Prospective randomized study to determine whether use of Rhopressa™ accelerates corneal clearing after removal of Descemet membrane for treatment of Fuchs dystrophy

Name of investigational compound:	Netarsudil ophthalmic solution 0.02%
Investigational phase:	Physician-sponsored IND
Principal Investigator:	Francis W. Price, Jr. MD
Co-Investigators:	Matthew T. Feng, MD Kathleen Kelley, OD Faye Peters, OD Ashlyn Ferguson, OD Katelyn Lucas, OD
Telephone number:	317-844-5530 (24 hours)
Email address:	fprice@pricevisiongroup.net
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Sponsor:

Francis W. Price, Jr. MD

Cornea Research Foundation of America

9002 N. Meridian St., Suite 212

Indianapolis, IN 46260

Phone: 317-814-2990, FAX: 317-814-2806

1. Purpose of the Study and Background

1.1 Purpose of the Study:

The study objective is to determine whether use of Rhopressa accelerates migration of host peripheral corneal endothelial cells to restore the central endothelial cell layer after removal of dysfunctional host endothelium and guttae-covered Descemet membrane from a central 4 to 5-mm diameter area to treat Fuchs endothelial corneal dystrophy (FECD).

1.2 Background

The leading reason for corneal transplantation in the United States is FECD, which is characterized by deposition of abnormal, vision-distorting deposits on Descemet membrane and subsequent apoptosis of corneal endothelial cells resulting in corneal edema. Deposition of guttae begins centrally and progresses peripherally. The current treatment for FECD is endothelial keratoplasty, in which a central 8-mm diameter area of Descemet membrane and dysfunctional endothelium is removed and replaced with healthy donor tissue. This results in rapid visual rehabilitation but requires long-term use of topical corticosteroids to prevent rejection of the donor endothelium. While the chance of rejection of the graft is reduced with Descemet's membrane endothelial keratoplasty (DMEK) relative to other corneal transplants, the risk is still present as is the risk of graft failure, requiring a repeat graft. If a patient's own cells could be used instead of donor tissue, then the need for long-term topical corticosteroids with the secondary risk of steroid-induced glaucoma would be reduced or eliminated.

The peripheral endothelium and Descemet membrane are often relatively healthy in FECD and studies have shown that the peripheral corneal endothelial cells can migrate to cover denuded areas.[1-3] Therefore, some surgeons have investigated the possibility of removing the central dysfunctional endothelium and most densely guttae-covered area of Descemet membrane in FECD patients without implanting any donor tissue. When a 6-mm diameter area is stripped, the recovery tends to be slow and unreliable.[1] Stripping a smaller area (4-mm diameter) accelerates recovery in many cases, yet some corneas still fail to fully clear within a reasonable time period and delayed clearing can lead to scar formation that degrades vision.[2-3] A pilot study found that use of ROCK inhibitor eye drops (ripasudil, available outside the USA) resulted in faster and more reliable corneal clearing following Descemet stripping only (DSO) for FECD.[3]

Unpublished data from outside the US indicates that Rhopressa™ may be superior to ripasudil for promoting endothelial cell migration and possible regeneration.

1.3 Study Design

- Prospective, randomized, double-masked, placebo-controlled clinical trial
- Main Outcome Measure: rate of corneal clearing after DSO for FECD

2.0 Characteristics of the Research Population

2.1 **Number of Subjects:** up to 60 FECD patients will be enrolled.

2.2 **Gender of Subjects:** both men and women will be enrolled

2.3 **Age of Subjects:** 18-90 years of age. The rationale for not including minors is that endothelial keratoplasty is performed to treat endothelial dysfunction, a condition usually seen in adults over 40 years of age.

2.4 **Racial and Ethnic Origin:** Subjects may be of any racial or ethnic origin.

2.5 **Inclusion criteria.** The following are requirements for study inclusion:

- At least 18 years of age
- Male or female patient undergoing Descemet stripping only for Fuchs dystrophy.
- Patient is able and willing to administer eye drops.
- Patient is able to comprehend and has signed the Informed Consent form.

2.6: Exclusion criteria. Patients with any of the following cannot participate in the study:

- Active intraocular inflammation, corneal ulceration, keratitis, or conjunctivitis.
- Known sensitivity to any of the ingredients in the study medications.
- Abnormal eyelid function.
- History of herpetic keratitis.
- History of non-compliance with using prescribed medication.
- Current or planned pregnancy within the study duration.
- Concurrent involvement or participation in another randomized clinical trial within 30 days prior to enrollment in this study.
- Any ocular or systemic condition (i.e., UNCONTROLLED systemic disease) or situation which in the investigator's opinion may put the patient at significant

risk, confound the study results, or interfere significantly with the patient's participation in the study.

