

Protocol Title: The effect of Lumify™ (Brimonidine Tartrate Ophthalmic Solution 0.025%) on palpebral fissure height.

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1) **Protocol Title**

The effect of Lumify™ (Brimonidine Tartrate Ophthalmic Solution 0.025%) on palpebral fissure height.

2) **Objectives***

Aim 1: To determine the in vivo effect of Lumify™ (Brimonidine Tartrate Ophthalmic Solution 0.025%) on palpebral fissure height.

Hypothesis: We hypothesize application of Lumify™ Brimonidine Tartrate Ophthalmic Solution 0.025% will cause an increase in subjects' palpebral fissure height.

3) **Background***

Eyelid ptosis most commonly results from malfunctioning levator palpebrae superior muscle or Müller's muscle. Müller's muscle, a smooth muscle with a predominance of α_1 -adrenergic receptors, contracts in response to sympathetic stimulation or topical adrenergic agonists. (Skibell 2007) Therefore, topical ocular administration of compounds that agonize adrenergic receptors causes an increase in interpalpebral fissure height via contraction of Müller's muscle, which helps mitigate ptosis effects as well as lending the cosmetically beneficial effect of an eye that is more open. (Munden 1991) Compounds such as apraclonidine, a medication with mixed α_1 and α_2 properties, have been shown to reverse ptosis caused by Horner's syndrome and botulinum injections, and to help assess blepharoptosis preoperatively. Although the primary mechanism of apraclonidine is α_2 agonism, which inhibits norepinephrine release from sympathetic nerve terminals, it is also a weak α_1 agonist, and allows for direct stimulation of smooth muscle. Multiple studies have observed the ability of topical apraclonidine to increase palpebral fissure height by elevating the upper lid. (Kirkpatrick 2018, Yazici 2008, Koc 2005) Brimonidine is a very similar medication; like apraclonidine, it is a selective adrenergic agonist with a much weaker affinity for the receptor. (Torkildsen 2017) Brimonidine was originally used to treat patients with open-angle glaucoma and ocular hypertension (brimonidine 0.2%). It decreases intraocular pressure by intensifying uveoscleral outflow and reducing aqueous humor inflow. (Derrick 1997) Its uses have since expanded to vasoconstriction for the skin and ocular tissue, which make it an

effective compound to reduce ocular redness (brimonidine 0.025%), and pupillary dilation, which can help camouflage anisocoria associated with Horner's syndrome. (Torkildsen 2017; McLaurin 2018; DeSouza 2007) In addition, when used as a glaucoma medication, brimonidine has been observed to elevate patients' eyelids via its α activation of Müller's muscle. (Burroughs 2007) Although apraclonidine is also effective at lowering intraocular pressure, as well as causing conjunctival blanching and mydriasis, it is not recommended as long term therapy due to its high rate of side effects—the most common being loss of Snellen acuity—and tachyphylaxis. (Yuksel 2002; Araujo 1995) In contrast, a study of 0.025% brimonidine for relief of ocular redness observed no serious adverse effects (the most common side effect was instillation site pain and dry eye) and no tachyphylaxis during the treatment period. (Torkildsen 2017) For this reason, although Kirkpatrick et al studied apraclonidine as a potential substitute for surgical treatment of mild upper eyelid ptosis, brimonidine may be an even safer alternative. (Kirkpatrick 2018) Patients suffering from ptosis who are either poor candidates for surgical repair or who do not want a surgery, in addition to patients who underwent surgery but still have a small amount of residual ptosis, would benefit from a safe and effective medical treatment. In addition, there may be a beneficial cosmetic effect in patients without significant ptosis. To the authors' knowledge, there is currently no study objectively observing the effects of brimonidine on upper eyelid position and the potential variability of this effect in different individuals. In this randomized controlled study, we aim to record changes in palpebral fissure height before and after administration of 0.025% brimonidine, in hopes to gain a deeper understanding of brimonidine's therapeutic potential.

