

Effect of Nailfold Application of Latanoprostene Bunod on Nailfold Capillary Blood Flow

PI: Dr. James Tsai

NCT03949244

Document Date: 12-18-2019



Icahn School of Medicine at Mount Sinai
Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital
Mount Sinai Queens
New York Eye and Ear Infirmary
of Mount Sinai
Mount Sinai St. Luke's
Mount Sinai West

**Program for the Protection
of Human Subjects**
Institutional Review Boards
Mount Sinai Health System
One Gustave L. Levy Place, Box
1081
New York, NY 10029-6574
T 212-824-8200
F 212-876-6789
irb@mssm.edu
icahn.mssm.edu/pphs

Initial Application
IRB-18-01336
Robert Ritch

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1. Summary - Title**Protocol Title**Effect of Nailfold Application of Latanoprostene Bunod on Nailfold Capillary Blood Flow

Principal Investigator

Robert Ritch

When the application is complete, it will be sent to the PI for submission***When the application is complete, it will be sent to the PI for submission*****Primary Department**

Ophthalmology

When the application is complete, it will be sent to the PI for submission**Application Initiated By**Harriet Lloyd

Lay Summary

In this study, we investigate the effect of topically-applied latanoprostene bunod (LTB) on the blood flow at the nail fold of the 4th finger in patients with primary open angle glaucoma. LTB is a new anti-glaucoma eye drop which received FDA clearance in early November 2017. It has two components: the prostaglandin analog (PGA) which decreases intraocular pressure (IOP) by enhancing the drainage of the aqueous (the fluid in the front part of the eye) from the eye, and the nitric oxide (NO) moiety which naturally dilates arteries in the body. The capillaries at the nail fold are comparable to those of the optic nerve head, which makes them a reasonable surrogate for evaluation of the effect of LTB on the blood flow. Therefore, this study may provide indirect evidence for the beneficial effect of LTB on blood flow to optic nerve which can potentially save the optic nerve from glaucomatous damage.

Primary open angle glaucoma is a progressive condition and is the most common cause of irreversible blindness worldwide. Primary open angle glaucoma (POAG) is a subset of the glaucomas defined by an open, normal appearing anterior chamber angle and raised intraocular pressure (IOP), with no other underlying disease.

In addition to LTB, we will use latanoprost (L), an-FDA approved PGA anti-glaucoma eye drop and normal saline (NS: the physiologic solution composed of 0.9% salt and water), as controls to make sure the effects of LPB on nail fold capillary blood flow is not due to its PGA (as L is) or due to the placebo effect (as NS is).

This study may also serve as background information for the development of new anti-glaucoma medications which can be injected into the eye to facilitate blood flow to the optic nerve.

We will recruit 120 subjects with POAG at New York Eye and Ear Infirmary of Mount Sinai. Participation in this study will take approximately 60 minutes in one visit, and entails having NFC videos recorded after application of cedar oil and again after application of glaucoma drops, as well as having basic medical information recorded, such as height, weight, BMI, pulse and blood pressure.

IF Number

IF2532592

2. Summary - Setup

Funding Has Been Requested / Obtained	Yes
Application Type	Request to Rely on Mount Sinai IRB
Research Involves	Prospective Study ONLY
Consenting Participants	Yes
Requesting Waiver or Alteration of Informed Consent for Any Procedures	No
Humanitarian Use Device (HUD) Used Exclusively in the Course of Medical Practice	No
Use of an Investigational Device to Evaluate Its Safety or Effectiveness	No
Banking Specimens for Future Research	No
Cancer Related Research that Requires Approval from the Protocol Review and Monitoring Committee (PRMC).	No

Is this Cancer Related Research? Cancer Related Research is defined as research that has cancer endpoints or has a cancer population as part of or all of its targeted population. This includes protocols studying patients with cancer or those at risk for cancer.

Clinical Trial Yes

**** A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).***
**** Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.***

Drugs / Biologics Yes

**** Drugs / Biologics That Are Not a Part of Standard Practice***
**** Controlled Substances***
**** Drugs / Biologics Supplied by the Research Sponsor or Purchased with Study Funds***

Ionizing Radiation for imaging or therapy, including X-Ray, Fluoroscopy, CT, Nuclear Medicine, PET and/or Radiation Therapy:

**** Purely for standard of care:*** No
**** In frequency or intensity that exceeds what is necessary for standard of care:*** No

Hazardous Materials No

**** Recombinant DNA***
**** Viral Vectors***

- * ***Plasmids***
- * ***Bacterial Artificial Chromosomes***
- * ***Toxic Chemicals, Potentially Toxic Medications, Carcinogens***
- * ***Autologous Cell Lines***

Request Use of Clinical Research No
Unit Resources

3. Summary - Background

Objectives

The objective of this study is to assess changes in the nail fold capillary (NFC) blood flow after nailfold (NF) application of latanoprostene bunod (LTB) in primary open angle glaucoma (POAG) patients compared to change in NFC blood flow after NF application of latanoprost 0.005% or saline.

Background

Nitric Oxide (NO)-mediated vasodilation in response to vascular shear stress operates via the intracellular receptor soluble guanylyl cyclase (sGC) stimulating production of cyclic guanosine monophosphate (cGMP) (1). Impaired NO signaling plays an important role in POAG. Impaired retinal arteriole (2) and brachial (3) artery autoregulation has been demonstrated in POAG after increased shear stress. Furthermore, reduced resting blood flow in the retina, choroid, and extraocular vessels exists in POAG (4-6).

NF capillaroscopy is a noninvasive technique for in vivo imaging of capillaries near the fingernail and has a role in diagnosis of rheumatic conditions (7). NFC morphological (8) and hemodynamic (9) abnormalities have been demonstrated in POAG. These abnormalities may be mediated in part by impaired NO signaling. LTB is a dual acting antiglaucoma agent that contains a PGA and a NO donor.