2.7 Vulnerable Subjects:

No potentially vulnerable subjects will be enrolled because there may be no direct benefit to the patient; rather, important knowledge which may benefit future subjects is being sought. As such, the direct benefit would not outweigh risks for vulnerable populations.

Minors will not be enrolled into this study because Fuchs endothelial dystrophy is an adult-onset condition.

Pregnant women will not be enrolled into this study as potential risks and harm to the fetus is unknown.

This study plans to exclude any person who does not speak English as non- English speaking patients are not normally seen at the study site so a translator would not be available to translate the consent form into the patient's native language.

3.0 Methods & Procedures

3.1 Study procedures and assessments.

- Screening and Enrollment: Prospective subjects will be considered for entry into the study. Subjects meeting the inclusion and exclusion criteria will be informed of the opportunity to participate in the study. Subjects will be entered into the study after providing written informed consent. Each subject will be instructed that if they decide not to participate, they may withdraw at any time.
- Randomization: Netarsudil ophthalmic solution 0.02% and placebo eye drops will be dispensed to study subjects in 2.5 ml bottles, identical in appearance. A designated, unmasked, dosing coordinator will apply a coded sticker to each bottle. A computer generated randomization table will be generated. After the study subject signs the informed consent document, the subject will be randomly assigned to receive netarsudil or placebo (netarsudil vehicle). Both the subject and the investigator will remain masked as to the assigned treatment. If a study participant elects to have both eyes enrolled in the study, the dosing coordinator will automatically assign the second eye to the opposite treatment group from that of the first eye.
- Study Treatment Regimen: Subjects will be instructed to instill the assigned eye drop into the study eye once nightly for the 3-month study duration or until 2 weeks after corneal clearing is complete, whichever occurs sooner.

- Study Drug Accountability: Subjects will be asked to bring back to the clinic all study bottles, both used and un-used. All study drug bottles will be reconciled and recorded.
- Rescue Medication: If corneal clearing is not complete or seems to have stalled at the 5-week exam, the investigator can ask the dosing study coordinator to reveal the randomization assignment. If the eye was randomized to placebo it can be treated once daily (at night) with netarsudil (open label) for 7 weeks, whereas if the eye was originally randomized to netarsudil, it can be treated twice daily with netarsudil (open label) for 7 weeks or until complete clearing, whichever is sooner, in lieu of using the masked study drop.
- Examinations:
    - Schedule: Study visits include screening, as well as 1 day, 1 week, 3 weeks, 5 weeks, 7 weeks, 9 weeks and 12 weeks after DSO (Table 1). If complete healing is noted at the 3-, 5- or 7-week exam, the next following exam can be omitted.
    - Procedures: Medical and ophthalmic histories will be updated, adverse events will be recorded, and visual acuity will be assessed at each visit. A slit lamp examination will be performed at each visit to assess corneal clearing and to document any conjunctival or lid hyperemia, stromal inflammation, superficial punctate keratitis, other surface toxicity of the cornea, neovascularization of the cornea, and cells or flare in the anterior chamber. Subjects will also complete a 15-question visual disability questionnaire validated for use with FECD.[5] Manifest refraction, intraocular pressure, ultrasonic pachymetry, and corneal imaging with anterior segment optical coherence tomography will be performed at selected exams as indicated in the Table. Corneal endothelial cell density will be measured by specular microscopy if possible at the 9- and 12-week exams. Any routine exam procedures that were already performed within 90 days of study enrollment do not have to be repeated at the screening exam.
    - Records release: Subjects may be asked to sign a records release form in case the subject sees another eye specialist while enrolled in the study.
    - Unscheduled examinations: Subjects will be instructed to return for extra examinations if they note any problems with the eye.
    - Study completion: Subjects will be considered to have completed the study after they complete the 12-week examination.

- Subject withdrawal or discontinuation: Each subject may voluntarily discontinue the study at any time they choose. Subjects who cannot complete the study for administrative reasons (e.g., non-compliance, failure to meet visit schedule, etc.) will be discontinued from the study**.** Discontinued subjects may be replaced. For subjects withdrawn from the study, the same measurements and assessments should be performed as done at the 3-month exit exam. Adverse events should be followed up until resolution or stabilization of the adverse event.

Table 1.