Bibliography and References Cited [1-11]

1. Skibell, B.C., et al., *Adrenergic receptors in the ptotic human eyelid: correlation with phenylephrine testing and surgical success in ptosis repair*. *Ophthalmic Plast Reconstr Surg*, 2007. **23**(5): p. 367-71.
2. Munden, P.M., et al., *Palpebral fissure responses to topical adrenergic drugs*. *Am J Ophthalmol*, 1991. **111**(6): p. 706-10.

3. Kirkpatrick, C.A., et al., *Upper Eyelid Response to Topical 0.5% Apraclonidine*. Ophthalmic Plast Reconstr Surg, 2018. **34**(1): p. 13-19.
4. Yazici, B. and U. Beden, *Use of 0.5% apraclonidine solution in evaluation of blepharoptosis*. Ophthalmic Plast Reconstr Surg, 2008. **24**(4): p. 299-301.
5. Koc, F., et al., *The sensitivity and specificity of 0.5% apraclonidine in the diagnosis of oculosympathetic paresis*. Br J Ophthalmol, 2005. **89**(11): p. 1442-4.
6. Torkildsen, G.L., et al., *Evaluation of Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution, 0.025% for Treatment of Ocular Redness*. Curr Eye Res, 2018. **43**(1): p. 43-51.
7. McLaurin, E., et al., *Brimonidine Ophthalmic Solution 0.025% for Reduction of Ocular Redness: A Randomized Clinical Trial*. Optom Vis Sci, 2018. **95**(3): p. 264-271.
8. deSousa, J.L. and R. Malhotra, *Brimonidine for anisocoria*. Ophthalmology, 2007. **114**(7): p. 1419.
9. Burroughs, J.R., et al., *Preoperative assessment of the eye and periocular region*. Semin Plast Surg, 2007. **21**(1): p. 5-17.
10. Yuksel, N., et al., *A comparison of the short-term hypotensive effects and side effects of unilateral brimonidine and apraclonidine in patients with elevated intraocular pressure*. Ophthalmologica, 2002. **216**(1): p. 45-9.
11. Araujo, S.V., et al., *Long term effect of apraclonidine*. Br J Ophthalmol, 1995. **79**(12): p. 1098-101.

4) **Inclusion and Exclusion Criteria***

A total of 40 eligible participants will be recruited for inclusion in the study.

Inclusion Criteria

- Adults age 18 and above able to provide informed consent to participate
- Subject with stable ocular health, defined as no ocular conditions requiring ongoing topical therapy or recent surgical intervention

Exclusion Criteria

- Adults unable to consent
- Individuals less than 18 years of age
- Prisoners
- Pregnant women.
 - o Patients will be asked if they are pregnant by research staff before participation in the study.
- Known contradictions or sensitivities to study medication (brimonidine)
- Ocular surgery within the past 3 months or refractive surgery within the past six months
- Grossly abnormal lid margins, anatomical abnormalities, previous eyelid or orbital surgery
- Variable ptosis or eyelid position (e.g., myasthenia gravis, thyroid eye disease, or blepharospasm)
- Significant pre-existing ptosis of any cause (defined as MRD1 < 1mm)
- Any ocular or systemic condition that, in the opinion of the investigator, would confound study data, interfere with the subject's study participation, or affected the subject's safety or trial parameters
- Presence of an active ocular infection
- Prior (within 5 days of beginning study treatment) use of eye whiteners (eg, vasoconstrictors), decongestants, antihistamines (including over the counter and herbal topical ophthalmic medications), phenylephrine dilating drops, any other topical ophthalmic agents
- Inability to sit comfortably for 15 – 30 minutes

5) **Procedures Involved***

Subject Identification and Recruitment

Potential subjects will be identified during their normal clinic visit at the Bascom Palmer Eye Institute, primarily within the oculoplastics department. The attending physician will ask eligible patients if they are interested in hearing about the study. No phone calls for recruitment will be made prior to the regular clinic visit. Patients may additionally be referred from other providers within the Bascom Palmer Eye Institute during their regular visits or from the emergency room. Bascom Palmer employees and University of Miami Miller School of Medicine students would also be invited to participate if interested.