Improving optic nerve head microcirculation may protect the optic nerve from glaucomatous degeneration. The NF microcirculation has layers of hairpin looped capillaries that are comparable to the optic nerve circulation (10).

NF application of LTB may result in increased levels of cGMP (11) or S-nitrosylation of hemoglobin which may enhance conductive vasodilation (12). We do not expect LTB applied to the NF to have an effect on optic nerve microcirculation; however, should intracameral delivery of LTB be developed, the data generated here may be useful background information for optic nerve microcirculatory studies that would ensue.

References:

1. Buys ES, Ko YC, Alt C, Hayton SR, Jones A, Tainsh LT, et al. Soluble guanylate cyclase alpha1-deficient mice: a novel murine model for primary open angle glaucoma. *PloS one*. 2013;8(3):e60156.
2. Feke GT, Pasquale LR. Retinal blood flow response to posture change in glaucoma patients compared with healthy subjects. *Ophthalmology*. 2008;115(2):246-52.
3. Fadini GP, Pagano C, Baesso I, Kotsafti O, Doro D, de Kreutzenberg SV, et al. Reduced endothelial progenitor cells and brachial artery flow-mediated dilation as evidence of endothelial dysfunction in ocular hypertension and primary open-angle glaucoma. *Acta ophthalmologica*. 2010;88(1):135-41.
4. Logan JF, Rankin SJ, Jackson AJ. Retinal blood flow measurements and neuroretinal rim damage in glaucoma. *The British journal of ophthalmology*. 2004;88(8):1049-54.
5. Yin ZQ, Vaegan, Millar TJ, Beaumont P, Sarks S. Widespread choroidal insufficiency in primary open-angle glaucoma. *Journal of glaucoma*. 1997;6(1):23-32.
6. Kaiser HJ, Schoetzau A, Stumpfig D, Flammer J. Blood-flow velocities of the extraocular vessels in patients with high-tension and normal-tension primary open-angle glaucoma. *American journal of ophthalmology*. 1997;123(3):320-7.
7. Cortes S, Cutolo M. Capillaroscopic patterns in rheumatic diseases. *Acta reumatologica portuguesa*. 2007;32(1):29-36.
8. Pasquale LR, Hanyuda A, Ren A, Giovino M, Greenstein SH, Cousins C, et al. Nailfold Capillary Abnormalities in Primary Open-Angle Glaucoma: A Multisite Study. *Invest Ophthalmol Vis Sci*. 2015(1552-5783 (Electronic)).
9. Gasser P, Flammer J. Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. *American journal of ophthalmology*. 1991;111(5):585-8.
10. An L, Johnstone M, Wang RK. Optical microangiography provides correlation between microstructure and microvasculature of optic nerve head in human subjects. *J Biomed Opt*. 2012;17(11):116018.
11. Cavet ME, Vollmer TR, Harrington KL, VanDerMeid K, Richardson ME. Regulation of Endothelin-1-Induced Trabecular Meshwork Cell Contractility by Latanoprostene Bunod. *Investigative ophthalmology & visual science*. 2015;56(6):4108-16.
12. Zhang R, Hess DT, Reynolds JD, Stamler JS. Hemoglobin S-nitrosylation plays an essential role in cardioprotection. *J Clin Invest*. 2016;126(12):4654-8.

Primary and Secondary Study Endpoints

We will assess change in NFC blood flow after NF application of LTB in POAG patients. This is a parallel, masked 3-arm randomized trial consisting of normal saline, latanoprost 0.005% and LTB 0.024%. Patients will have baseline NFC blood flow measurements after application of cedar oil. Then we will use NF application of either normal saline, latanoprost 0.005% or LTB 0.024% in random sequence. The patient and imager will know which study drug is applied. NFC blood flow will be remeasured after 15 minutes. NF article application will occur on a

specially designed well applied to the 4th digit of the nondominant hand. The readers will make all NFC blood flow measurements in masked fashion.

The endpoint of the study is to measure the change in NFC blood flow 15 minutes after NF application to the 4th digit of the nondominant hand.

The secondary endpoint is to determine if the change in NFC blood flow after LTB will be greater than the change seen with either normal saline or latanoprost.

Protocol Was Already Approved by the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB) Under a Different Principal Investigator	No
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Protocol Was Previously Submitted to an External(non-ISMMS) IRB	No
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4. Research Personnel

Name/Department	Role/Status	CC	Access	Obtaining Consent	Phone	Email
Robert Ritch / Ophthalmology	PI /	Yes	SIGNAUTH	Yes	2126735140	
Ahmad Najafi / Ophthalmology	Co-Investigator /	Yes	EDIT	Yes		
Erica B. Jacobs / Ophthalmology	Study Coordinator /	Yes	READONLY	Yes		
Maria Scolaro / Ophthalmology	Study Coordinator /	Yes	EDIT	Yes		
Elena Alvarado / Ophthalmology	Study Coordinator /		READONLY	Yes	212-477-7540 ext 5371	
Emily Seo / Ophthalmology	Study Coordinator /	Yes	SIGNAUTH	Yes		
Harriet Lloyd / Ophthalmology	Admin (non-FCOI) /	Yes	SIGNAUTH		2129794672	
Katy Tai / Ophthalmology	Admin (non-FCOI) /	Yes	SIGNAUTH			
Louis Pasquale / Ophthalmology	Co-Investigator /	Yes	SIGNAUTH	Yes		
Mark Gentile / Ophthalmology	Study Coordinator /	Yes	SIGNAUTH	Yes		