	Screening Randomization	1 day after DSO	7 ± 2 days after DSO	3 ± 1 weeks after DSO	5 ± 1 weeks after DSO	7 ± 1 weeks after DSO	9 ± 1 weeks after DSO	Exit visit 12 ± 2 wks after DSO
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical and ophthalmic history	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Uncorrected visual acuity (Snellen)	X	X	X	X	X	X	X	X
Visual disability questionnaire	X			X	X	X	X	X
Assignment to netarsudil or placebo	X							
Manifest refraction and corrected distance vision (Snellen) if possible	X			X	X	X	X	X
Slit lamp exam	X	X	X	X	X	X	X	X
Endothelial cell density (if possible)							X	X
Intraocular pressure	X				X	X	X	X
Ultrasonic pachymetry	X				X	X	X	X
Anterior segment optical coherence tomography	X			X	X	X	X	X

3.2 Data Analysis and Data Monitoring:

The primary endpoint is the proportion of corneal clearing at 4 and 6 weeks after DSO. Based on previous pilot studies, we estimate that the mean proportion of corneal clearing in the placebo

arm will be 0.6 vs. 0.8 in the Rhopressa arm. The standard deviation is estimated to be ± 0.30. A sample size of 29 per study arm (total = 58) would provide 80% power to detect a statistically significant difference between groups at a 5% significance level (one-sided test). The planned enrollment is 60 subjects; this anticipates 3% drop out prior to the 4-week primary endpoint.

Statistical analysis will be conducted on an intent-to-treat basis (i.e. all randomized subjects will be included in the analysis). Data will be analyzed with Statistical Analysis Software (SAS Version 9.4, SAS Institute, Cary, NC).

3.3 Data Storage and Confidentiality: Research data will be stored in a locked cabinet or locked room and on a password protected server to prevent unauthorized access to data. The investigators and research staff will have access to the data. Subject identifiers will be removed and data will be aggregated for publication or presentation of study results.

4.0 Risk/Benefit Assessment

4.1 Risks and Anticipated Adverse Events:

Risks: This study is considered mild risk. It entails off-label use of netarsudil, which is approved for reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension.

A number of complaints and complications are anticipated in patients who have had DSO, regardless of whether they participate in this study. Therefore, the presence or absence of the following anticipated complaints and complications in the study eye will be recorded on the electronic case report form (eCRF) for each exam rather than on separate adverse event forms.

- Complaints of ocular discomfort: (examples include: eye pain, irritation, burning, itching, scratchy feeling, foreign body sensation, tired/fatigued feeling, achy/tender/sore feeling, pressure sensation, tightness, twinge/twitchy feeling, dry eyes, tearing/watering, eye redness) These are expected secondary to corneal decompensation with bullae in the area where Descemet's membrane has been removed and endothelial cells have not yet repopulated.
- Complaints of visual symptoms or disturbances: (examples include: glare or fluctuating vision, haloes around lights, diplopia, blurry, hazy, cloudy, filmy or out of focus vision,

ghosting or shadowing, difficulty reading, difficulty with night driving, floaters, spots in vision, light sensitivity, decreased vision, light reflections from intraocular lens or peripheral iridotomy). These are expected secondary to corneal decompensation with bullae in the area where Descemet's membrane has been removed and endothelial cells have not yet repopulated.

- Increased ptosis is expected secondary to corneal decompensation with bullae in the area where Descemet's membrane has been removed and endothelial cells have not yet repopulated.
- Puffy eyelids are expected secondary to corneal decompensation with bullae in the area where Descemet's membrane has been removed and endothelial cells have not yet repopulated.
- Delayed resolution of corneal haze or edema
- Subconjunctival hemorrhage
- Epithelial defect (within the first month of surgery) is expected secondary to corneal decompensation with bullae in the area where Descemet's membrane has been removed and endothelial cells have not yet repopulated.
- Development of capsular haze
- Superficial punctate keratitis

Anticipated adverse events in subjects who had cataract surgery combined with DSO include cystoid macular edema and capsular haze. Cataract formation or progression is an anticipated adverse event in any eye that was phakic and underwent DSO without combined cataract surgery. These anticipated surgical adverse events will be recorded on the electronic case report form (eCRF) for each exam rather than on separate adverse event forms.

The most common anticipated adverse events associated with use of Rhopressa™ include: eye discomfort, irritation, itching or pain, foreign body sensation, increased tearing, blurry vision, conjunctival hyperemia, conjunctival hemorrhage, eyelid swelling, and verticillata. Additional adverse events reported with use of Rhopressa™ include: reduced visual acuity, allergic conjunctivitis, dry eye, keratitis, conjunctival swelling, photophobia, and corneal staining.

Adverse events: The type, severity, duration and frequency of the following anticipated adverse experiences and any other unanticipated ocular adverse events will be tabulated. If a patient experiences an adverse reaction, appropriate medical treatment will be provided. Examples may include:

- Intraocular pressure elevation which requires intervention
- Development of capsular haze which requires intervention
- Cystoid macular edema
- Iritis

Anticipated rare adverse events include retinal detachment, iris synechiae/atrophy, epiretinal membrane, infectious keratitis or conjunctivitis, branch retinal vein occlusion, or endophthalmitis.

