

**Hyperopia Correction using the  
NTK Optimal Keratoplasty (Opti-K™) System**

PROTOCOL NUMBER: OK-001

DATE: September 2, 2010

Amended: January 6, 2016

VERSION: 1.4

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## TABLE OF CONTENTS

<b>1.0 Background</b> .....	<b>4</b>
<b>3.0 Objectives</b> .....	<b>5</b>
<b>4.0 Safety and Efficacy Endpoints</b> .....	<b>5</b>
<b>5.0 Study Design</b> .....	<b>6</b>
<b>6.0 Subject Population</b> .....	<b>7</b>
<b>6.1 Inclusion Criteria</b> .....	<b>7</b>
<b>6.2 Exclusion Criteria</b> .....	<b>8</b>
<b>7.0 Study Duration and Examination Schedule</b> .....	<b>9</b>
<b>7.1 Study Duration</b> .....	<b>9</b>
<b>7.2 Examination Schedule</b> .....	<b>10</b>
7.2.1 Primary Treatment .....	10
<b>8.0 Study Procedures</b> .....	<b>10</b>
<b>8.1 Bilateral and Fellow Eye Treatment</b> .....	<b>10</b>
<b>8.2 Preoperative Evaluation (Day -30 to Day 0)</b> .....	<b>10</b>
8.2.1 Screening Eye Examination.....	11
8.2.2 Contact Lens Discontinuation and Stability Check .....	12
8.2.3 Concomitant Medication.....	12
<b>8.3 Opti-K™ Treatment Nomogram</b> .....	<b>12</b>
8.3.1 Primary Treatment (Treatment #1).....	12
<b>8.4 Outpatient Opti-K™ Surgical Procedure (Day 0)</b> .....	<b>14</b>
8.4.1 Treatment Procedure – Device and Materials Preparation .....	14
8.4.2 Treatment Procedure – Patient Preparation .....	14
8.4.3 Treatment Procedure - Pre-Treatment Centration.....	15
8.4.4 Primary Treatment Procedure.....	17
8.4.5 Treatment Procedure - Post-Treatment Centration Measurement .....	17
8.4.7 Operative Report.....	18
8.4.8 Postoperative Care .....	18
<b>8.5 Follow-Up Visits (1 Day, 1 Week, 1, 3, 6, 9, 12 and 24 months)</b> .....	<b>18</b>
<b>8.6 Retreatment</b> .....	<b>20</b>
<b>8.7 Safety Monitoring</b> .....	<b>20</b>
<b>8.8 Post-Study Procedures</b> .....	<b>20</b>
<b>8.9 Device Accountability</b> .....	<b>20</b>
<b>8.10 Early Withdrawal from Study</b> .....	<b>20</b>
<b>9.0 Data Analysis and Statistical Considerations</b> .....	<b>20</b>

<b>9.1</b>	<b>Sample Size</b> .....	<b>21</b>
<b>9.2</b>	<b>Analysis by Indication</b> .....	<b>22</b>
<b>9.3</b>	<b>Accountability</b> .....	<b>22</b>
<b>9.4</b>	<b>Screening</b> .....	<b>23</b>
<b>9.5</b>	<b>Subject Characteristics</b> .....	<b>23</b>
<b>9.6</b>	<b>Primary Efficacy Criteria</b> .....	<b>23</b>
<b>9.8</b>	<b>Clinical Safety Endpoint Criteria</b> .....	<b>25</b>
9.8.1	Adverse Events and Complications .....	25
9.8.2	Key Safety Parameters .....	26
<b>9.9</b>	<b>Other Outcome Measures</b> .....	<b>26</b>
<b>9.10</b>	<b>NEI-RQL-42</b> .....	<b>26</b>
<b>9.11</b>	<b>Subjective Symptom Questionnaire</b> .....	<b>28</b>
<b>9.12</b>	<b>Retreatments</b> .....	<b>28</b>
<b>9.13</b>	<b>Dropouts/Lost-to-Follow-up</b> .....	<b>28</b>
<b>9.14</b>	<b>Poolability</b> .....	<b>28</b>
<b>9.15</b>	<b>Missing data</b> .....	<b>28</b>
<b>10.0</b>	<b><i>Ethical and Regulatory Considerations</i></b> .....	<b>29</b>
<b>10.1</b>	<b>Informed Consent</b> .....	<b>29</b>
<b>10.2</b>	<b>Institutional Review Board</b> .....	<b>29</b>
<b>10.3</b>	<b>Complications and Adverse Events</b> .....	<b>29</b>
10.3.1	Serious and Unanticipated Adverse Device Effects .....	30
<b>10.4</b>	<b>Monitoring</b> .....	<b>31</b>
<b>10.5</b>	<b>Source Documents / Case Report Forms</b> .....	<b>31</b>
<b>10.6</b>	<b>Deviation from the Protocol</b> .....	<b>31</b>
	<b><i>APPENDIX A: STUDY FLOW CHART AND EXAMINATION SCHEDULE</i></b> .....	<b>33</b>
	<b><i>APPENDIX B: CFR 50.25 - ELEMENTS OF INFORMED CONSENT</i></b> .....	<b>35</b>
	<b><i>APPENDIX C: TEST METHODS</i></b> .....	<b>36</b>

## **1.0 BACKGROUND**

This study is being conducted to evaluate the safety and effectiveness of an optimal keratoplasty treatment using the NTK Optimal Keratoplasty (Opti-K™) system for treating hyperopic manifest refractive errors.

## **2.0 DEVICE DESCRIPTION**

The device used in this study is the NTK Optimal Keratoplasty (Opti-K™) System. The Opti-K™ System is a continuous wave (cw) thulium fiber laser (TFL) device for irradiation of corneas that are in contact with a sapphire applanation window/suction ring (SAWSR) for protection of the cornea epithelium from thermal damage.

The device includes a continuous wave (cw) thulium fiber laser (TFL) whose output beam is divided by beamsplitters into 4 “beamlets” that are transmitted through optical fibers and directed onto the cornea in a symmetrical square ring pattern (See Section 8.3). The laser output is at 1.93  $\mu\text{m}$  wavelength. The laser is typically operated with a total delivered power (from the optical fibers) between 0.9 to 1.8 W for a period of 150 ms. The delivered energy (from the optical fibers) is in the range of 30 to 60 mJ/spot. (When uncoated sapphire windows are used in a sapphire applanation window/suction ring, the actual delivered energy to the cornea is reduced by Fresnel reflection losses – *ca.* 9% total - at the air/sapphire and sapphire/cornea interfaces.) 16 spots are delivered in symmetrical arrays (See Section 8.3).

## **3.0 OBJECTIVES**

The primary objective of this study is to investigate the safety and effectiveness of the NTK Enterprises Optimal Keratoplasty (Opti-K™) System for performing optimal keratoplasty for the treatment of hyperopic manifest-based refractive errors to achieve temporary improvement in distance uncorrected visual acuity.

Data from this study will be used to support a marketing application to obtain FDA approval for use of the Opti-K™ System for performing optimal keratoplasty treatments for hyperopia correction.

