Prospective randomized study to determine whether use of Rhopressa™ can ammeliorate corneal edema associated with Fuchs dystrophy

Name of investigational compound:	Netarsudil ophthalmic solution 0.02%
Investigational phase:	Physician-sponsored IND
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1. Purpose of the Study and Background

1.1 Purpose of the Study:

The study objective is to determine whether use of Rhopressa improves the ability of corneal endothelial cells to maintain appropriate corneal hydration in patients with Fuchs endothelial corneal dystrophy (FECD), which could help delay or prevent the need for a corneal transplant.

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.[1] It would be very useful to find a treatment that could bolster the corneal endothelium's ability to maintain appropriate corneal hydration in FECD and thereby postpone or prevent the need for a cornea transplant.

Even if such a treatment only resolved corneal edema for relatively short time, it could be of major benefit. The age of onset of symptomatic Fuchs dystrophy overlaps the age of onset of symptomatic cataracts, so Fuchs dystrophy patients often undergo cataract surgery before or combined with corneal transplantation. However, it is significantly more difficult to hit the refractive target when cataract surgery is performed in an eye with corneal edema, because it distorts the preoperative imaging needed to calculate the optimal intraocular lens power. Therefore, it would be valuable to find a treatment that could resolve corneal edema, even short-term, to refine the preoperative imaging and refractive outcomes for these patients.

Rhopressa is a drug known as a ROCK inhibitor. It increases aqueous outflow through the trabecular meshwork and is approved for treatment of glaucoma. ROCK inhibitors also activate corneal endothelial cell migration and possibly proliferation. Some corneal surgeons have reported anecdotally that they tried Rhopressa in patients with FECD and it seemed to reduce corneal edema (unpublished data). The purpose of this study is to test the hypothesis that use of Rhopressa can reduce corneal edema in patients with FECD.

1.3 Study Design

- Prospective, randomized, double-masked, placebo-controlled clinical trial

- Main Outcome Measures: central corneal thickness and patient-reported outcomes on the 15-item visual disability questionnaire that has been validated for use with FECD patients

2.0 Characteristics of the Research Population

2.1 **Number of Subjects:** up to 30 FECD patients will be enrolled.

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

2.3 **Age of Subjects:** at least 18 years of age. The rationale for not including minors is that FECD is an adult-onset condition.

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 diagnosed with FECD and corneal edema evident by slit lamp exam and/or corneal tomography.
- 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 are 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.
- 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.
- Examinations:
    - Schedule: Study visits include screening, 1 week (optional), 4 weeks, , and 12 weeks after randomization (Table 1).

- Procedures: Medical and ophthalmic histories will be updated, adverse events will be recorded, and visual acuity will be assessed with Snellen charts 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 corneal surface toxicity, corneal neovascularization, and cells or flare in the anterior chamber. Subjects will also complete a 15-question visual disability questionnaire validated for use with FECD.[2] Manifest refraction and intraocular pressure will be assessed and the cornea will be imaged with anterior segment optical coherence tomography, Scheimpflug corneal tomography, corneal topography and biometry.
- 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 exit exam. Adverse events should be followed up until resolution or stabilization of the adverse event.

Table 1.

	Screening Randomization	7 ± 2 days (optional)	4 ± 2 weeks	12 ± 4 weeks
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical and ophthalmic history	X	X	X	X
Adverse Events	X	X	X	X
Uncorrected visual acuity (Snellen)	X	X	X	X
Visual disability questionnaire	X	X	X	X
Assignment to netarsudil or placebo	X			
Manifest refraction and corrected distance vision (Snellen) if possible	X	X	X	X
Slit lamp exam	X	X	X	X
Intraocular pressure	X	X	X	X
Ultrasonic pachymetry	X			X
Anterior segment optical coherence tomography	X	X	X	X
Scheimpflug imaging	X	X	X	X
Optical biometry with the Lenstar	X		X	X
Corneal topography	X		X	X

3.2 Data Analysis and Data Monitoring:

The primary outcomes are the change in central corneal thickness from baseline to 1 month and from baseline to 3 months after randomization. The secondary outcomes are the change in scores on the visual disability questionnaire and the change in corrected distance visual acuity (CDVA) from baseline to 3 months after randomization. An exploratory outcome is he change in the corneal surface asymmetry index (SAI assessed by corneal topography).

A sample size of 13 eyes per arm would provide 80% power to detect a 70-micron between-group difference in central corneal thickness reduction, assuming a 2-tailed alpha of 0.05 and a standard deviation of 60 microns.

An interim data analysis is planned after enrollment of 15 subjects to assess safety and the statistical power assumptions.

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.

Adverse events:

A number of complaints and adverse events are anticipated in patients with FECD, regardless of whether they participate in this study. New complaints or problems or worsening of complaints or problems from the baseline level noted at the screening exam will be carefully recorded at each visit.

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.

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 a study subject 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. Some subjects may realize improvement in symptoms associated with corneal edema.

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. Kocaba V, Katikireddy KR, Gipson I, Price MO, Price FW, Jurkunas UV. Association of the Gutta-Induced Microenvironment With Corneal Endothelial Cell Behavior and Demise in Fuchs Endothelial Corneal Dystrophy. JAMA Ophthalmol. 2018;136:886-892.

2. 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.