Serious Adverse Event: A serious adverse event is one that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. In the event of a serious adverse event, the investigator will maintain complete documentation and promptly inform the study drug manufacturer and the governing Institutional Review Board (IRB) of the serious adverse event within their required reporting period.

Fellow eye: Patients in this population tend to be affected with the eye condition bilaterally, so many of the study subjects may undergo surgery on the fellow eye during study participation. Routine fellow-eye post-surgical complications will not be transcribed to the eCRF unless the fellow eye is enrolled in the study at the time of the event.

4.2 Protection Against Risks: Every effort will be made to minimize any risks or discomforts to study subjects. The investigator will ensure appropriate training of study personnel and monitoring of subjects and will provide appropriate treatment for eye-related adverse events or referral for treatment of non-eye-related adverse events. The subject and or

their health insurance plan will be responsible for payment for treatment, counseling or follow up.

The **Data Safety Monitoring Committee (DSMC)** will be chaired by Dr. Gerald Clarke, an independent ophthalmologist practicing in Menasha, Wisconsin. The DSMC will review any serious adverse events as they occur. The DSMC will also review the interim data (including adverse events and subject compliance) every 6 months, to determine if any modifications to the original study plan may be warranted. The DSMC meeting minutes and recommendations will be documented and shared with IRBCo, Inc. and with the provider of the investigational product, Aerie Pharmaceuticals.

4.3 Potential Benefits to the Subjects: Study subjects may not realize any direct benefit from participation in the research; rather, important knowledge which may benefit future subjects is being sought. A potential benefit will be either healing or more rapid healing of the endothelial cell defect and avoidance of corneal transplant such as DMEK or DSEK which often require long term use of topical corticosteroids and the risk of secondary glaucoma.

4.4 Study termination: The study may be prematurely terminated if, in the opinion of the investigator or the Sponsor, there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator or Sponsor by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete or evaluable.
- Plans to modify, suspend or discontinue marketing of the Study Product.

5.0 Method of Subject Identification and Recruitment

5.1 Process of Consent The process of obtaining the consent consists of explaining the eye condition and explaining the risks and benefits of the proposed treatment and alternatives. In

addition, the patient will be allowed to read the consent and ask questions prior to signing the informed consent form. The patient may take home an unsigned copy of this consent form to think about or discuss with family or friends before making a decision.

Study coordinators, who have been trained in obtaining consent by the investigator and who have experience in consenting subjects for clinical trials, will obtain informed consent. Consent will be obtained in a private exam room with the door closed to protect the privacy of participants. The study will be explained to participants and if subjects have specific questions which the study coordinator cannot address, the principal investigator will be available to answer the questions.

5.2 Subject Capacity: All subjects will be evaluated for capacity to consent through the use of the Cornea Research Foundation of America Evaluation to Sign a Consent Form. Any subjects who do not answer the Evaluation questions satisfactorily will be considered cognitively impaired and will not be enrolled into the study as they would not meet the study's inclusion/exclusion criteria.

5.3 Subject/Representative Comprehension: Subjects will be allowed time to ask questions, and study information will be explained until it is clear that all information presented is understood.

5.4 Debriefing Procedures: Not applicable; this is not a psychological study and no information will be purposely withheld from the subject.

6.0 Consent Forms

6.1 Documentation of Consent Patient's medical records and informed consent documents will be maintained and stored with access limited to the authorized personnel. All research records will be kept separate and locked with limited access by research personnel only.

6.2 Costs to the Subject: The subject and or their health insurance plan will be responsible for payment for treatment, counseling or follow up.

6.3 Payment for Participation: Subjects will be provided with the assigned study drug (netarsudil or placebo eye drops) for the duration of study participation. Subjects will not receive any payment for study participation.

7.0 References

1. Arbelaez JG, Price MO, Price FW Jr. Long-term follow-up and complications of stripping descemet membrane without placement of graft in eyes with Fuchs endothelial dystrophy. Cornea 2014;33:1295-9.
2. Moloney G, Petsoglou C, Ball M, et al. Descemetorhexis without grafting for Fuchs endothelial dystrophy – supplementation with topical ripasudil. Cornea 2017;36:642-648.
3. Borkar DS, Veldman P, Colby KA. Treatment of Fuchs endothelial dystrophy by Descemet stripping without endothelial keratoplasty. Cornea 2016;35:1267-1273.
4. Soh YQ, Mehta JS. Regenerative therapy for Fuchs endothelial corneal dystrophy. Cornea 2018;37:523-527.
5. Wacker K, Baratz KH, Bourne WM, Patel SV. Patient-reported visual disability in Fuchs' endothelial corneal dystrophy measured by the Visual Function and Corneal Health Status instrument. Ophthalmology 2018;125:1854-1861.