## **4.0 SAFETY AND EFFICACY ENDPOINTS**

The primary efficacy parameters will be refractive predictability, refractive stability, and uncorrected distance visual acuity.

Safety assessments will include a tabulation of complications and adverse events, patient symptoms, loss of best spectacle-corrected visual acuity, changes in contrast sensitivity, and induced astigmatism. Quality of vision will be assessed using the National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL-42).<sup>1</sup>

Specific methods of analysis are provided in Section 9.0, Data Analysis.

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<sup>1</sup> National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL-42™), Version 1.0; Rand Institute, 2001.

## **5.0 STUDY DESIGN**

This safety and effectiveness study is a prospective, single arm, non-randomized, unmasked multicenter clinical study in which the primary control is the preoperative status of the treated eye.

The initial (feasibility) clinical study will be limited to three clinical sites with a total enrollment of 40 patients. One objective of the initial clinical study will be to refine the treatment nomogram in preparation for an expanded clinical study. Information from both the International Clinical Study and the initial U. S. Clinical Study will be used to determine the final treatment nomogram which will be then be used for the expanded U.S. Clinical Study. The final treatment nomogram will not be modified after the expanded U. S. Clinical Study begins. The expanded study will include additional clinical sites and will bring the total enrollment to a sufficient number of patients to have 350 treated eyes (of which at least 300 eyes will be in the completed cases cohort). All treated eyes (bilateral Treatments plus unilateral Treatments, if any) will be included in the study; safety and effectiveness analyses will be completed using all treated eyes. Initial patient enrollment is estimated to be 3 to 6 months following study initiation. Each patient will be followed for 24 months following treatment. The total duration of this study is estimated to be 36 months.

All study eyes will be evaluated at the screening/baseline examination, Day 0 (Opti-K™ treatment day), and 1 day, 1 week, and 1, 3, 6, 9, 12, 18, and 24 months after the Opti-K™ treatment. Corneal topography, manifest refraction, and measurements of uncorrected and best spectacle-corrected visual acuity will be obtained at baseline and at appropriate times after the Opti-K™ treatment to evaluate the effectiveness of the treatment. Safety monitoring throughout the study will include observations at appropriate times for subjective complaints, complications, and adverse events, as well as clinically significant findings on ophthalmic examination, dilated fundus examination, slit lamp examination, specular microscopy, and contrast sensitivity testing. Patient questionnaires will be used to evaluate subjective visual complaints, quality of vision, and quality of life preoperatively and postoperatively.

## 6.0 SUBJECT POPULATION

This study is a multicenter study that will be conducted initially at three (3) investigational sites located in the U.S. with forty (40) patients enrolled in the initial pilot study phase. Each investigator is expected to contribute approximately 50% of the study population in the pilot study. Upon receipt of FDA approval, the study will be expanded to up to 10 investigational sites with up to 350 eyes treated to provide 300 evaluable eyes. In the expanded study, each investigator is expected to contribute at least 20 eyes to the study and no investigator should enroll more than 25% of the study population (88 eyes total). Permission from the sponsor is required to exceed enrollment of 88 eyes at any single site.

### 6.1 Inclusion Criteria

Subjects in whom the study eye meets all of the following criteria are candidates for this study:

1. Male or Female
2. Any race
3. Patient is at least 40 years old.
4. Patient has bilateral sight with at least one eye with low hyperopia within the specified manifest refraction range as follows:
  - a. Sphere between +1.0 to +2.5 D;
  - b. Absolute Cylinder  $\leq$  0.75 D; and,
  - c. MRSE between +0.63 to +2.5 D.
5. Documented stable refraction defined as 0.5 D or less change in MRSE per year for 12 months or longer prior to primary Opti-K™ treatment, based on refractions, medical records or prescription history.
6. Able to tolerate full cycloplegic refraction while not under cycloplegia.
7. Distance uncorrected visual acuity (D-UCVA) between 20/63-2 and 20/32+2 (*i.e.*, from 58 to 77 letters on an ETDRS chart)
8. Distance best spectacle corrected visual acuity (D-BSCVA) of 20/40 or better (*i.e.*, 70 letters or better on an ETDRS chart in both eyes.
9. Patient has normal videokeratography (*i.e.*, without distorted or unclear corneal mires).
10. Is not a contact lens wearer or, if wearing contact lenses, has discontinued wearing contact lenses for the required period of time and completed the contact lens stability check as described below.
  - a. Contact Lens Wearers Only: Demonstration of a stable refraction, defined as two manifest refractions that are within  $\pm$  0.5 D MRSE of each other as determined under the following conditions:
    - i. The two refractions are performed at least 7 days apart; and,
    - ii. Contact lenses are not worn for at least the specified period of time prior to the first refraction used to establish stability and through the day of surgery:

Contact Lens Type	Minimum Discontinuation Time
Soft	3 Days
Soft Extended Wear	1 Week
Soft Toric	2 Weeks
Rigid gas permeable	2 Weeks

11. Patient is willing and able to comply with all pre-treatment and follow-up requirements, including the ability to read English to complete the NEI-RQL questionnaire
12. Patient understands the nature of the procedure, as well as potential risks or limitations of the treatment, and provides informed consent.

## 6.2 Exclusion Criteria

Subjects in whom the study eye meets any of the following criteria are will be excluded from this study:

1. Latent hyperopia  $> 1.0$  D (*i.e.*, baseline MRSE and CRSE should not differ by more than 1.0 D)
2. Nystagmus
3. Previous intraocular or corneal surgery (except strabismus surgery is permitted)
4. Significant conjunctivochalasis
5. Residual, recurrent or active ocular disease or corneal abnormality, including any of the following:
  - a. corneal diameter  $< 9$  mm
  - b. central corneal thickness  $< 500$   $\mu$ m
  - c. moderate to severe dry eye disease
  - d. uncontrolled uveitis;
  - e. severe blepharitis;
  - f. lagophthalmos;
  - g. glaucoma;
  - h. intraocular pressure  $> 21$  mm Hg;
  - i. cataract;
  - j. history of uveitis;
  - k. corneal shape disorders (keratoconus, keratoglobus, pellucid marginal degeneration, significant irregular corneal astigmatism, topography with irregular mires, *etc.*);
  - l. history of herpes zoster/simplex keratitis
6. Cloudy cornea or cloudy anterior chamber
7. Allergy to anesthetics or postoperative medications
8. History or current evidence of chronic allergic reactions, tearing and/or ocular irritation that might confound the outcome or increase the risk of the study.
9. The use of systemic medications that may confound the outcome or increase the risk of the study, including, but not limited to: corticosteroids,



