in this study if they have given their written informed consent. To do so, they will first receive spoken and written information from their doctor on: the aim of the study, the duration of their participation, the procedures that will be followed, the benefits, the predictable risks, the disadvantages that may result from the treatments administered or examinations undergone, the confidentiality of the data, insurance cover, and management of the costs associated with this study.
All this information will be summarized in an information sheet that will be given to each patient.

11.1.2 Enlightened consent

Patients may only participate in this study if they have given their written informed consent. Two copies of the consent form will be signed by the subject and the investigating doctor. One copy of this document will be given to the person participating in the study, and the investigator must keep the second copy in his or her archives for a minimum period of 15 years.

11.2 Benefit / risk ratio

All the surgical treatments currently on offer are aggressive for the nasal mucosa and present a risk of perforation of the nasal septum.

Patients' participation in this study will not compromise their possibility for future medical or surgical treatment.

The expected adverse events in this study are:

- Skin burning or irritation at the application site (approximately half of the patients). These symptoms are usually mild to moderate and generally go away within one week of using Protopic. Administration could be easily stopped in case of adverse reaction.
- The risk of systemic adverse events related to tacrolimus is low given the very low doses of tacrolimus administered to the patients. Tacrolimus in blood is monitored and the treatment will be stopped in case of absorption.
- Risk for the blood test may be of the hematoma type at the puncture point or fainting.

If the efficacy of the treatment is shown, the treatment will be proposed to all the patients who have received the placebo.

The risk / benefit ratio for a patient participating in this study is thus perfectly acceptable.

11.3 Confidentiality of the data

Everyone taking part in the study will be bound by the confidentiality agreement regarding the protocol, and linked by professional confidentiality with regard to the participants.
The information sheet will summarize the rights of access of the participants to the nominative information concerning them either directly or indirectly.
All the data collected will be processed anonymously and will be covered by the laws of medical confidentiality.
On the case report forms, or on all other documents, the patients must be identified by their initials and their study number only.
We request that the investigator allow the representatives of the sponsor and/or legal authorities to have direct access to the patients' original medical files for verification of the procedures of the study and the data. The investigator must inform the patient that the files concerning him or her and in relation to the study will be reviewed by the aforementioned representatives without any breach of confidentiality.

11.4 Confidentiality and Good Clinical Practices

In conformity with the dispositions regarding the confidentiality of the data to which the people in charge of controlling the quality of the biomedical research will have access (article L.1121-3 of the French public health code), those people with direct access will take all the precautions necessary with a view to ensuring the confidentiality of the information concerning the people participating in the study and in particular with regards to their identity and the results obtained.
These people, as well as the investigators themselves, are subject to professional confidentiality restrictions (in accordance with the conditions defined by articles 226-13 and 226-14 of the French penal code).
During the biomedical research, or after its termination, the data collected on the people taking part will be rendered anonymous by the investigators (or any other specialized people).
These data must not under any circumstances reveal the names of the participants or their addresses. Only the initials of the subjects will be recorded, accompanied by a code number specific to the study and that indicates the chronological order of inclusion of the subjects.
Every person agreeing to participate in the research will have given his or her written agreement to have access to the individual data concerning him or her and which is strictly necessary for controlling the quality of the research.

11.5 Submitting the protocol to the CPP and ANSM

A request for authorization will be sent by the sponsor of the study to the ANSM. The protocol will be submitted to a randomly selected French CPP for assessment.

11.6 Amendments to the protocol

Any modifications to the protocol will be validated by the Scientific Committee and the sponsor of the study and submitted to the selected CPP and the ANSM for authorization if applicable.

11.7 Computerization of the data

The information collected during this study will be the subject of data processing. The file will be declared at the CNIL and will be put together in conformity with the law governing information technology, files and personal rights (law 78-17 of January 6, 1978, modified by law 2004-801 of August 6, 2004): commitment to conformity with the MR-001 (deliberation n°2016-262 of July 21, 2016).

In conformity with the Information Technology and Freedom law currently in force, patients have the right to access, communicate, oppose and rectify any nominative information. This right can be exercised directly by the patient or by the doctor of his or her choice from the doctor investigators participating in the study.