5. Sites

Site Name	New York Eye and Ear Infirmary of Mount Sinai
Other External Site Name	
Contact Details	
Approved	1
Approval Document	IRB-18-01336 approval letter.pdf
Funded By Mount Sinai	0
Reviewed By	Mount Sinai IRB
Other IRB	

Site Name	Other External Site
Other External Site Name	Mount Sinai Doctors - East 85th Street
Contact Details	
Approved	0
Approval Document	
Funded By Mount Sinai	0
Reviewed By	Mount Sinai IRB
Other IRB	

6. Subjects - Enrollment

Site Name	New York Eye and Ear Infirmary of Mount Sinai
Subjects To Be Enrolled	
120	
Site Name	Other External Site
Subjects To Be Enrolled	
Total Number of Subjects to be Enrolled Across All Listed Sites Above (Auto Populated)	120

7. Subjects - Setting and Resources

Setting of Human Research Faculty Practice Associates, Clinical Research Unit (CRU)

Total Number of Subjects Needed To Complete Study 60

Feasibility of Meeting Recruitment Goals

120 Patients with primary open angle glaucoma (POAG) will be pre-screened and identified by the treating physician, and by searching the NYEEI medical records and collaborating with our in-house medical staff for referrals to the study. The glaucoma practice at NYEEI will be able to provide a more than sufficient number of potential subjects.

Facilities To Be Used for Conducting Research

New York Eye and Ear Infirmary of Mount Sinai (NYEEIMS), Einhorn Clinical Research Center at NYEEIMS.

Multi-Center Study No

Community-Based Participant Research Study No

PI must attest to the following.

**** Process is adequately described to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.***

8. Subjects - Populations

Inclusion Criteria

- 1) 40 years old to 80 years old
- 2) all participants will have open angles and no signs of secondary glaucoma such as exfoliation syndrome
- 3) untreated intraocular pressure (IOP) may be #21mmHg or #21mmHg in both eyes
- 4) the cup-to-disc ratio (CDR) #0.6 in both eyes and CDR asymmetry #0.2.
- 5) POAG patients will have reliable Humphrey Visual Field (HVF) loss consistent with optic nerve damage
- 6) POAG patients can have any stage of POAG and be on any form of treatment for their disease.
- 7) willingness to sign informed consent and comply with study procedures.

Exclusion Criteria

- 1) History of non-POAG forms of glaucoma
- 2) pregnancy
- 3) Inability to give informed consent

Enrollment Restrictions Based Yes
Upon Gender, Pregnancy,
Childbearing Potential, or Race

Justify Restriction(s)

While there have been no adverse effects of latanoprost drops on pregnant women of fetuses, we will be excluding pregnant women out of an overabundance of caution. This is a pilot study with a small number of subjects being recruited. No treatments or therapies are being considered in this project.

Age Range(s) 18 to 64 Years, 65 Years and Over

Targeted Population(s) Adults - Patients

Other Aspects that Could Increase Subjects Vulnerability

We will recruit patients from age 25 to age 80 among a population able to provide informed consent, but not recruit from any other vulnerable populations e.g. fetuses, neonates, pregnant women, prisoners, or institutionalized individuals. The risk to human subjects will be minimal, and there are no other aspects that could increase subjects' vulnerability.

Safeguards to protect Subjects rights and welfare

Safeguards included in this project includes the responsibility of the investigator to ensure that all regulations and documentation is handled in a compliant and timely manner.

9. Subjects - Participation

Duration of an Individual Subjects Participation in the Study

60 minutes during one visit.

Duration Anticipated to Enroll All Study Subjects

One year.

Estimated Date for the Investigators to Complete This Study Within 5-10 years

Procedures for Subjects to Request Withdrawal

We will emphasize that subjects are free to withdraw from the study at any time without any penalty, even after having provided written consent/assent.

Subjects will need to provide written withdrawal when withdrawing HIPAA authorization specifically.

Procedures for Investigator to Withdraw Subjects

The investigator and the consent will document that the subject may stop being in the research study and any collected data will be withdrawn.

Participants Will Be Recruited Yes

Recruitment Method(s) Clinical Practice

How Participants Will Be Identified

Participants will be identified by their treating physician as having met the inclusion/exclusion criteria. They will also be identified by searching the NYEEI medical records and collaborating with our in-house medical staff for referrals to the study. Eligible patients for recruitment will be screened for by the doctor. The charts may be earmarked for recruitment on the day of their visit.

Who Will Initially Approach Potential Participants Treating Physician

How Research Will Be Introduced to Participants

The research projects will be introduced to potential subjects by the treating physician. If participants are interested then the treating physician will call the study staff and formally introduce each other. The study staff will approach the potential participant to explain the study and obtain consent.

How Participants Will Be Screened

Research procedures will take place only after subjects have provided their consent to participate. All subjects will receive a complete eye examination ETDRS visual acuity, refraction, slit lamp and dilated fundus examination will be performed to evaluate whether the subject will be eligible based on the inclusion & exclusion criteria.

We will also obtain baseline height, weight, blood pressure, pulse, and NF capillaroscopy (which requires placing a drop of cedarwood oil on the cuticle to facilitate visualization) pre-intervention.

10. Subjects - Risk and Benefits

Risks to Subjects

There are no essential risks to the subjects. LTB is an FDA-approved drug with essentially no systemic side effects. NF capillary drug application is equivalent to taking a single ocular dose of medicine that delivers 0.76 micrograms of drug to a volume of circulation of 70 liters.

Risks of application of cedarwood oil: A very rare but potential effect of mild irritation when applying cedar essential oil to the skin has been reported.

Risks of LTB and Latanoprost: There is also the remote possibility that the glaucoma drops could cause an allergic reaction or cause irritation to the nailfold, both of which would result in redness and itching and would be easily treated by washing the affected area with soap and water.

Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

The research team that has been assembled has sufficient expertise and experience to conduct the research. The inclusion/exclusion criteria will allow us to enroll only the desired population of interest. The experimental procedure will take place while the subject is here for their standard of care examination. Data will be stored in such a way that it is impossible to connect research data directly to the individuals from whom or about the data pertain. Access to key codes will be limited and stored separately from the data.

Provisions for Research Related Harm / Injury

In case of injury due to the study, the investigator will be alerted and medical care will be provided. Care for such injury will be billed in the ordinary manner to the subject.

Expected Direct Benefit to Subjects

There are no expected direct benefits to subjects. This is a proof of principle study to demonstrate that LTB may have acute microculatory effects.

Benefit to Society

The benefit from the data obtained may be useful scientifically and we hope to learn from this study which will potentially benefit the patients in the future

Provisions to Protect the Privacy Interests of Subjects

The investigator will establish ahead of time what de-identified information will be revealed to whom and under what circumstances, and will communicate these provisions to protect the privacy interests of the subjects in a clear language through the informed consent process.

Authorized medical release forms will be requested from the subject should they decide to dictate whom is allowed to view their results.

In all disclosures outside of Mount Sinai, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number.

Economic Impact on Subjects

All research procedures will be paid for by the study. Being in this research study will not lead to extra costs for the subject.

11. Procedures - Narrative

Description of the Study Design

We will assess change in NFC blood flow after NF application of LTB in POAG patients. This is a parallel, masked 3-arm randomized trial consisting of normal saline, latanoprost 0.005% and LTB 0.024%.

Description of Procedures Being Performed

Patients will be consented prior to any study-related interventions. Patients will have baseline NFC blood flow measurements after application of cedar oil. Then we will use NF application of either normal saline, latanoprost 0.005% or LTB 0.024% in random sequence. The patient and imager will know which study article is applied. NFC blood flow will be remeasured after 15 minutes. NF article application will occur on a specially designed well applied to the 4th digit of the non-dominant hand.

We believe that the same capillaries will be visualized before and after treatment, due to the limited width of the fingertip. The procedure for NFC videography is to sample consecutive capillaries, pausing on each capillary until blood flow was visualized. If no blood flow is visualized after 10 seconds in focus, the immediate medial capillary is assessed in similar fashion. Blood flow for 10 seconds on each of the first five visible capillaries is captured. We believe that this method will allow us to capture flow in the same capillaries pre- and post-treatment.

We will measure pulse and blood pressure at baseline and after NF drug application for safety purposes. We will also collect height and weight in order to adjust for body mass index in our analyses.

The readers will make all NFC blood flow measurements in masked fashion.

We will assess change in NFC blood flow after NF application of LTB in POAG patients. This is a parallel, masked 3-arm randomized trial consisting of normal saline, latanoprost 0.005% and LTB 0.024%. Patients will have baseline NFC blood flow measurements after application of cedar oil. Then we will use NF application of either normal saline, latanoprost 0.005% or LTB 0.024% in random sequence. The patient and imager will know which study article is applied. NFC blood flow will be remeasured after 15 minutes. Preliminary data on controls suggests that 15 minutes is sufficient time to see a change in blood flow. NF article application will occur on a specially designed well applied to the 4th digit of the non-dominant hand. Two masked observers will evaluate NFC blood flow using the method described below.

Description of Nailfold Video Capillaroscopy:

A BK-XW880 nailfold video capillaroscope at 300x magnification (Biobase Meihua Trading Co., Jinan, Shandong, China) will be used to image nailfold capillaries. Cedarwood oil is applied to the finger skin to achieve adequate focus. The subject orients their hand in the prone position and the lateral-most edge of the nailfold of the fourth finger of the non-dominant hand is imaged. We chose this sampling protocol to minimize the effect of local trauma on nailfold capillary hemodynamics. Consecutive capillaries are sampled, pausing on each capillary until blood flow is visualized. If no blood flow is visualized after 10 seconds in focus, the immediate medial capillary is assessed in similar fashion. Blood flow for 10 seconds on each of the first five visible capillaries is captured. This method is repeated pre- and post-NF article application.

Nailfold videos are converted to image sequences and imported into ImageJ software (National Institutes of Health, Bethesda, MD) to measure blood speed, diameter, and flow. Each capillary is cropped out of the image sequence spanning the duration of visible blood flow for the given capillary. The cropped image sequence is registered using StackReg, an open-source ImageJ plugin. Two readers masked to case status will validate the measurement methods. Because morphological abnormalities such as tortuosity and hemorrhaged capillaries are present in POAG and morphology may affect resistance to blood flow within the vessel, a straight segment of the capillary is used for analysis. Each reader will track the first visible void in the blood column between the first pair of consecutive frames in which the blood column void is clearly defined in both frames as performed in other studies. The time elapsed between consecutive frames is calculated based on the frame per second rate of the video (25 frames per second). The distance in microns covered by the blood column void is divided by the reciprocal of the frames per second rate to generate blood speed in microns per second. Each reader will also measure diameter of the vessel in the vicinity of the blood column void. Assuming a circular geometry for the lumen on the vessel, the cross-sectional area of the vessel is then calculated. Capillary blood flow is calculated by multiplying blood speed by cross-sectional area of the vessel.

Description of the Source Records that Will Be Used to Collect Data About Subjects

All data collected will be primary source data. We will collect the diagnosis of POAG from the subject's electronic medical record. We will obtain medical history data from electronic charts as well. Interventional data that will be

collected specifically for this project include NF capillaroscopy, blood pressure and pulse readings, which will be performed by the imager and recorded in an electronic data file using de-identified subject id numbers.