- antimetabolites, amiodarone, isotretinoin, sumatriptan, or other medications that may affect wound healing.
10. Patients with a recent history (within one week prior to treatment) of using ophthalmic medications containing preservatives (benzalkonium chloride, *etc.*) and/or other ocular drugs that are cytotoxic.
  11. Acute or chronic illness that might increase the risk or confound the outcome of the study (e.g., diagnosed autoimmune disease, systemic connective tissue disease, clinically significant atopic disease, diabetes mellitus with ocular involvement, *etc.*)
  12. Pregnant, planning to be pregnant or lactating women
  13. Patients participating in other ophthalmic clinical trials during this clinical investigation
  14. Persons who, in the determination of the investigator, are not competent to understand the procedure or the actions asked of them as research subjects or have unrealistic expectations.
  15. Persons who may not be able to complete the requirements of returning to the investigator's clinic over the period of the study, or who may be difficult to locate or contact on short notice. This does not preclude vacations or travel.
  16. Persons who cannot achieve corneal applanation using the SAWSR device or cannot tolerate application of the SAWSR device or who cannot remain motionless for at least 5 seconds after verifying proper SAWSR mounting.
  17. Patients who are likely to be exposed to high levels of ultraviolet radiation (from sunlight, tanning lights, *etc.*) without protective eyewear during the one year period following Opti-K™ treatment.
  18. Presence or history of any other condition or finding that, in the opinion of the investigator, makes the patient unsuitable as a candidate for Opti-K™ treatment or study participation or may confound the outcome of the study
  19. Mesopic pupil diameter >5.6 mm
  20. Presence of a pupil irregularity (e.g., decentered pupil or irregular shape) in the eye to be treated that could predispose the eye to a centration error during the treatment.

## **7.0 STUDY DURATION AND EXAMINATION SCHEDULE**

### **7.1 Study Duration**

The study duration is scheduled for a total of 24 months for all study subjects.

The sponsor may file a Pre-Market Approval (PMA) application when refractive stability for the cohort has been determined and 80% of the eyes in the cohort have completed the confirmatory examination that is the next scheduled visit after refractive stability for the cohort is achieved.

If the PMA is filed before study conclusion, subjects enrolled in the study will continue through the Month 24 visit unless permission to conclude the study early is requested and received from FDA.

## **7.2 Examination Schedule**

### **7.2.1 Primary Treatment**

All patients are expected to return for follow-up examinations at 1 day, 1 week, and 1, 3, 6, 9, 12, 18 and 24 months post-primary treatment. Recommended visit windows for the primary treatment are:

- Screening: -30 to -1 days
- Primary Treatment: Day 0
- 1 Day (1D): 1 to 3 days
- 1 Week (1W): 5 to 9 days
- 1 Month (1M): 3 to 5 weeks
- 3 Months (3M): 10 to 14 weeks
- 6 Months (6M): 21 to 26 weeks
- 9 Months (9M): 35 to 43 weeks
- 12 Months (12M): 11 to 14 months
- 18 Months (18M): 17 to 20 months
- 24 Months (24M): 23 to 27 months

All final exam procedures will be completed at the Month 24 visit. If a subject drops out or is withdrawn from the study before completing the Month 24 examination, a Final Exam should be completed whenever possible, following the Month 24 Final Exam procedures. If a final examination cannot be performed, the last scheduled examination completed by the subject will be considered the final examination.

## **8.0 STUDY PROCEDURES**

Subjects who elect to participate in this study will complete the study as outlined below. All tests and measurements will be obtained in accordance with the procedures specified in this protocol. General instructions for use of Opti-K™ System are provided in the Instructions for Use for the device. If there are differences between the Instructions for Use and this protocol, the instructions provided in this protocol should be followed.

### **8.1 Bilateral and Fellow Eye Treatment**

Patients in the initial clinical study will be treated unilaterally in their dominant eyes. Fellow eyes cannot be treated in this study. Fellow eyes requiring refractive treatment may be treated with any other approved technology. Data will be captured on the non-study fellow eye and may be presented as a control.

### **8.2 Preoperative Evaluation (Day -30 to Day 0)**

All screening examination procedures will be performed by the investigator or trained personnel working under the investigator's supervision. Study candidates who are evaluated preoperatively by referring doctors will sign a consent form and have the screening procedures repeated preoperatively by study personnel. Screening data from referring doctors will not be used as the screening data for the study, except to document

preoperative refractive changes. Procedures or evaluations that were performed by study personnel during routine non-study visits may be used for the screening examination if the testing was completed: (1) within the 30 day screening window; (2) in accordance with the protocol requirements; and, (3) as part of the investigator's usual and customary examination procedures. Subjects will sign a consent form before any procedures or tests specific to the study protocol are performed.

### 8.2.1 Screening Eye Examination

Potential Opti-K™ candidates will undergo a complete screening eye examination to determine their eligibility for study participation. Demographics and a complete ocular history, medical history and medication history will be obtained. The complete eye examination and ocular history will include:

- UCVA distance (ETDRS chart)
- UCVA near
- BSCVA distance (ETDRS chart)
- BSCVA near
- Binocular UCVA distance
- Binocular UCVA near
- Manifest refraction
- Cycloplegic refraction
- Topography/Keratometry
- Pachymetry
- Aberrometry (report as 6 mm, 8<sup>th</sup> order) with pupil dilated to at least 6.5 mm
- Intraocular pressure
- Slit lamp examination of the cornea, anterior chamber and lens
- Mesopic pupil diameter
- Dilated fundus examination
- Contrast sensitivity [substudy at AEC clinical site only]
- Specular microscopy [substudy at AEC clinical site only]
- NEI-RQL-42 questionnaire
- Subjective complaint questionnaire

Topography, manifest refraction, and visual acuities should be done *before* dilation and before the completion of the cycloplegic refraction and any other potential tear disruptions tests (e.g., IOP measurement) so that the tear film is not altered. Aberrometry should be performed after dilation and before applanation tonometry.

Other optional diagnostic tests may be performed at the investigator's discretion (e.g., corneal hysteresis, OCT, topography and wavefront measurements with other devices such as the Oculyzer and iTrace) to further evaluate the subject for refractive surgery. Optional diagnostic tests should be performed *after* the examination requirements of the study have been completed.

Manifest refractions may be recorded on the source documents in the investigator's usual notation (plus or minus cylinder format) and will be recorded onto the case report forms using the standard notation (plus cylinder) designated by the sponsor.

## 8.2.2 Contact Lens Discontinuation and Stability Check

Contact lens wearers should discontinue contact lens wear for at least the following period of time before the screening examination and continue to abstain from contact lens wear through the day of surgery for the primary treatment:

- At least 3 days for spherical soft lenses,
- At least 1 week for soft extended-wear lenses,
- At least 2 weeks for soft toric
- At least 2 weeks for rigid gas-permeable lenses

Contact lens wearers will complete an additional examination that is at least 7 days after the screening examination to confirm refractive stability after contact lens discontinuation. A manifest refraction will be performed at this visit. Contact lens wearers should exhibit a stable refraction, defined as two manifest refractions performed at least 7 days apart that are within  $\pm 0.5$  D MRSE of each other. If a difference greater than  $\pm 0.5$  D MRSE is observed, the subject should either: (1) be declared a screening failure; or, (2) be examined at additional visits until stability ( $\leq 0.50$  D MRSE difference between consecutive examinations at least 7 days apart) is attained.