11.8 Curriculum vitae and signature of the protocol

Before starting the study, the main investigator will provide the representatives of the sponsor with a copy of his or her signed and dated personal curriculum vitae, as well as that of his or her co-investigators, and a signed and dated (signature page) copy of the final protocol of the study.

11.9 Insurance

The Hospices Civils de Lyon (3 Quai des Célestins, BP 2251, 69229 Lyon Cedex 02) will be the sponsors of the study and will take out an insurance policy in their name and at their expense (Compagnie SHAM, 18 rue Edouard Rochet, 69008 Lyon, contrat n°XXXX).

11.10 Study report and publications

The final report of the study will be written in collaboration with the investigator, co-investigators and person responsible for analyzing the data.
This report will be submitted to each of the investigators for approval and once a concensus has been obtained, the final version will be officially approved by the signature of each of the investigators.

The results, regardless of their nature, will be submitted for publication in the international journals with peer review committees interested in this disease.
One main publication is planned, and will focus on the efficacy of nasal administration of tacrolimus on the population studied. The main investigator will write and sign the article as the leading author, providing the main results from the study. The other authors will include the co-investigators, and a representative of the department having carried out the statistical analysis. The ranking of the authors will be decided by concensus, validated ultimately by the main investigator.
Indication of the sponsorship by the Hospices Civils de Lyon will be made in all or any publication.

12 Organization of the study

12.1 Scientific committee

The Scientific Committee for the study, presided over by the study's main investigator, will be composed of investigators (one ENT specialist, one geneticist), the methodologist and the sponsor of the study. The committee will be responsible for validating the definitive version of the protocol, supervising the implementation and running of the study, and for writing the reports and publications resulting from the study.

12.2 Independent monitoring and safety committee for the study

Monitoring the safety of administration of the product, motivated by the iatrogenic risks, justifies the setting up of a specific independent monitoring and safety committee.

This committee will meet as defined in paragraph 2.3. The first meeting will occur after collection of adverse events and observance of the treatment after 30 days for the 8 first patients included.
The committee will give its recommandations on the continuation of the study.
DSMB recommendations will be forwarded to ANSM for information.
There will be two or three meetings depending on the tolerance of the product.

It will be composed of:

- a specialist of the disease not involved in the study,
- a ENT specialist,
- a statistician specializing in the methodology of clinical trials.

13 Medium and long term perspectives

Nosebleeds are a significant morbidity factor in HHT, not solely because of the anemia they provoke, but also because of the handicap that they represent in the daily lives of active patients.
In total, around 95% of the patients followed for HHT are concerned by nosebleeds. Although the mortality rate for the patients followed for this disease is low, the morbidity rate is severe and the psychosocial impact of HHT is almost constant in adults.

For most patients with severe nosebleeds, a regular nasal administration of tacrolimus should make it possible in terms of clinical development to:

- obtain a significant reduction in nosebleed duration.
- decrease the monthly number of nosebleeds,
- increase hemoglobin and serum ferritin concentrations,
- decrease the number of local surgical and packing treatments, as well as the intravenous perfusions of iron,
- decrease the number of blood transfusions sometimes needed in case of a too great loss of blood,
- improve air flow and decrease nasal obstructions,

- improve patient quality of life (possibility of going shopping, going to a restaurant, enjoying meals with family, having a professional activity, etc.),
- decrease the number of consultations and/or hospitalizations,
- decrease the cost of management of severe nosebleeds given their current costs (transfusions, iron supplementation, etc.).

The possible efficacy of a nasal administration of tacrolimus on nosebleeds would be extremely interesting and would constitute significant progress to the extent that no current treatments, either medical or surgical, have made it possible to significantly decrease nosebleeds in the long term, with the exception of the closure of the nasal cavities which remains an aggressive, last resort act.

In the long term, and should the product prove to be effective, it would be possible to imagine regular nasal administrations of tacrolimus.

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15 Appendices

15.1 Appendix 1: Nosebleed monitoring sheet

RENDU-OSLER : FICHE DE SURVEILLANCE DES EPISTAXIS

Nom : Prénom : Né(e) le :

ANNEE : 20

MOIS :

Inscrire dans la colonne correspondant au jour du mois, **la durée en minutes** de chaque épistaxis.