Patients who qualify for the study and express an interest in participating will have the study explained to them by a research study member and have the opportunity to ask questions. They will receive information on risks and benefits to research participation. They will receive a copy of the consent form and if desired may be able to take the consent form home prior to signing for further consultation. Those who are interested in participation will be given a scheduled appointment to meet with research staff.

Number of Subjects

The time and resource constraints of our current pilot study allow for only approximately 40 participants.

Study Timelines

Recruitment will occur for 1 year and will end once 40 patients are accrued. The study length for the patient is expected to be only the length of clinic visit. The study is expected to last about 1 year from time of IRB approval to completion of all study activities, including analysis of identifiable data.

Lumify™ Drug Product

Lumify™ is FDA approved drug for the treatment of ocular redness due to minor eye irritation available for use without a prescription. It is available in a drop formulation. This agent should be considered exempt from IND requirements as the study is using the drug in realm of FDA indications. Drug insert is available attached to the IRB protocol.

Procedures Involved

We anticipate that procedures listed below will take about 30 to 40 minutes per patient. The procedures below are not considered standard of care and are being conducted for the study alone.

A. Part 1: Photographing subjects

- All images will be taken by the same examiner, in a room with the same conditions.
- With a modified slit lamp, the subjects' heads will be placed on a chin rest with forehead support to position them on a consistent plane in relation to the camera and to generate standardized images of the eyelids. A dedicated camera mounted at a fixed distance and height will be used to

photograph the patients. A clamp will be affixed to the brow bar, and will be used to hold the camera at a standardized distance from the patients and aligned vertically with respect to their lateral canthus. Subjects will be instructed to relax. A small circular sticker will be placed on the back of the iPhone, facing the patients. The subjects will focus on the sticker with their eyes in primary gaze. The camera zoom will be adjusted so that the eyes take up the full width of the frame –from lateral canthus to lateral canthus- thus limiting the acquired photograph to the eyes and rendering it unidentifiable.

- All photographs will be taken with the dedicated camera. The aperture, shutter speed, and exposure time will be based on the external lighting conditions. A camera flash will be used in order to standardize the light reflex in the eyes of subjects.
 - Photographs will be interfaced to a personal computer (PC) and saved as JPG files (1200 9 797 pixels, 24-bit, RGB) in a locked folder. When not in use the camera will be secured in a locked drawer.
- B. Part 2: Lumify™ application
- The left and right eye of each subject will be randomized to receive either Lumify™ or balanced saline placebo.
 - Based on the randomization results, the examiner will apply Lumify™ eye drops and saline to subject's eyes.
- C. Part 3: Photographing subjects
- Subjects will wait 5 minutes after they receive eye drops in the waiting area.
 - After time has elapsed, subjects will be photographed again according to the procedure described above.
 - The two steps described above will be repeated at 15 minutes and 30 minutes after the patients received the eye drops.
- D. Part 4: Measuring Intraocular Pressure
- Subjects will have their intraocular pressure measured using a Tonopen prior to applying Lumify™, and 30 minutes after receiving Lumify™ and after being photographed.
 - Measuring intraocular pressure using a Tonopen is a standard of care procedure during ophthalmic examinations.
- E. Part 5: Data analysis
- Data will be recorded and stored in a secure Microsoft Office Excel (Microsoft Corporation, Redmond, WA, U.S.A.) spreadsheet. Data will be graphically analyzed and represented with Adobe Photoshop (Adobe, Inc., San Jose, CA, U.S.A).
 - User performing analysis will be blinded to which eye received study drug.