Contact lens wear in the Opti-K™ treated eye may not be resumed after the treatment during the study period.

## 8.2.3 Concomitant Medication

Subjects are permitted to take prescribed or non-prescription medications and supplements before and after the Opti-K™ procedure at the discretion of the investigator.

## 8.3 Opti-K™ Treatment Nomogram

Optimal keratoplasty (Opti-K™) treatment outcomes are a function of laser irradiation conditions, as well as patient factors such as age and wound healing response. Initially, the treatment nomogram will be based on visual acuity improvements observed in an international clinical study on *in vivo* human eyes. However, this initial treatment nomogram is based on a small number of patient eyes with a relatively short follow-up time (3 to 9 months), so the nomogram will be improved as more eyes are treated and examined at longer follow-up times.

### 8.3.1 Primary Treatment (Treatment #1)

For intended primary effective refractive change ( $\Delta$ MRSE), 16 spots of laser energy are delivered to the cornea in two concentric 8-spot rings of 6.0 mm and 7.2 mm centerline

diameters, with spots on radials, as shown in Figure 8.3.1-1 below. Laser energy is delivered in sets of 4 spots per irradiation as follows:

- 1) 4 spots (at 0°, 90°, 180° and 270°) on the inner ring (6.0 mm diameter),
- 2) 4 spots (at 45°, 135°, 215° and 305°) on the inner ring (6.0 mm diameter),
- 3) 4 spots (at 0°, 90°, 180° and 270°) on the outer ring (7.2 mm diameter), and
- 4) 4 spots (at 45°, 135°, 215° and 305°) on the outer ring (7.2 mm diameter).

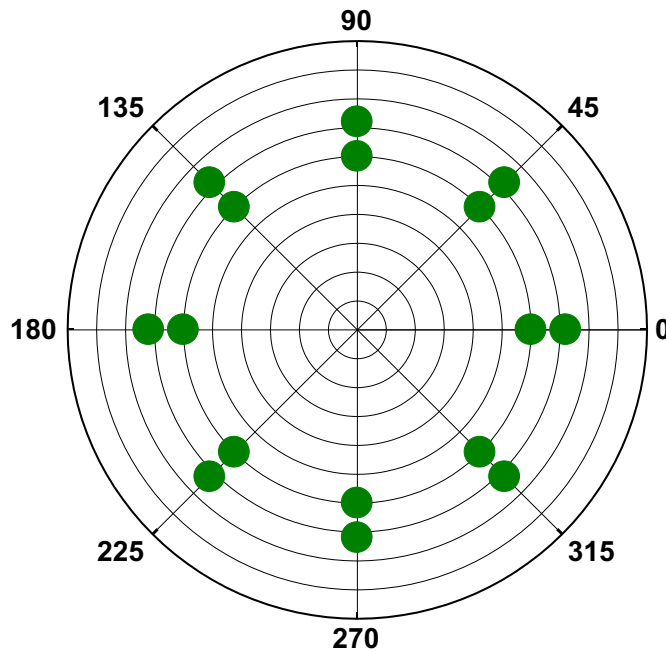


Figure 8.3.1-1: 16-Spot Opti-K™ primary treatment pattern. Concentric rings are at 1 mm diameter intervals and are centered with respect to the pupillary center; treatment spots are located symmetrically and radially on rings at 6.0 and 7.2 mm centerline diameters.

**All primary Treatments for patient eyes with hyperopia with MRSE in the range of +1.0 to +2.5 D should be completed at a primary Treatment energy density  $F$  of between 40 and 48 mJ/spot as noted below.**

<b>Pre-Tx MRSE (D)</b>	<b>F' (mJ/spot)</b>
+1.00	40
+1.13	44
+1.25	48
+1.38	48
+1.50 to +2.50	48

Table 8.3.2-1: Primary treatment nomogram for Treatment pattern #1 (6.0/7.2 mm diameter rings) for eyes with hyperopia with pretreatment MRSE in the range of +1.0 to +2.5 D

#### **8.4 Outpatient Opti-K™ Surgical Procedure (Day 0)**

##### **8.4.1 Treatment Procedure – Device and Materials Preparation**

Prior to the procedure, the NTK Opti-K™ System should be in proper working order. This is confirmed by turning on the NTK Opti-K™ System, allowing it to initialize and then performing laser energy calibrations. All calibrations are to be performed by a Sponsor representative. The system is described in Section 2.0.

Recommended supplies for use during the surgical procedure include:

- Topical anesthetic - preservative-free 0.5% proparacaine HCl – freshly obtained and stored in a refrigerator until use
- Irrigating solution – solute-free water
- Anti-inflammatory medication – Prolensa (bromfenac ophthalmic solution 0.07%, Ista Pharmaceuticals, Irvine, CA)
- Artificial tears – PF Blink Tears (Abbott Medical Optics, Santa Ana, CA)

Equipment [sapphire applanation window assembly, *etc.*] that will touch ocular surfaces should be cleaned and disinfected using alcohol (ethanol) prior to use. The cleaned surfaces should be dried thoroughly using compressed air immediately following disinfection.

##### **8.4.2 Treatment Procedure – Patient Preparation**

Prior to patient preparation, the physician should instruct the patient regarding the treatment and what to expect, including a rehearsal of fixation and SAWSR placement. The patient shall lie down in a reclining position with eyes looking upward at the flashing fixation light. The fellow eye should be covered with an occlusive patch. Preoperative sedation or anti-anxiety medication may be given at the investigator's discretion or if requested by the patient. One drop of a topical anesthetic (preservative free 0.5%

proparacaine HCl – freshly obtained and stored in a refrigerator until use) shall be instilled into the eye to be treated approximately two minutes pre-treatment. The patient should close his or her eyelids for *ca.* 1 minute to obtain an anesthetic effect. Then, the lids should be opened.

### 8.4.3 Treatment Procedure - Pre-Treatment Centration

#### Fixation Light and Guide Circle Reticule

A very functional fixation light has been developed using a miniature battery-powered light emitting diode (LED) mounted on the center of the iPad3 telescope objective lens. The mini LED (Part # APG1608CGKC/T; Kingbright Corporation, City of Industry, CA) emits light at 525 nm wavelength (green) and is battery operated. This provides a target on which patients can fixate their gaze. A circular gunsight reticule was added to the sapphire application window as seen in Figure 8.4.3-1 to provide better visual cues for accurate centration. To help minimize parallax, guide circles were added to the iPad3 monitor. They are perfectly centered on the monitor itself and nearly the same diameters as the inner sapphire appplanation window/suction (SAWSR) ring (small guide circle) and the inner illumination accessory ring (large guide circle), as shown in Figure 8.4.3-2.