Jour	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Episode 1																															
Episode 2																															
Episode 3																															
Episode 4																															
Episode 5																															
Episode 6																															
Episode 7																															
Episode 8																															
Total																															

ADMINISTRATION DE LA POMMADE PROTOPIC OU PLACEBO. FAIRE UNE CROIX TOUS LES JOURS POUR CHAQUE ADMINISTRATION																															
Jour	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Matin																															
Soir																															

Jour	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Transfusion Nb CGR																															
Injection Fer IV (mg)																															
Hemoglobine																															

Noter la liste des évènements que vous jugez importants survenus pendant cette période, la date de début et de fin, la prise d'autres traitements :

Date :	Commentaire :

15.2 Appendix 2: ESS questionnaire

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 who are involved in a Research Study. For more information regarding the meaning of this score, please discuss this with you health care provider.
Please answer each of the following questions as they pertain to your TYPICAL nosebleed symptoms DURING THE PAST 6 WEEKS.

Please answer all questions.

How often do you TYPICALLY have nose bleeding?
0 — Less than monthly
1 — Once per month
2 — Once per week
3 — Several per week
4 — Once per day
5 — Several each day

How long do your TYPICAL nose bleeds last?
0 — <1 minute
1 — 1–5 minutes
2 — 6–15 minutes
3 — 16–30 minutes
4 — >30 minutes

How would you describe your TYPICAL nose bleeding intensity?
0 — Not typically gushing
1 — Typically gushing or pouring

Have you every sought medical attention for nose bleeding?
0 — No
1 — Yes

Are you anemic (low blood count) currently?
0 — No
1 — Yes

Have you ever received a red blood cell transfusion specifically because of nose bleeding?
0 — No
1 — Yes

15.3 Appendix 3: ENT monitoring examination

ENT: NASAL examination

Visit |__|__|**Date** |__|__| |__|__| |__|__|

Septal perforationYes ☐No ☐

DysosmiaYes ☐No ☐

Nasal obstructionYes ☐No ☐ If yes, give details…….

Lesions

Comments:……
……
……
……
…….

Scabs

Right nasal cavity:**Left nasal cavity**:

Number:☐ None☐ None

☐ <50% of the visible surface☐ <50% of the visible surface

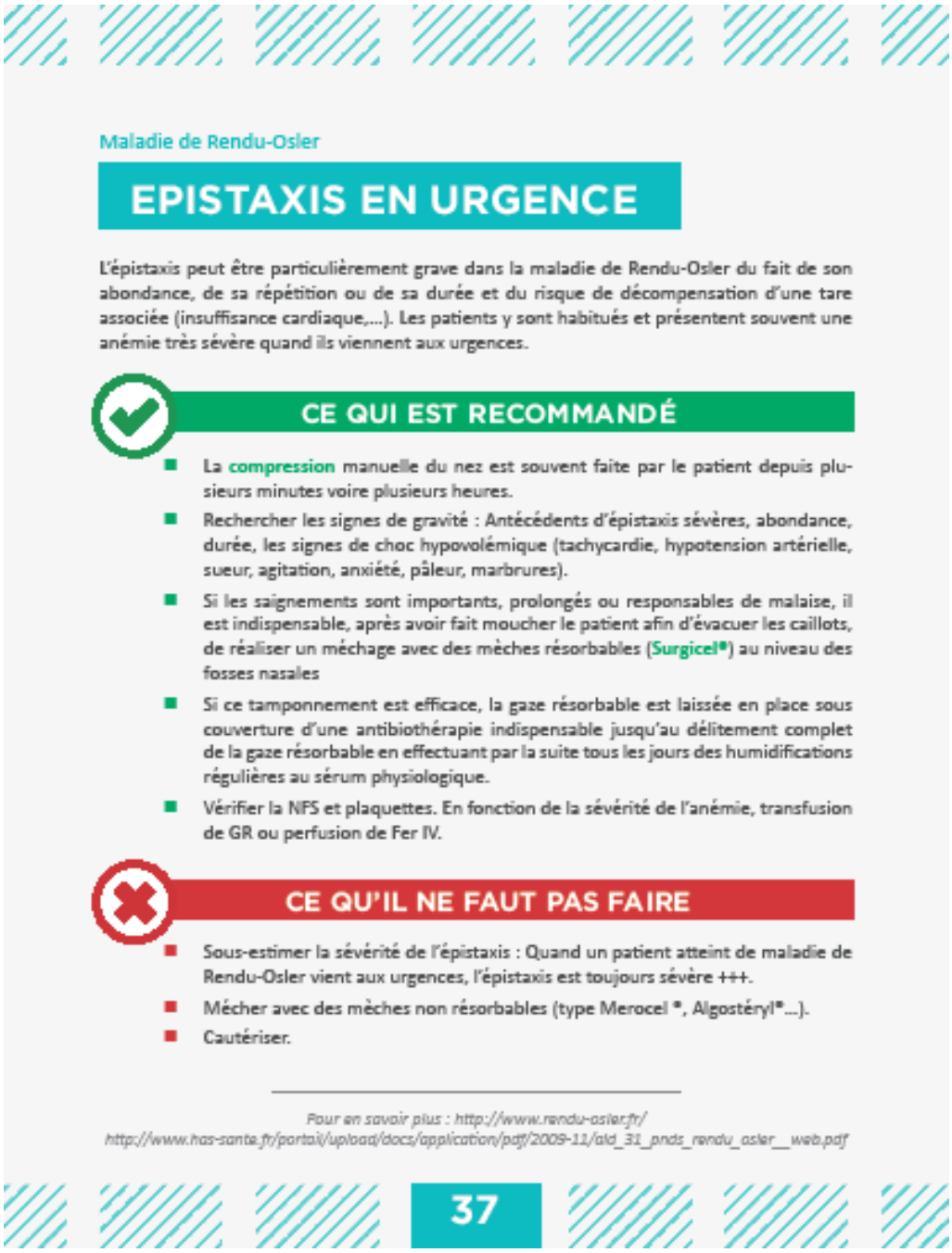
☐ >50% of the visible surface☐ >50% of the visible surface

Comments:……
……
……

Name of the doctor: ……..

Signature:

15.4 *Appendix 4: Epistaxis emergency*



Maladie de Rendu-Osler

EPISTAXIS EN URGENCE

L'épistaxis peut être particulièrement grave dans la maladie de Rendu-Osler du fait de son abondance, de sa répétition ou de sa durée et du risque de décompensation d'une tare associée (insuffisance cardiaque,...). Les patients y sont habitués et présentent souvent une anémie très sévère quand ils viennent aux urgences.

CE QUI EST RECOMMANDÉ

- La **compression** manuelle du nez est souvent faite par le patient depuis plusieurs minutes voire plusieurs heures.
- Rechercher les signes de gravité : Antécédents d'épistaxis sévères, abondance, durée, les signes de choc hypovolémique (tachycardie, hypotension artérielle, sueur, agitation, anxiété, pâleur, marbrures).
- Si les saignements sont importants, prolongés ou responsables de malaise, il est indispensable, après avoir fait moucher le patient afin d'évacuer les caillots, de réaliser un méchage avec des mèches résorbables (**Surgicel®**) au niveau des fosses nasales
- Si ce tamponnement est efficace, la gaze résorbable est laissée en place sous couverture d'une antibiothérapie indispensable jusqu'au délitement complet de la gaze résorbable en effectuant par la suite tous les jours des humidifications régulières au sérum physiologique.
- Vérifier la NFS et plaquettes. En fonction de la sévérité de l'anémie, transfusion de GR ou perfusion de Fer IV.

CE QU'IL NE FAUT PAS FAIRE

- Sous-estimer la sévérité de l'épistaxis : Quand un patient atteint de maladie de Rendu-Osler vient aux urgences, l'épistaxis est toujours sévère +++.
- Mécher avec des mèches non résorbables (type Merocel ®, Algostéryl®...).
- Cautériser.

Pour en savoir plus : http://www.rendu-osler.fr/
http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-11/ald_31_pnds_rendu_osler__web.pdf

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