No additional follow-up outside of the patient's next routine clinic visit will be needed. Patients who do have symptoms concerning any post-procedural complications will be instructed to notify study staff immediately. A phone number will be provided. Clinical examination post-procedure will be at Bascom Palmer Eye Institute.

Withdrawal of Subjects

Patients may withdraw at any time at their discretion. Subject withdrawn from and/or terminated from research with or without their consent are those who are found to not meet inclusion/exclusion criteria, and/or are not able to complete the research protocol in its entirety. For any subjects who withdraw from research, including partial withdrawal from procedures, study data of the withdrawn subject will not be included in statistical analysis and will be shredded.

6) Data and Specimen Banking*

Not applicable.

7) Data Management*

Steps to Secure Data

The study coordinator will assign each patient a specific ID number and place this information on a separate spreadsheet. The study coordinator will collect the sex, patient's age, and dates of service, but no other identifiable information. No names will be used in the forms. Presentations and publications will not identify individual patients. Data from the subjects' medical records will be encrypted and stored securely as detailed below. Identifiable data will not be stored for future use beyond the timeframe of this study. The release of data will be only to study members and no other outside organization.

Data will be kept under lock and key in Dr. Wendy Lee's office at the Bascom Palmer Eye Institute Oculoplastics Research Laboratory on the 4th floor (900 NW 17th Street, Miami, FL 33136), data encoded in the computer will be password-protected and will be available only to study personnel, and protected health information will not be re-used or disclosed for other purposes. Study members will be trained on how to log in and log out of the computers. The study coordinator will assign each patient a specific ID number and the sex, patient's age and date of on a separate spreadsheet. The study coordinator will record the study results including which eye received the study medication with the specific sample ID on another spreadsheet.

Data Analysis

Statistical analysis will be performed by the Oculoplastics Research Laboratory research fellow. A paired t-test will be used to analyze the difference in palpebral fissure height. Forty subjects will be required to perform perimetric statistics.

8) Risks to Subjects*

The primary risks to the subjects are adverse reactions to the medication. These risks are explained to patients prior to their arrival to the Oculoplastics Clinic. Previously described potential adverse reactions to brimonidine include instillation site discomfort and dry eye symptoms. However, the incidence of these side effects has been shown to be very low (up to 7.9% for dry eye). (Torkildsen 2017) Potential psychosocial risks to

subjects include time taken from their day to undergo tests, potentially missing work, and anxiety or discomfort from the eye drop instillation process. This study is not collecting sensitive information, thus no potential risk to reputation or legal risks should occur.

Subjects will be instructed to call immediately for an appointment if they notice a change in their vision, eye redness or the development of pain in either eye. Care will be taken by all study members to prevent the occurrence of any adverse events.

There are no well-controlled studies of brimonidine in pregnant women, and the risks to the fetus or embryo are unknown/unforeseen. Brimonidine is classified as AU TGA pregnancy category B3, and US FDA pregnancy category B.

- AU TGA pregnancy category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
- US FDA pregnancy category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Participants will be informed of the above information, and reserve the right to decline participation in the study.

Risks to measuring intraocular pressure using a Tonopen are extremely low, and include risk of infection and corneal abrasion.

Unanticipated problems or complications will be reported to the IRB according to posted guidelines.

Risks of the study are listed above and will be minimized by the following:

- Intraocular pressure measurements with a Tonopen will be performed according to the standard of care procedure by a trained member of the research staff.
- Study will be discontinued if subjects experience any negative effect from the medication
- Patients with a known sensitivity or history of adverse reaction to brimonidine or similar medications will be excluded from the study

As with any study, there is a risk of confidentiality breach. The research members will assign each patient a specific ID number and place this information on a separate spreadsheet. No names will be used in the forms. Presentations and publications will not identify individual patients.

9) **Potential Benefits to Subjects***

There will be no direct benefit to patients participating in the study. Their involvement may provide satisfaction for aiding in future research, particularly if they would be

interested in personally using the agent to increase their own palpebral fissure height in the future.