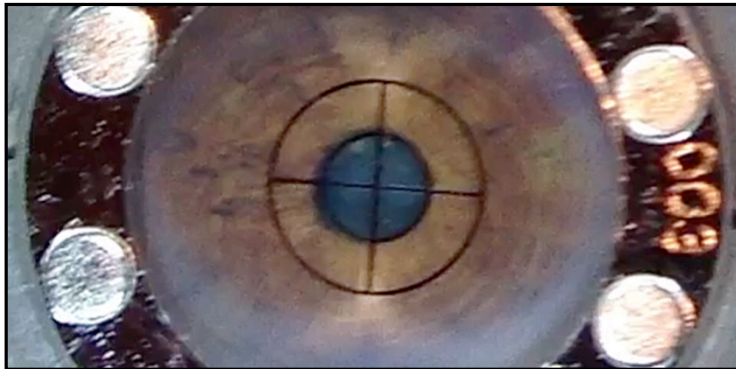
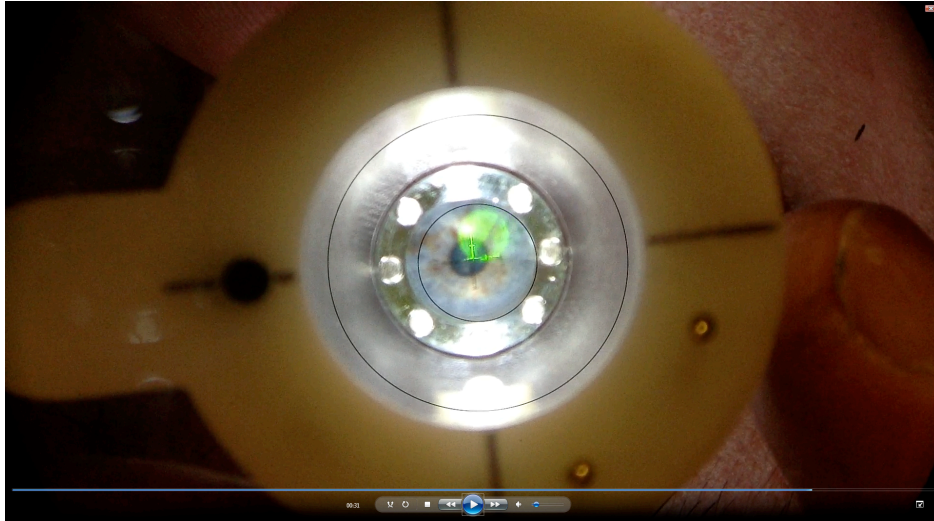


Figure 8.4.3-1. View from the iPad of the reticule aligned over a subject's cornea.



*Figure 8.4.3-2.* SAWSR assembly mounted on left eye (OS). Two black guide circles (on the monitor) are nearly the same diameters, and are nearly concentric with, the inner SAWSR ring (small guide circle) and the inner illumination accessory ring (large guide circle). A retroreflection of the fixation light from the sapphire window is visible as a green spot partly overlapping the pupil.

By overlapping the rings formed by the SAWSR assembly with those of the monitor, the SAWSR assembly can be properly mounted on the eye without significant tilt or displacement. Mounting can be further facilitated if the iPad3 monitor is at the physician's eye level.

The fixation light is very visible to the patient as a small bright green spot until the cornea is applanated, at which time it appears larger and looks like a speckle pattern. There should be no problem in having the patient watch the fixation source through applanation and SAWSR assembly mounting. After mounting, the retroreflection of the fixation light shows that the sapphire window is normal (*i.e.*, perpendicular) to the direction of propagation of the LED beam and hence to the optical axis of the telescope.

A small angular misorientation (*ca.* 10° counterclockwise) is evident in Figure 8.4.3-2. The physician can watch for this and correct the angular orientation.



#### 8.4.4 Primary Treatment Procedure

The physician should view the patient's eye to be treated on the iPad monitor under good background illumination by turning on the light emitting diodes (LEDs) mounted on the sapphire appplanation window/suction ring assembly (SAWSR - see Section 2.0). One drop of solute-free water should be placed on the cornea to prevent drying of the cornea and to aid hydration and lubrication. The patient should keep both eyes open and should look vertically upward at the fixation light. If the patient has excessive eye motion (*i.e.*, presents a moving target), the physician should postpone the treatment. Physician counseling of the patient about the procedure should obviate nervousness that can cause excessive eye motion.

The sapphire window with suction ring (SAWSR) should then be centered on the pupil using the round reticles in the window and monitor screen. Once in position, the window of the SAWSR should be applanated onto the cornea such that the tear film visibly spreads across it. At this point (when centration and appplanation are achieved), an assistant holding a hand held vacuum pump squeezes the handle until the gauge measures 20-30 cm/hg of external pressure on the suction ring (at no time should the pump exceed a level that causes the central retinal artery to be occluded)..

The evacuation port on the SAWSR should be projecting temporally when the SAWSR is mounted. The SAWSR is also equipped with four groups of three magnets per group. The center magnet of each group is used to engage the magnets on the fiber delivery holder (FDH) for primary treatment (Treatment). The physician should then position the fiber delivery holder (FDH) on the SAWSR so that its magnets (mounted on a collar on the FDH shaft) attach to the correct magnets (center of each set of 3 magnets for primary Treatment) on the SAWSR. The patient should be treated as soon as possible after mounting of the SAWSR and positioning of the FDH.

The patient should be instructed not to move during the treatment (and preferably to hold his/her breath during the treatment), which takes *ca.* 2.5 seconds. The patient should not feel any pain during the treatment. It is important that the patient's eye (and the patient) remain motionless during treatment.

The physician should verify that the FDH is correctly mounted and then deliver laser light through the FDH by pushing the footswitch that starts an automated sequence of shutter opening/closing and fiber translation steps. After the treatment is completed, vacuum pressure should be released and the FDH and SAWSR removed from the eye. One drop of Prolensa (bromfenac ophthalmic solution 0.07%, Ista Pharmaceuticals, Irvine, CA) should be instilled into the eye immediately post-Treatment. Immediate post-Treatment exams should then be completed.

#### 8.4.5 Treatment Procedure - Post-Treatment Centration Measurement

As a post-treatment check on technique, decentration measurements are made after delivering treatments, using slit-lamp biomicroscope images obtained with a digital

camera. Images are printed out on 8½" X 11" paper, resulting in *ca.* 25X magnification. Treatment centers (TCs) and pupil centers (PCs) are located on these printouts; TCs are located by intersection of straight line connectors drawn between pairs of Treatment spots oriented 180° apart around Treatment rings and PCs are located by intersection of straight line connectors between pairs of pupil edges oriented 180° apart. Distances between TCs and PCs are measured and converted to absolute distances using inner ring spot separations as a scale. Using a ruler with mm resolution and images with 25X magnification, a typical TC-PC distance can be located to *ca.* 0.04 mm absolute distance accuracy.

#### 8.4.7 Operative Report

An immediate post-treatment report should be completed for all treated patients, and for those patients for whom a treatment was attempted but not completed. The immediate post-treatment report should include information on intended and actual treatment variables (energy/spot), time for entire procedure, procedure variations (*e.g.*, SAWSR remounting), and drug treatment before, during and after procedure.

