PROSPECTIVE ANALYSIS OF LOTEPREDNOL ETABONATE OPHTHALMIC SUSPENSION 0.25% FOR PREVENTION OF IMMUNOLOGIC REJECTION AFTER DESCEMET MEMBRANE ENDOTHELIAL KERATOPLASTY

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- CLINICAL PROTOCOL -

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Principal Investigator and Sponsor

Francis W. Price, Jr. MD
9002 N. Meridian St., Suite 100
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 purpose of this study is to assess off-label use of loteprednol etabonate 0.25% ophthalmic suspension for prevention of immunologic rejection after Descemet membrane endothelial keratoplasty (DMEK).

1.2 Background

Topical corticosteroids have long been the mainstay for preventing and treating corneal graft rejection.[1] Typically, topical corticosteroids are dosed 4 times a day for several months, followed by tapered dosing for an extended period of time, sometimes indefinitely, after surgery.[1] If a patient experiences an immunologic graft rejection episode, corticosteroid use is increased in an effort to save the graft.

A number of side effects are associated with long-term corticosteroid use. In particular, up to one third of patients with no previous diagnosis of glaucoma experience intraocular pressure elevation with prolonged use of prednisolone acetate 0.1% ophthalmic suspension,[2] which is commonly used to prevent rejection following corneal transplantation.[1]

In our earlier studies, DMEK recipients used prednisolone acetate 1% four times daily for 1 month and then were randomized to a tapering dose of prednisolone acetate 1% ophthalmic suspension, fluorometholone 0.1% ophthalmic suspension, or loteprednol etabonate 0.5% gel. The loteprednol etabonate 0.5% gel and fluorometholone 0.1% suspension were as effective as prednisolone acetate 1% at preventing immunologic rejection episodes and were associated with significantly lower rates of steroid-induced ocular hypertension. [3,4]

This study will assess the use of a tapering dose of loteprednol etabonate 0.25% suspension from one month to one year after DMEK. The rates of immunologic rejection episodes and steroid-induced ocular hypertension will be compared with the respective rates observed in the earlier studies with use of prednisolone acetate 1% suspension, loteprednol etabonate 0.5% gel, or fluorometholone 0.1% suspension.

1.3 Study Design

- Prospective, open-label clinical study
- Main Outcome Measures
    - Rate of intraocular pressure elevation
    - Rate of initial immunologic graft rejection episodes

2.0 Characteristics of the Research Population

2.1 **Number of Subjects:** up to 75 DMEK recipients may enroll 1 eye into the study at the 1-month postoperative exam.

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 DMEK 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 who had DMEK within the past 1 to 7 weeks.
- 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 11-month study duration.

2.6: Exclusion criteria:

- A history of a previous rejection episode in the study eye
- A patient exhibiting 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 with primary open angle glaucoma.
- 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.
- 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: Prospective subjects, who have recently undergone DMEK, will be considered for entry into the study.

- Enrollment: 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.

- Study Treatment Regimen: At one month after DMEK (or at the time of study enrollment if that is more than one month after DMEK) participants will discontinue use of the prednisolone acetate 1% ophthalmic suspension that was prescribed for use after

DMEK, and they will be provided with loteprednol etabonate 0.25% ophthalmic suspension for use 4 times daily for 2 months, 3 times daily for a month, twice daily for a month, then once daily until the 12-month postoperative exam.

- Rescue medication: if a study subject experiences inflammation or a questionable immunologic rejection episode in the study eye within the first month after enrollment, they will be instructed to use prednisolone acetate 1% ophthalmic suspension up to 8x/day for one week, 6x/day for 1 week, 4x/day for one week and 3x/day for one week). The study subject will then restart the study dosing schedule. The month of rescue treatment will allow those with greater than average inflammation to remain in the study by providing an additional month of increased steroid strength before resuming a weaker steroid regimen.

- Examinations:
    - Schedule: Each subject will be examined at 1, 3, 6 and 12 months after DMEK as detailed in Table 1. The examination schedule and procedures are standard of care for DMEK patients.
    - Procedures: At each exam, medical and ophthalmic histories will be updated, adverse events will be recorded, and measurements of manifest refraction, visual acuity, 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. Since the primary and secondary outcome measures (slit lamp examination for evidence of rejection and intraocular pressure measurement) are routine ophthalmic exams, the subject may have some of the exams performed by a local eye doctor if getting back to the study site 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 one-year postoperative 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 one year. Adverse events should be followed up until resolution or stabilization of the adverse event.

Table 1

	Screening (~1 month after DMEK)	3 months after DMEK	6 months after DMEK	One year after DMEK
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical and ophthalmic history	X	X	X	X
Adverse Events		X	X	X
Uncorrected visual acuity (Snellen)	X	X	X	X
Corrected Distance visual acuity (Snellen)	X	X	X	X
Manifest refraction	X	X	X	X
Endothelial cell density (if possible)	X	X	X	X
Intraocular Pressure	X	X	X	X
Ultrasonic Pachymetry	X	X	X	X

3.2 Data Analysis and Data Monitoring: The primary outcome measures are the incidence of clinically significant intraocular pressure (IOP) elevation (defined as IOP ≥ 24mmHg or a relative increase over the pre-transplant IOP of ≥ 10mmHg), and the incidence of initial allograft rejection episodes or necessity to increase corticosteroids

because of breakthrough corneal or anterior chamber inflammation. The data will be analyzed using Kaplan Meier survival analysis and the log rank test.

A statistical power analysis indicated that a sample size of 70 participants would provide 80% power to detect a statistically significant difference in the rate of IOP elevation between loteprednol etabonate 0.25% and prednisolone acetate 1%, based on observed rates of IOP elevation in an earlier study that compared loteprednol 0.5% gel with prednisolone 1% suspension.[4]

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 from study data released to the Sponsor or for publication.

4.0 Risk/Benefit Assessment

4.1 Risks and Anticipated Adverse Events:

Risks: This study is considered to entail minimal risk for study subjects because topical corticosteroids are routinely used off label to prevent cornea transplant rejection.

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 without further intervention
- 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: Each subject may enroll one eye into the study. 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 the year of study participation. Routine fellow-eye post-transplant complications will not be transcribed to the eCRF.

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. Urgent data and safety monitoring reports (e.g. reports indicating an unanticipated problem involving risk) will be reported to the IRB within 10 business days of the Sponsor receipt of the report. Routine reports will be submitted to the IRB with the Sponsor's Study Status Report.

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 topical corticosteroid for the duration of the study. Subjects will not receive any payment for study participation.

7.0 References

1. 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.
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3. 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.
4. 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.