10) **Vulnerable Populations***

Bascom Palmer employees and Miller School of Medicine students are considered vulnerable populations as they would be invited to participate in the study if they were interested.

11) **Setting**

Study location will be at the Bascom Palmer Eye Institute, primarily within the 4th floor Oculoplastics clinic.

12) **Resources Available**

Principal investigator will be in charge of the studies and has been involved in multiple human clinical trials at the University of Miami.

Resident physician has experience in clinical research, slit lamp examination, and obtaining clinical photographs.

Research fellow at the Bascom Palmer Eye Institute has years of experience with data collection and analysis.

13) **Prior Approvals**

None.

14) **Recruitment Methods**

Wendy Lee, MD, the principle investigator of this study, will assess patients for study eligibility by reviewing the medical record. These patients will be coming in during their normal visit at the Bascom Palmer Eye Institute Oculoplastics Clinic. Dr. Lee will ask eligible patients if they are interested in hearing about the study. No phone calls for recruitment will be made prior to the regular clinic visit. Patients may additionally be referred from other providers within the Bascom Palmer Eye Institute during their regular visits. No payment will be provided to patients for their participation.

Patients who qualify for the study and express an interest in participating will have the study explained to them by a research study member and have the opportunity to ask questions. They will receive information on risks and benefits to research participation. They will receive a copy of the consent form and if desired may be able to take the

consent form home prior to signing for further consultation. Those who are interested in participation will be given a scheduled appointment to meet with research staff.

15) Local Number of Subjects

The goal of this pilot study is to assess the ability of Lumify™ in patients as an agent to increase eyelid height. The time and resource constraints of our current pilot study allow for only approximately 40 participants.

16) Confidentiality

An adequate plan to protect identifiers from improper use and disclosure is included in our study. Minimal risk for use of protected health information will be followed. Patient data will be collected under patient initials only. Data will be kept under lock and key in Dr. Wendy Lee's office at the Bascom Palmer Eye Institute Oculoplastics Research Laboratory on the 4th floor (900 NW 17th Street, Miami, FL 33136), data encoded in the computer will be password-protected and will be available only to study personnel, and protected health information will not be re-used or disclosed for other purposes. Certificates of confidentiality and separation of identifiers and data during storage, use and transmission will be implemented. Additionally, paper shredding and erasure of electronic data will be done at the earliest opportunity. Data collected from medical charts includes patient age, gender, race, and initials. Study records, consents and data will be stored as detailed below, and will be stored beyond the study completion date for six years following study closure.

17) Provisions to Protect the Privacy Interests of Subjects

An adequate plan to protect identifiers from improper use and disclosure is included in our study. Patient data will be collected under patient initials only. Data will be kept under lock and key in Dr. Wendy Lee's office at the Bascom Palmer Eye Institute Oculoplastics Research Laboratory on the 4th floor (900 NW 17th Street, Miami, FL 33136), data encoded in the computer will be password-protected and will be available only to study personnel, and protected health information will not be re-used or disclosed for other purposes. Separation of identifiers and data during storage, use and transmission will be implemented. Additionally, paper shredding and erasure of electronic data will be done at the earliest opportunity.

18) Consent Process

After identifying eligible study subjects, those who are interested in participating will be given a scheduled appointment to meet with research staff to review the consent form. The consent process will take place in Oculoplastics Clinic at Bascom Palmer Eye Institute. Adequate time will be devoted to the consent discussion; the patients will be

given ample time to review the consent form and ask questions. If patients have a different language than English, such as Spanish as their native language, a translator will be used to explain the research process. A separate consent translated in that appropriate language will be made prior to signing the consent. A witnessed will be used if the patient has vision impairment and is unable to read the consent.

19) Process to Document Consent in Writing

This research is no more than minimal risk of harm to subject. Witten documentation of consent will be provided.