#### 8.4.8 Postoperative Care

Postoperative instructions will be given to each subject and reviewed prior to discharge. The following postoperative eye drops will be prescribed for the following minimum times:

1. Prolensa 1 drop immediately after the primary treatment, then 1 drop in the treated eye at bedtime on the day of the treatment and the following morning (3 drops total).
2. Preservative-free artificial tears PRN (*e.g.* Blink Tears sterile, single-use)

All postoperative eye drop usage will be recorded in the subject's chart. Other prescription or nonprescription medications, including pain medications and medically indicated ophthalmic medications, may be taken as needed throughout the study. Use of any ophthalmic drops containing benzalkonium chloride is not recommended during the first week after the treatment.

### **8.5 Follow-Up Visits (1 Day, 1 Week, 1, 3, 6, 9, 12 and 24 months)**

A study flow chart summarizing the follow-up examination schedule and required procedures to be performed at each study visit is provided in Appendix A. All subjects will be seen at 1 day, 1 week and 1, 3, 6, 9, 12, 18 and 24 months after the Opti-K™ treatment. All final exam procedures will be completed at the 24-month visit. If subject drops out or is withdrawn from the study before completing the Month 24 examination, the Month 24 procedures should be performed as the Final Exam whenever possible. If a final examination cannot be performed, the last scheduled examination completed by the subject will be considered the final examination.

The following procedures will be performed at each visit unless noted otherwise.

- Documentation of interim medical, ocular, and medication histories since previous visit

- UCVA distance
- UCVA near
- BSCVA distance
- BSCVA near
- Binocular UCVA distance
- Binocular UCVA near
- Contrast sensitivity (Months 1, 6, 12, and 24)<sup>2</sup>
- Mesopic pupil diameter (Months 1, 6, 12, and 24)
- Manifest refraction
- Cycloplegic refraction (Months 1, 6, 12, and 24)
- Keratometry (Months 1, 6, 12, and 24)
- Corneal topography
- Aberrometry (report as 6 mm, 8<sup>th</sup> order) with pupil dilated to at least 6.5 mm<sup>3</sup>
- Intraocular pressure (omit Day 1)
- Specular microscopy (Week 1 post-secondary treatment; Months 1, 3, 6, 12, and 24)<sup>3</sup>
- Pachymetry (Months 6, 12, and 24)
- Slit lamp examination of the cornea, anterior chamber and lens
- Dilated fundus exam (Months 6, 12, and 24)
- NEI RQL-42 questionnaire (Months 1, 3, 6, 12, and 24)
- Subjective complaint questionnaire (Months 1, 3, 6, 12, and 24)
- Adverse events/complications
- Other diagnostic tests (at investigator's discretion)

Topography, manifest refraction, and visual acuities should be done *before* dilation and the before the completion of the cycloplegic refraction and any other potential tear disruptions tests (e.g., IOP measurement) so that the tear film is not altered. Aberrometry should be performed after dilation and before applanation tonometry.

Other optional diagnostic tests may be performed at the investigator's discretion (e.g., corneal hysteresis, OCT, topography and wavefront measurements with other devices such as the Oculyzer and iTrace) to further evaluate the subject's postoperative outcome. Optional diagnostic tests should be performed *after* the examination requirements of the study have been completed. The results of optional diagnostic tests will not be recorded on the case report forms.

Reasonable effort will be made by telephone and mail to contact subjects who miss a scheduled follow-up visit.

Any observations of known optimal keratoplasty postoperative events will be documented in the subject's medical records and evaluated by the investigator and the sponsor to determine whether it is a reportable event.

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<sup>2</sup> Contrast sensitivity and specular microscopy are performed as substudies at a single clinic.

<sup>3</sup> Pupils should be dilated pharmacologically using a short-acting mydriatic or cycloplegic agent, such as phenylephrine or tropicamide (Mydriacyl).

## **8.6    *Retreatment***

No retreatments will be performed during the study.

## **8.7    *Safety Monitoring***

Subjects will be observed closely to detect any adverse events or complications that may have occurred. On the day of treatment and at each follow-up visit, a non-leading question, such as “How are you seeing?,” may be used to determine whether any complications or adverse events might have occurred since the last visit. The presence or absence of adverse events or complications will be documented.

Ophthalmic safety will be evaluated by slit lamp examination of the operated eye, measurement of refraction, and measurement of visual acuity. In the case of an adverse event or complication, these tests, and any others deemed necessary, may be repeated before the next scheduled visit at the investigator’s discretion. Appropriate supportive and/or definitive therapy may be administered as required. Any complications or adverse events will be recorded in the medical record/case report form.

## **8.8    *Post-Study Procedures***

Subjects will be discharged from the study after the final examination is complete.

## **8.9    *Device Accountability***

All use of the Opti-K™ System will be under the direct supervision of the principal investigator or his designee.

## **8.10   *Early Withdrawal from Study***

Subjects will be advised that they are free to withdraw from the study at any time. The investigator may discontinue a subject if a serious adverse event occurs and it is in the subject's best interest not to continue in the study or if the subject moves and the subject cannot complete the remainder of the follow-up visits. When a subject withdraws early from the study, a final examination will be performed at the time of withdrawal if possible.

## **9.0    *DATA ANALYSIS AND STATISTICAL CONSIDERATIONS***

A detailed statistical analysis plan (SAP) will be developed for analysis of all data for this study. Required analyses and target endpoints that will be included in this SAP are summarized below. The methods by which each of these analyses is performed will be included in the SAP. The required analyses and target endpoints include, but are not limited to those listed below.

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software. All subjects who are enrolled in this study will be included in the safety analysis. All two sided testing and confidence intervals will use a significance level of 5%.

## 9.1 Sample Size

In the initial (feasibility) clinical study, 40 sighted patients will be treated unilaterally in their dominant eyes. Following demonstration of safety and effectiveness in initial clinical study sighted eyes (based on an initial treatment nomogram – see Table 8.3.2-1), the treatment nomogram will be refined and used in an expanded study.

After expansion, it is estimated that at least 300 patient eyes will be treated in the full study. This sample size is based on the expected observation of zero subjects with a serious adverse event such that the upper one-sided 95% confidence limit is less than 1.0%. With 300 eyes, the upper one-sided exact confidence limit is 1.0 %. The computation for the number of eyes  $n$  is taken from application of the exact binomial distribution:

$$\binom{n}{0}(0.01)^0(1-0.01)^n < 0.05$$

which reduces to:

$$(1-0.01)^n < 0.05$$

which is solved by taking logarithms of both sides:

$$n \log(0.99) < \log(0.05)$$

so  $n > [\log(0.05)/\log(0.99)]$  or  $n > 298.0725$  which was rounded up to 300.