Description of Data that Will Be Collected Including Long-Term Follow-Up

1. Obtain baseline height, weight, blood pressure, pulse.
2. Perform NF capillaroscopy (including placing a drop of cedarwood oil on the patient's cuticle) pre-intervention.
3. Obtain blood pressure, pulse, and NF capillaroscopy 15 minutes after intervention.
4. Obtain medical history from electronic chart after visit: age, sex, ancestry, body mass index, baseline blood pressure, baseline pulse, hypertension (yes/no), diabetes mellitus (yes/no), current smoker (yes/no), use of antiplatelet or anticoagulant, maximum known IOP, current IOP, current cup-disc ratio, current mean deviation and pattern standard deviation from worse eye from the latest reliable Humphrey visual field test.

There will not be any long-term followup for this study.

Research Requires HIV Testing No

12. Procedures - Genetic Testing

Genetic Testing Will Be Performed No

Guidance and Policies > Future Use Data Sharing and Genetic Research

13. Procedures - Details

Surveys or Interviews	No
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Audio / Photo / Video Recording	Yes
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Subjects Will Be Identifiable	No
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Media Will Be Discarded When the Research Study is Completed	Yes
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How Media Will Be Stored to Ensure Confidentiality

Data is coded with Subject study ID and stored on the PI's password protected file and password protected computer.

Media Will Be Shared with Others	No
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Audio / Photo / Video Recording is Required for Participation	Yes
--	-----

Deception	No
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Results of the Study Will Be Shared with Subjects or Others	Yes
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How the Results Will Be Shared

Results of the study will be shared as publications in peer-reviewed journals and at scientific meetings. All data to be shared will be de-identified. Study subjects may request to learn the results of the study, which will be provided orally by the study staff, or they will be referred to any publications.

When the Results Will Be Shared

At the end of the entire study, after IRB review and approval to share the final results.

14. Procedures - Compensation

Compensation for Participation	Yes
Type	Cash
Amount Per Visit	20
# of Visits	1
Line Total	20
Justification	Time
Who Will Pay	
Specify Who Will Pay	
Comment	
Total Compensation	20

PI must attest that all of the following are true.

**** Credit for payment accrues as the study progresses.***

**** Payment is not contingent upon completing the entire study.***

**** The amount of payment and the proposed method and timing of disbursement is neither coercive nor presented undue influence.***

**** Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.***

**** All information concerning payment, including the amount and schedule of payments, is in the informed consent document.***

**** Compensation does not include a coupon good for a discount on the purchase price of the product once it has been approved.***

15. Consent - Obtaining Consent

Consent Process

Adult Consent

Where and When Consent Will Be Obtained

The study will be verbally explained to the potential subject by the participating physicians and study staff after their standard of care visit, who will provide all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.), and will allow the potential subject ample opportunity to ask questions. Following this verbal explanation, the potential subject will be provided with a consent form and will be afforded sufficient time to consider whether or not to participate in the research. After allowing the potential subject time to read the consent form, the investigator or study staff will answer any additional questions the potential subject may have and will obtain verbal agreement and written agreement to participate in the research, by signing the informed consent form. The entire informed consent process will take place in a private room at the study site, Suite 500 of the South Building of the New York Eye and Ear Infirmary,

Waiting Period for Obtaining Consent

The subject will be afforded sufficient time to consider whether or not to participate in the research. Sufficient time in this study should be minutes, which should be how long it would reasonably take to evaluate the procedures, risks, potential benefits, and potential alternatives.

SOP HRP-090 Informed Consent

Yes

Process for Research Is Being Used

PPHS Worksheets, Checklists and SOPs

Process to Document Consent in Writing

Will Use Standard Template

Non-English Speaking Participants Will Be Enrolled

No

Justification for Not Enrolling Non-English Speaking Participants

This is a study to measure the NFC blood flow after NF application of LTB in 120 POAG patients compared to change in NFC blood flow after NF application. The study is powered to assess the hemodynamic effects for pre- vs. post-nailfold application of LTB. We do not have resources to generate consents in different languages or to employ interpreters. There is no therapeutic benefit for study participation.

16. Consent - Documents

Consent Documents

Type	informed consent
Name	IDEATE CONSENT Nailfold
Upload	IDEATE CONSENT Nailfold.pdf

Consent Templates

17. Data - Collection

Health Related Information Will Be Viewed, Recorded, or Generated Yes

Description of Health Information That Will Be Viewed, Recorded, or Generated

Health information that will be viewed, recorded or generated include:

baseline height, weight, blood pressure, pulse, and NF capillaroscopy, medical history including: age, sex, ancestry, body mass index, baseline blood pressure, baseline pulse, hypertension (yes/no), diabetes mellitus (yes/no), current smoker (yes/no), use of antiplatelet or anticoagulant, max known intraocular pressure, current intraocular pressure, current cup-disc ratio, current mean deviation and pattern standard deviation from worse eye from latest reliable Humphrey visual field test.

Non-Health Related Information Will Be Viewed or Recorded No

HIV / AIDS Related Information Will Be Viewed or Recorded No

Data That Will Be Viewed, Recorded, or Generated Contains ANY of the Following Directly Identifiable Information Yes

Will Be Viewed

Name, Medical Record Number, Address by street location, Telephone number, Fax number, Geographical Subdivisions Smaller Than a State, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date)

Will Be Recorded

Name, Medical Record Number, Address by street location, Telephone number, Fax number, Geographical Subdivisions Smaller Than a State, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date)

Data Collection Sheet

A Data Collection Sheet is required if you are either performing a retrospective review, or your study meets the category of exempt 4 research, or your study meets the category of expedited 5 research. Please upload it here.

