Randomized, double-masked, placebo-controlled evaluation of netarsudil for prevention of corticosteroid-induced intraocular pressure elevation

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 netarsudil significantly reduces the rate of steroid-associated intraocular pressure (IOP) elevation when used by cornea transplant recipients long-term as an adjunct to prednisolone acetate (PA) 1% ophthalmic solution (used to prevent transplant rejection).

1.2 Background

Topical corticosteroids are commonly used to control postoperative ocular inflammation. They are also the mainstay for preventing and treating corneal transplant rejection and for treating ocular conditions involving immune hyper-reactivity.[1] The principal drawbacks include steroid-induced ocular hypertension and steroid-induced glaucoma. The incidence varies with the type of glucocorticoid and its formulation, the dosing frequency, and the treatment duration.

Prednisolone acetate 1% ophthalmic solution is the most commonly used topical corticosteroid in the U.S.[2] Treatment duration ranges from a few weeks, for controlling postoperative inflammation, to years, for preventing cornea transplant rejection.[2] Up to 35% of patients without a prior glaucoma diagnosis and up to 80% with pre-existing glaucoma experience clinically significant post-keratoplasty IOP elevation with long-term topical corticosteroid use.[3] Intraocular pressure elevation is associated with reduced visual acuity and increased risk of transplant failure.

Corneal transplantation offers a unique opportunity to evaluate potential methods for preventing IOP elevation associated with long-term use of topical corticosteroids, without the confounding factors present with immune hyper-reactivity disorders.

1.3 Study Design

- Prospective, randomized, double-masked, placebo-controlled clinical trial
- Main Outcome Measure
    - Rate of intraocular pressure elevation

2.0 Characteristics of the Research Population

2.1 **Number of Subjects:** up to 186 cornea transplant (endothelial keratoplasty) 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 membrane endothelial keratoplasty
- Patient is able and willing to administer eye drops.
- Patient is able to comprehend and has signed the Informed Consent form.
- Patient is likely to complete the nine-month course of the study.

2.6: Exclusion criteria:

- A patient exhibiting pre-operative intraocular inflammation.
- A patient with a known sensitivity to any of the ingredients in the study medications
- A patient who has a condition (i.e., UNCONTROLLED systemic disease) or is in a situation which in the investigator's opinion may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- A patient with abnormal eyelid function.
- A patient that is exhibiting active corneal ulceration, keratitis, or conjunctivitis, or who has a history of herpetic keratitis.
- A patient who has been diagnosed with uncontrolled glaucoma, prior aqueous shunt or trabeculectomy, or with preoperative IOP > 22 mm Hg in the potential study eye.
- Presence of any ocular disease that would interfere with the evaluation of the study treatment. However, patients with a history of cystoid macular edema, age-related macular degeneration, corneal neovascularization, and other non-interfering comorbidities may be enrolled.
- A patient with a history of non-compliance with using prescribed medication.
- A patient who is concurrently involved in or participated in another randomized clinical trial within 30 days prior to enrollment in this study.
- Patients who are pregnant or planning to become pregnant within the duration of 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 the conditions being studied under this protocol are not typical problems for minors. Endothelial keratoplasty is performed to treat endothelial dysfunction, a condition usually seen only in older (>40 years of age) adults.)

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. During the routine follow up exam 1 or 2 days after transplantation, the study subject will be randomly assigned to receive netarsudil or AR-13324 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 9-month study duration. As standard of care to prevent cornea transplant rejection, subjects will use prednisolone acetate 1% eye drops 4 times daily for the first 3 months, then 3 times daily during month 4, twice daily during month 5, and once daily during months 6 to 9.
- 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 a study subject develops IOP elevation (a measurement ≥ 24 mm Hg or an increase over the screening pre-operative reading of ≥ 10 mm Hg), the dosing coordinator will be notified. If the affected eye was assigned to the placebo group, the subject will be offered the opportunity to crossover to the netarsudil group to determine whether that adequately reduces IOP. Depending upon the severity of the IOP increase, the investigator may decide whether it is in the patient's best interest to reduce corticosteroid strength and/or dosing frequency and/or initiate use of approved glaucoma medications.
- Examinations:

- Schedule: Each subject will be examined at screening, 1, 3, 6 and 9 months after endothelial keratoplasty as detailed in Table 1. The examination schedule and procedures are standard of care for endothelial keratoplasty patients.
- Procedures: At 5 day, 1, 3, 6, and 9 month exams, medical and ophthalmic histories will be updated, adverse events will be recorded, and measurements of visual acuity will be made. At 1, 3, 6 and 9 month exams, measurements of manifest refraction, corneal thickness (pachymetry) and intraocular pressure will be made. Corneal endothelial cell density will be measured by specular or confocal microscopy if possible.. A slit lamp examination will be performed to assess the health of the transplant and document any conjunctival or lid hyperemia, stromal inflammation, superficial punctate keratitis, other surface toxicity of the cornea, neovascularization of the cornea, cells or flare in the anterior chamber, or evidence of transplant rejection.
- 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. This will allow the investigator to determine if there is a rejection episode or elevated intraocular pressure at examinations made with other physicians. The primary outcome (intraocular pressure) is a routine ophthalmic exam procedure, so the subject may have some exams performed by a local eye doctor if returning to the study site for all exams is too burdensome.
- Unscheduled examinations: Subjects will be instructed to return for extra examinations if they note any problems with the eye or any early signs of a possible rejection episode, such as a change in vision, redness to the eye, increased light sensitivity, burning sensation, or foreign body sensation.
- Study completion: Subjects will be considered to have completed the study after they complete the 9-month 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 9-month exit exam. Adverse events should be followed up until resolution or stabilization of the adverse event.

Table 1

	Screening	Randomization (1 or 2 days after DMEK)	5 day after DMEK	4 (± 2) weeks after DMEK	3 (± 1) months after DMEK	6 (± 1) months after DMEK	9 (± 1) months after DMEK
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical and ophthalmic history	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Uncorrected visual acuity (Snellen)	X	X	X	X	X	X	X
Assignment to netarsudil or placebo		X					
Corrected distance visual acuity (Snellen)	X			X	X	X	X
Manifest refraction	X			X	X	X	X
Endothelial cell density (if possible)	X			X	X	X	X
Intraocular pressure	X			X	X	X	X
Ultrasonic pachymetry	X			X	X	X	X

3.2 Data Analysis and Data Monitoring: The primary outcome measure is the incidence of clinically significant IOP elevation (defined as IOP ≥ 24 mm Hg or a relative increase over the baseline reading of ≥ 10 mm Hg). Previous study results conservatively suggest that the rate of IOP elevation will be 20% or greater in the placebo-control arm.[4,5] Based on the mechanism of action and clinical trial results, we estimate that the relative odds ratio will be 0.25 in the netarsudil study arm. A sample size of 84 per study arm (total = 168) would provide 80% power to detect a statistically significant difference between groups at a 5% significance level (two-sided test). Assuming up to 10% drop out, the required recruitment is 186 study eyes.

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) using Kaplan Meier survival analysis and proportional hazards analysis.

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 moderate risk. Netarsudil is an investigational drug - a New Drug Application (NDA) was recently submitted to the U. S. Food and Drug Administration.

A number of complaints and complications are anticipated in patients who have received a cornea transplant, 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)
- 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).
- Increased ptosis (within the first 6 months of surgery)
- Puffy eyelids (within the first 3 months of surgery)
- Delayed resolution of corneal haze or edema (within the first 6 months of surgery)
- Subconjuntival hemorrhage (within the first 3 months of surgery)
- Epithelial defect (within the first month of surgery)
- Folds in the transplant

- Partial graft detachment without further intervention
- Development of capsular haze
- Superficial punctate keratitis
- Pupillary block (within the first 3 months of surgery)

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:

- Graft detachment which requires intervention
- Immunologic graft rejection episode
- Graft failure and/or regraft
- Intraocular pressure elevation which requires intervention
- Development of capsular haze which requires intervention
- Iris synechia
- 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 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.

A **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.

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 given time to ask any 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) and with the prednisolone acetate 1% eye drops used to prevent transplant rejection for the duration study participation. Subjects will not receive any payment for study participation.

7.0 References

1. Fini ME, Schwartz SG, Gao X, Jeong S, Patel N, Itakura T, Price MO, **Price FW** Jr, Varma R, Stamer WD. Steroid-induced ocular hypertension/glaucoma: Focus on pharmacogenomics and implications for precision medicine. Prog Retin Eye Res 2016 [Epub ahead of print].
2. Price FW, Price DA, Ngakeng V, Price MO. Survey of steroid usage patterns during and after low-risk penetrating keratoplasty. Cornea 2009;28:865-70.
3. Vajaranant TS, Price MO, Price FW, Gao W, Wilensky JT, Edward DP. Vision and intraocular pressure after Descemet-stripping endothelial keratoplasty in patients with and without pre-existing glaucoma. Ophthalmology 2009;116:1644-50.
4. Price MO, Feng MT, Scanameo A, Price FW Jr. Loteprednol etabonate 0.5% gel vs. prednisolone acetate 1% solution after Descemet membrane endothelial keratoplasty: prospective randomized trial. Cornea 2015;34:853-8.
5. Price MO, Price FW Jr, Kruse FE, Bachmann BO, Tourtas T. Randomized comparison of topical prednisolone acetate 1% versus fluorometholone 0.1% in the first year after Descemet membrane endothelial keratoplasty. Cornea 2014;33:880-6.