For effectiveness, the proportion of eyes with an improvement of 2 or more lines of D-UCVA at 12 months post-treatment will be reported. The hypothesis is that the proportion of eyes that achieve a minimum of 2 lines improvement over baseline at 12 months after treatment will be greater than 85%. In statistical terms, the hypothesis is written as:

$$H_0: P_t \leq 0.85$$

*versus*

$$H_a: P_t > 0.85$$

where  $P_t$  is the proportion of eyes with at least a 2-line improvement in D-UCVA. Early results from a clinical study outside the United States indicate that the expected proportion of eyes that achieve 2 or more lines improvement in D-UCVA is approximately 90%. With 300 eyes, the power is 80.9% to detect a statistically significant improvement in D-UCVA above 85% with a one-sided exact binomial test with alpha of 0.05.

The sample size is increased to account for a potential 10% non-completion rate. Thus the number of eyes that need to be recruited is  $300/0.9 = 333$ . Rounding upwards, up to 350 eyes will need to be enrolled in the pivotal arm of the trial to assess the primary endpoints.

### Study Populations

There are two study populations identified in the study. The first is the completed cases (CC) population that includes those patients who complete the study through one year of

follow-up. The second is the intent to treat (ITT) population that includes all patients who enter the study and are treated with the laser. The primary safety analysis will be done on the ITT population and the primary effectiveness analysis will be done on the ITT followed by a confirmatory analysis in the CC population.

## **9.2 Analysis by Indication**

All eyes enrolled in the study are being treated for hyperopia with the treatment target of emmetropia. Thus, no analysis by indication will be performed.

## **9.3 Accountability**

Accountability by postoperative visit will be calculated as illustrated in Table 9.3-1 below.

Table 9.3-1: Accountability by Postoperative Visit

		1 Month	3 Months
Available for Analysis <sup>2</sup>	n/N <sup>1</sup> (%)		
Missed Visit <sup>3</sup>	n/N <sup>1</sup> (%)		
Discontinued <sup>4</sup>	n/N <sup>1</sup> (%)		
Active <sup>5</sup>	n/N <sup>1</sup> (%)		
Lost to follow-up <sup>6</sup>	n/N <sup>1</sup> (%)		
% Accountability = $\frac{\text{Available for Analysis}}{\text{Enrolled} - \text{Discontinued} - \text{Active}}$			

Where,

- <sup>1</sup> Enrolled (N) = total number of subject eyes enrolled in the study.
- <sup>2</sup> Available for analysis = total number of eyes for whom data are available at each postoperative interval.
- <sup>3</sup> Missed visit = total number of eyes that missed the visit, but were otherwise accounted for. Includes those eyes that missed the visit but were seen at a later visit.
- <sup>4</sup> Discontinued = total number of eyes that discontinued follow-up prior to completion of the study for any reason (e.g., retreatment, moved away).
- <sup>5</sup> Active (not yet eligible for the interval) = total number of eyes that have not yet reached the visit interval.
- <sup>6</sup> Lost to follow-up = total number of eyes for whom a visit at the prescribed visit or later was not completed and who are not considered to be active or discontinued.

#### 9.4 Screening

The screening data for all subjects who are screened but do not meet eligibility criteria will not be analyzed or tabulated nor collected on the case report forms.

#### 9.5 Subject Characteristics

The number of subjects included in the safety and/or effectiveness evaluations, subjects completing the study, and the reasons for any withdrawals will be tabulated by counts and percents. Continuous demographic data will be summarized using descriptive statistics. Categorical demographic data will be summarized using counts and percents.

Abnormal medical histories, ocular histories, and prior/concurrent medications obtained on the screening visit will be presented in data line listings.

#### 9.6 Primary Efficacy Criteria

- The following effectiveness endpoints and target values will be addressed at all post-treatment examinations for all treated eyes:
- **E1.** The proportion of eyes (target: at least 85%) that achieve successful distance uncorrected visual acuity (D-UCVA) improvement defined as 2 lines (10 letters) or more improvement in D-UCVA following Treatment will be reported.

- **E2.** The proportion of eyes (target: at least 85%) that achieve distance uncorrected visual acuity (D-UCVA) of 20/40 or better following Treatment and the proportion of eyes that achieve D-UCVA of 20/40 or better following Treatment as a function of the pre-Treatment D-UCVA will both be reported.
- **E3.** The proportion of eyes that achieve predictability (achieved versus attempted) of distance uncorrected visual acuity (D-UCVA) within  $\pm 2$  lines (target: at least 85%) and within  $\pm 1$  line (target: at least 50%) of the intended value (20/20) at the point at which stability is first reached will be reported.
- **E4.** The percentage of eyes that achieve predictability (achieved versus attempted) of manifest refraction, spherical equivalent (MRSE) within  $\pm 1.0$  D (target: at least 75%) and within  $\pm 0.5$  D (target: at least 50%) of the intended value (0.0 D) will be reported based on aberrometry readings.
- **E5.** In an expanded clinical study, after the treatment nomogram has been refined, the percentage of eyes that achieve stability (as defined below) will be reported; means  $\pm$  standard deviations of MRSE will also be reported for pre-Treatment as well as post-Treatment exams.
- Stability analyses, to be performed for the time intervals between all consecutive pairs of scheduled postoperative refractions, are:
  1. A – Percentage of eyes that achieve:
    - A1 – a change of less than or equal to 1.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
    - A2 – a change of less than or equal to 0.50 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
    - B – Mean overall change and change per month in MRSE between consecutive scheduled visits as determined by a paired analysis;
    - C – Mean  $\pm$  SD MRSE for the preoperative and each postoperative visit;
    - D – Assessment of cylinder stability for correction of spherocylindrical refractive errors.
      - Note: refractive stability is generally accepted to have been achieved at the latter of two postoperative refractions performed at least 3 months apart or at 3 months after surgery when compared to the 1-month interval, if all the following recommended criteria are met:
        - $\alpha$  – At least 95% of the treated eyes have a change of  $\leq 1.00$  D of MRSE between the two refractions;
        - $\beta$  – The mean rate of change of MRSE, as determined by a paired analysis, is  $\leq 0.5$  D per year (0.04 D/month) over the same time period;
        - $\gamma$  – The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;



- $\delta$  – The 95% confidence interval for the mean rate of change includes zero or a rate of change attributable to normal aging; and
  - $\epsilon$  – Stability is confirmed at least 3 months after the stability timepoint by a statistically adequate subgroup.
- **E6.** In an expanded clinical study, after the treatment nomogram has been refined, the proportion of eyes that achieve improvements (as well as reductions or unchanged values) of questionnaire items listed in the National Eye Institute – Refractive Error Quality of Life (NEI-RQL) instrument (see Appendix V) will be reported.

All of the above effectiveness measures will be reported for all treated eyes.