Data Collection Source(s)

Participant, Medical Chart (Paper or Electronic)

18. Data - HIPAA

Obtaining HIPAA Authorization Yes

How PHI Will Be Protected from Improper Use or Disclosure

PHI will be disclosed to the PI and NYEEIMS research staff associated to this project only. Proper password protected computers and data analysis sheets requiring password authorization will be in place.

**PHI Will Be Destroyed at the
Earliest Opportunity Consistent
with the Research** Yes

When and How PHI Will Be Destroyed

PHI will be destroyed after data analysis and estimated 6 years after post publication of final results.

PHI Will Be Shared No

PI must attest to the following.

**** I assure that the protected health information (PHI) will not be disclosed to any other person or entity not listed on this form except where required by law or for the authorized oversight of this research project. If at any time I want to reuse this PHI for other purposes or disclose it to other individuals or entities I will seek approval from the IRB.***

19. Data - Storage**Location Where Data Will Be Stored**

The PI and principal Study coordinator for this trial will be holding the needed protected health information below in a research study staff access, password protected computer and hard copies in a locked cabinet at the NYEEMS Clinical Research Center, 310 East 14th Street, Suite 500 South bldg.

How will the data be stored? With a Code That Can Be Linked to the Identity of the Participant

Research Personnel Responsible for: Robert Ritch

Accessing Data Yes

Receipt or Transmission of Data Yes

Holding Code That Can Be Linked to Identity of Participants Yes

Research Personnel Responsible for: Ahmad Najafi

Accessing Data Yes

Receipt or Transmission of Data Yes

Holding Code That Can Be Linked to Identity of Participants

Research Personnel Responsible for: Erica B. Jacobs

Accessing Data Yes

Receipt or Transmission of Data Yes

Holding Code That Can Be Linked to Identity of Participants

Research Personnel Responsible for: Maria Scolaro

Accessing Data Yes

Receipt or Transmission of Data Yes

Holding Code That Can Be Linked to Identity of Participants Yes

Research Personnel Responsible for: Elena Alvarado

Accessing Data Yes

Receipt or Transmission of Data Yes

Holding Code That Can Be Linked to Identity of Participants

Research Personnel Responsible for: Emily Seo

Accessing Data

Receipt or Transmission of Data

Holding Code That Can Be Linked to Identity of Participants

Research Personnel Responsible for: Harriet Lloyd

Accessing Data Yes

Receipt or Transmission of Data Yes

Holding Code That Can Be Linked to Identity of Participants

Research Personnel Responsible for:	Katy Tai
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Louis Pasquale
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Mark Gentile

Accessing Data
Receipt or Transmission of Data
Holding Code That Can Be Linked to Identity of Participants
Duration Data Will Be Stored

Study records will be maintained for approximately 6 years, for the purpose of analysis, published reports and followup. Although the study will consist of a single visit for each subject, the subjects will be asked for permission to be contacted at a future date.

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission

During the informed consent process, subjects will be informed of the precautions that will be taken to protect the confidentiality of the data and be informed of the parties who will or may have access (e.g., research team, FDA, OHRP). This will allow subjects to decide about the adequacy of the protections and the acceptability of the possible release of private information to the interested parties.

Provisions for protecting privacy and/or confidentiality are relevant at all stages of research, including subject identification and recruitment, research participation, and analysis of individually identifiable data.

To minimize potential risks, observations would be recorded whenever possible in a manner that does not allow participants to be identified, either directly or through identifiers linked to them. When identifiers are necessary for the research, adequate provisions for maintaining the confidentiality of the data are required.

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)

Chi squared and unpaired t-tests will be used for between group comparisons. Paired t-tests will be used for pre- to post-NF drug application comparisons. Multivariable analysis will be performed to determine if NFC LTB application is an independent predictor of change in NFC blood flow from baseline to after drug application.

Power calculations indicate that with our sample size of 120 we have 90% power to detect changes in blood flow difference between baseline and after NF application in the latanoprost group versus normal saline group and in the LTB group versus the normal saline controls. We have 80% power to detect changes in blood flow difference between baseline and after NF application in the LTB group versus latanoprost group. These calculations are based on a 1:2:2 sampling ratio, a type 1 error rate of 5% and 30% variance in measurement of NFC blood flow. We assume that because latanoprost itself will upregulate NO, that LTB will enhance NO donation by another 50%.

20. Data - Safety Monitoring

More Than the Minimum Data
Safety Monitoring Will Be Done

No

The following minimum requirements apply to all projects, including retrospective reviews of medical records, use of tissue samples, and many minimal risk studies, such as observational and survey research. Because these minimum requirements apply to all studies, a specific written DSMP will not usually be required for projects that do not pose greater than minimal risk to subjects. The MSSM PPHS may alter the required level of monitoring if appropriate.

For all projects, the principal investigator must have a plan to assure that data integrity will be maintained during its collection, storage and analysis. All research projects must adhere to MSSM recommendations on the storage of research data. Loss of data containing identifiable information is reportable to the IRB within 5 business days.

Any problems concerning the consent process and any subject complaints should be monitored by the investigator. Reports of such problems must be made at least annually. The discretion of the protocol director will guide the need to report these problems immediately or more frequently.

The principal investigator is, typically, the monitoring entity for the minimum DSMP. When a principal investigator is not a faculty member, the supervising faculty member must be responsible for the data and safety monitoring aspect of the protocol.

Will the Research Include Data
Coordinating Center Activities?

No

21. Funding

Funding Source Name	Bausch And Lomb
Contact	
Funding Category	Other
	Meditrack (https://contracts.tractmanager.com/Contracts/Login.aspx)
Grant or Contract Title	Effect of Nailfold Application of Latanoprostene Bunod on Nailfold Capillary Blood Flow; Grant ID 17291
Grant or Contract Number	18-2686-00001-01
Funding Status	Funded
Project Initiated By	Investigator
Grant / Contract Principal Investigator (PI)	Robert Ritch
Department	Ophthalmology
Department	Ophthalmology
Phone	2126735140
Email	rritch@nyee.edu
Protocol and Funding Proposal Match	Yes
Identify Substantive Differences Between Protocol and Funding Proposal	

22. Drugs / Biologics

Study Fund Account (or alternate departmental / fund account, if study is not yet established) 02444850

Generic Name Latanoprost 0.005%

Brand Name Xalatan

Drug Has Valid IND No

For each drug / biologic with an IND number, ensure that the application includes one of the following. * Sponsor protocol with the IND number. * Communication from the sponsor or the FDA with the IND number.

IND Number

Name of IND Holder

Type of IND Holder

Drug Meets One of the Following Categories for Exemption Yes

Category 1: * The drug is lawfully marketed in the United States. * The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug. * The research is not intended to support a significant change in the advertising for the product. * The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug. * The research is conducted in compliance with the marketing limitations described in 21 CFR §312.7. Category 2: * A clinical investigation for an in vitro diagnostic biological product that involves one or more of the following: (1) Blood grouping serum; (2) Reagent red blood cells; or (3) Anti-human globulin. * The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure. * The diagnostic test is shipped in compliance with 21 CFR §312.160. Category 3: * A clinical investigation involving use of a placebo when the investigation does not otherwise require submission of an IND.

Category for Exemption Category 1

Justification for Meeting Criteria Latanoprost 0.005% meets all of the criteria in Category 1.

To be a coordinating center, the Mount Sinai investigator is the Principal Investigator for multi-site participation in the trial. The Investigational Drug Service (IDS) may support trials as the coordinating center. IDS services include but are not limited to randomizing for other sites, storing and shipping drugs to participating sites, etc.

Icahn School of Medicine at Mount Sinai (ISMMS) Is the Coordinating Center

Role of the Investigational Drug Service (IDS)

Drug / Biologic Description (Manufacturer/Generic Name/Form/Strength)

Controlled Substance Schedule

In order for the Icahn School of Medicine at Mount Sinai (ISMMS) to be compliant with the regulations regarding controlled substance research, a New York State Department

of Health-issued Researcher license and DEA-issued Researcher Registration Number must be on file for each trial using controlled substances. The Investigational Drug Service maintains these licences and will make them available to our investigators to support our research. Refer to www.health.state.ny.us/professionals/narcotic and http://firstclinical.com/journal/2011/1112_DEA.pdf for more information.

**Using Investigational
Drug Service (IDS)
Research License**

**Use of this Drug /
Biologic Is Considered
Standard of Care**

**Requested Pharmacy
Services**

**Specify Other Requested
Pharmacy Services**

**Drug / Biologic Will Be
Supplied By**

**Specify Other Drug /
Biologic Supplier**

Using Placebo

**Placebo Will Be Supplied
By**

**Compounding Required
(Paid for by Study
Funds)**

**Where Drug / Biologic
Will Be Administered**

**Specify Location of
Private Office**

**Storage Requirements of
Drug / Biologic**

**Where Drug / Biologic
Will Be Stored**

**ALL of the Following
Storage Criteria Are Met**

* The storage area is well maintained, provides adequate lighting, ventilation, sanitation, space and security. * The temperature in the storage area is controlled and monitored using calibrated monitoring devices. * The temperature monitoring system has sensors for continuous monitoring and alarms set at the points representing the temperature extremes. * Records of temperatures and alarms are maintained and all excursions outside the labeled storage conditions are appropriately investigated and reported to the sponsor.

**Justification Why Any
of the Above Storage
Criteria Cannot Be Met**

**ALL of the Following
Distribution Criteria Are
Met**

* The investigator will not dispense the investigational agent to any person not authorized under the protocol to receive it. * The drug, agent, biologic may only be used in subjects under the investigators personal supervision or under the supervision of a physician who is directly responsible to the investigator. * The investigator will maintain adequate records for the receipt, storage, and disposition of the drug, including dates, quantity, and use by subjects. * The investigational agents will be stored in a secure area and in such a way to restrict access to authorized personnel only as defined in the protocol. Additionally, all associated records will be stored in a restricted area and/or locked.

**Justification Why Any of
the Above Distribution
Criteria Cannot Be Met**

Generic Name Latanoprostene bunod 0.024%

Brand Name Vyzulta

Drug Has Valid IND No

For each drug / biologic with an IND number, ensure that the application includes one of the following. * Sponsor protocol with the IND number. * Communication from the sponsor or the FDA with the IND number.

IND Number

Name of IND Holder

Type of IND Holder

**Drug Meets One of the
Following Categories for
Exemption** Yes

Category 1: * The drug is lawfully marketed in the United States. * The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug. * The research is not intended to support a significant change in the advertising for the product. * The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug. * The research is conducted in compliance with the marketing limitations described in 21 CFR §312.7. Category 2: * A clinical investigation for an in vitro diagnostic biological product that involves one or more of the following: (1) Blood grouping serum; (2) Reagent red blood cells; or (3) Anti-human globulin. * The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure. * The diagnostic test is shipped in compliance with 21 CFR §312.160. Category 3: * A clinical investigation involving use of a placebo when the investigation does not otherwise require submission of an IND.

Category for Exemption Category 1

**Justification for Meeting
Criteria** Latanoprostene bunod 0.024% meets all criteria listed for category 1.

To be a coordinating center, the Mount Sinai investigator is the Principal Investigator for multi-site participation in the trial. The Investigational Drug Service (IDS) may support trials as the coordinating center. IDS services include but are not limited to randomizing for other sites, storing and shipping drugs to participating sites, etc.

**Icahn School of Medicine
at Mount Sinai (ISMMS)
Is the Coordinating
Center**

**Role of the
Investigational Drug
Service (IDS)**

**Drug / Biologic
Description
(Manufacturer/Generic
Name/Form/Strength)**

**Controlled Substance
Schedule**

In order for the Icahn School of Medicine at Mount Sinai (ISMMS) to be compliant with the regulations regarding controlled substance research, a New York State Department of Health-issued Researcher license and DEA-issued Researcher Registration Number must be on file for each trial using controlled substances. The Investigational Drug Service maintains these licences and will make them available to our investigators to

**Using Investigational
Drug Service (IDS)
Research License**

**Use of this Drug /
Biologic Is Considered
Standard of Care**

**Requested Pharmacy
Services**

**Specify Other Requested
Pharmacy Services**

**Drug / Biologic Will Be
Supplied By**

**Specify Other Drug /
Biologic Supplier**

Using Placebo

**Placebo Will Be Supplied
By**

**Compounding Required
(Paid for by Study
Funds)**

**Where Drug / Biologic
Will Be Administered**

**Specify Location of
Private Office**

**Storage Requirements of
Drug / Biologic**

**Where Drug / Biologic
Will Be Stored**

**ALL of the Following
Storage Criteria Are Met**

* The storage area is well maintained, provides adequate lighting, ventilation, sanitation, space and security. * The temperature in the storage area is controlled and monitored using calibrated monitoring devices. * The temperature monitoring system has sensors for continuous monitoring and alarms set at the points representing the temperature extremes. * Records of temperatures and alarms are maintained and all excursions outside the labeled storage conditions are appropriately investigated and reported to the sponsor.

**Justification Why Any
of the Above Storage
Criteria Cannot Be Met**

**ALL of the Following
Distribution Criteria Are
Met**

* The investigator will not dispense the investigational agent to any person not authorized under the protocol to receive it. * The drug, agent, biologic may only be used in subjects under the investigators personal supervision or under the supervision of a physician who is directly responsible to the investigator. * The investigator will maintain adequate records for the receipt, storage, and disposition of the drug, including dates, quantity, and use by subjects. * The investigational agents will be stored in a secure area and in such a way to restrict access to authorized personnel only as defined in the protocol. Additionally, all associated records will be stored in a restricted area and/or locked.

**Justification Why Any of
the Above Distribution
Criteria Cannot Be Met**

23. Financial Administration

This information will help the Financial Administration of Clinical Trials Services (FACTS) office determine whether a Medicare Coverage Analysis (MCA) is needed for the research study. If you have any questions while completing this form, please contact the FACTS office at (212) 731-7067 or FACTS@mssm.edu.

Clinical Research Study Category Investigator Initiated

Payment Options:

**** Option 1: No protocol-required services will be billed to patients or third-party payers.***

Does Not Need MCA

**** Option 2: Protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Must Have MCA***

**** Option 3: Study is initiated and federally funded by a Government Sponsored Cooperative Group who will only pay for services that are solely conducted for research purposes and other protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Billing Grid Only Required, NO MCA***

**** Option 4: Study involves only data collection and has no protocol-required clinical services. Does Not Need MCA***

**** Option 5: Study is not described in any of the above options. Please describe the study and specify whether External Sponsor (i.e., industry, government, or philanthropic source) and/or patient/third party payer will pay for protocol required services. MCA MAY Be Required***

Payment Option

Option 5

MCA may be need to be prepared per option selected above.

Payment Option 5:

Please describe the study and specify whether External Sponsor (i.e., industry, government, or philanthropic source) and/or patient/third party payer will pay for protocol required services.

Payment Option 5

Protocol-required eye exam procedures are being done as part of the patients routine clinical care and are billable to the patient or their insurance. The nailfold video capillaroscopy procedure is not approved for insurance billing and will not be charged to patients.

24. Attachments

Type	Name	Version	Status	Filename	Uploaded Date
Funding Proposal / Grant Application	IRG Icahn School of Med ID 17291 041318 LOA.pdf	1	approved	IRG Icahan School of Med ID 17291 041318 LOA.pdf	11/23/2018
Contractual Scope of Work	IRG Icahn School of Med ID 17291 041318 LOA.pdf	1	approved	IRG Icahan School of Med ID 17291 041318 LOA.pdf	11/23/2018
Package Insert Document (DRUG NAME)	Xalatan Package Insert.pdf	1	approved	Xalatan Package Insert.pdf	11/23/2018
Package Insert Document (DRUG NAME)	vyzulta-prescribing-information.pdf	1	approved	vyzulta-prescribing-information.pdf	11/23/2018
Approval Document	IRB-18-01336 approval letter.pdf	1	approved	IRB-18-01336 approval letter.pdf	09/23/2019
Consent - Consent Document	18-01336 ICF CLEAN version 10-31-19	2	Deactivated		//
Consent - Consent Document	18-01336 ICF TRACKED version 10-31-19	2	Deactivated		//
Consent - Consent Document	18-01336 ICF Revised Common Rule v4 CLEAN.docx	1	approved	18-01336 ICF Revised Common Rule v5 CLEAN.docx	02/15/2019
Consent - Consent Document	18-01336 ICF Revised Common Rule v4 MARKED.docx	1	approved	18-01336 ICF Revised Common Rule v5 MARKED.docx	02/15/2019
COI - Conflict of Interest Committee Management Plan	COI Management Plan- Dr. Pasquale	1	approved	Management Plan - IF 2371320 - Effect of Nailfold Application of Latanoprostene Bunod on Nailfold Capillary Blood Flow.pdf	12/18/2019