## **9.8 Clinical Safety Endpoint Criteria**

The primary safety endpoint is the proportion of eyes with the occurrence of serious adverse events defined in the list below:

### Serious Adverse Events

1. Corneal infiltrate or ulcer
2. Persistent central corneal epithelial defect at 1 month or later post-Treatment
3. Corneal edema at later than 1 month post-Treatment
4. Corneal perforation
5. Uncontrolled intraocular pressure (IOP) with increase of >5 mm Hg above baseline, and any IOP above 25 mm Hg
6. More than 10% endothelial cell loss as measured by specular microscopy at 6 months or later post-Treatment
7. Retinal detachment
8. Retinal vascular accidents
9. Decrease in BSCVA of greater or equal to 2 lines ( $\geq 10$  letters ETDRS) not due to irregular astigmatism as shown by rigid contact lens refraction at 3 months or later
10. Any other vision-threatening event

The hypothesis is that the rate of serious adverse events defined above is less than 1.0% per type and less than 5.0% *in toto*. Rates of occurrence of each of these serious adverse events, together with the incidence of adverse events *in toto*, will be reported.

Other safety endpoints include: loss of 2 or more lines of D-BSCVA, D-BSCVA worse than 20/40 and induced manifest refractive astigmatism of > 2.0 D.

### **9.8.1 Adverse Events and Complications**

All subject questionnaire data, complications, and adverse events will be tabulated and summarized.

## 9.8.2 Key Safety Parameters

The following safety endpoints and target values will be tabulated and reported at all post-treatment examinations for all treated eyes:

- **S1.** Less than 5.0% of patients should lose more than 2 lines of distance best spectacle-corrected visual acuity (D-BSCVA).
- **S2.** Less than 1.0% of patients should have D-BSCVA worse than 20/40.
- **S3.** Less than 5.0% of patients should have induced manifest refractive astigmatism of  $>2.0$  D.
- **S4.** Less than 1.0% of patients should experience each type of serious adverse event and less than 5.0% of patients should experience serious adverse events *in toto*.

The following additional safety endpoints and target values will be tabulated and reported at each measurement timepoint:

- **S5.** Less than 1.0% of eyes should lose more than 10% of central or peripheral endothelial cell density (ECD).
- **S6.** Less than 1.0% of eyes should lose more than 0.3 log units of contrast sensitivity.

## 9.9 Other Outcome Measures

Intraocular pressure will be tabulated by counts and percents. Other outcome measures, such as pupil size, central pachymetry, slit lamp examinations, and dilated fundus examinations will be reported in data line listings.

## 9.10 NEI-RQL-42

The parameter evaluated will be the difference in the numeric score for the NEI-RQL-42 administered post treatment at the time point of stability to the pre-treatment or baseline composite score. The NEI-RQL-42 will be administered pre-treatment at screening to establish the subject's baseline and at all post operative time points after the primary treatment starting at 1 Month. It is believed that by the timepoint of refractive stability the positive effect of the surgery will have manifested itself in the visual function quality assessment.

Scoring will be calculated according the NEI-RQL-42 Scoring Manual.<sup>4</sup> Scoring the RQL-42 is a two-step process:

1. **Numeric Score:** Original numeric values from the survey are recoded following the scoring rules outlined in Table 1. All items are scored so that a high score

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<sup>4</sup> Hays, R. D., & Spritzer, K. L. (2002, February). National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL-42™), Version 1.0: A Manual for Use and Scoring. Los Angeles, CA.

represents better quality of life. Each item is then converted to a 0 to 100 possible range so that the lowest and highest possible scores are set at 0 and 100, respectively. In this format, scores represent the achieved percentage of the total possible score. For example, a score of 50 represents 50% of the highest possible score.

2. **Scale Scores:** Items within each scale are averaged together to create the 13 scale scores. Table 2 indicates which items contribute to each scale. Scales with at least one item answered can be used to generate a scale score. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Scores represent the average for all items in the scale that the respondent answered.

Scales included in the scale score analysis are:

- Clarity of vision
- Expectations
- Near vision
- Far vision
- Diurnal fluctuations
- Activity limitations
- Glare
- Symptoms 2b
- Dependence on correction 16
- Worry
- Suboptimal correction 2
- Appearance
- Satisfaction with correction

It is desired to determine whether the mean responses from a population at two different time points are equal to each other; therefore, the hypotheses to be tested are:

$$H_0: \mu_D = 0 \text{ versus } H_A: \mu_D \neq 0$$

where  $\mu_D$  is the mean difference in the numeric score between the two time points.

If it is assumed that the data from both time points are normally distributed, then the test statistic for testing the above hypothesis is a t-test. That is, the null hypothesis is rejected if  $t > t_{(df, 1-\alpha/2)}$ , where

$$t = \frac{(\bar{X}_D - 0)}{\sqrt{\frac{s_D^2}{n}}}$$

Published literature indicates that a difference of 6 points or more on the composite scores is a clinically significant change.<sup>5</sup>

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<sup>5</sup> Schein OD, Vitale S, Cassard SD, Steinberg EP. Patient outcomes of refractive surgery: The refractive status and vision profile. J Cataract Refract Surg. 2001 May;27(5):665-73.

### **9.11 Subjective Symptom Questionnaire**

The subjective symptoms patient questionnaire will be administered pre-treatment at the time of the screening examination or on the day of treatment to establish the subject's baseline and at all post operative time points starting at 1 month. The presence of each subjective symptom is rated on a 5-point scale that corresponds to: None (1), Mild (2), Moderate (3), Marked (4), Severe (5). Symptoms that are evaluated are: light sensitivity, difficulty driving at night, reading difficulty, double vision, fluctuation in vision, glare, halos, starbursts, dryness, pain, foreign body sensation, and other. Questions that evaluate patient satisfaction and patient willingness to have the procedure again will also be included on the questionnaire.

Severity ratings will be tabulated by counts and percents for each symptom for each postoperative visit, beginning at 1 month. Descriptive statistics will be presented for the changes in the degree of severity of patient symptoms compared to the baseline pre-treatment severity rating for the cohort at 6 months. The improvement in subjective complaints will be analyzed, as determined by the difference in the percentage of patients who have marked/severe ratings of each symptom at 6 months compared to the percentage who have marked/severe ratings of each symptom at baseline. For each time point of evaluation, descriptive statistics will be presented for the entire cohort.

### **9.12 Retreatments**

Retreatments cannot be performed in the study.

### **9.13 Dropouts/Lost-to-Follow-up**

Subjects may drop out at any time during the study. Effectiveness data from dropouts will be included through the last recorded subject visit, except in those instances where missing data precludes the analysis of serial or comparative data points. All treated subjects/eyes will be included in the safety analysis

### **9.14 Poolability**

The demographic data for all sites will be tested for homogeneity. This will include age, gender, and race. Also, the key baseline and final efficacy endpoints will be tested for differences among the sites. For baseline, the MRSE will be evaluated for differences among sites and for final efficacy, refractive predictability will be assessed for differences amongst the sites. Continuous variables will be assessed via ANOVA and categorical variables (sex and race) will be assessed using Fisher's exact test.

### **9.15 Missing data**

To assess the impact of missing data, a sensitivity analysis will be conducted. Under this analysis, the primary endpoints will be assessed in a worst case and best case scenario. For this study, the best case scenario is to use the last observation carried forward and the worst case is to use the baseline value. Since the number of missing data points in this

type of study has been extremely small, it is anticipated that the sensitivity analysis will yield results similar to the main analysis.

## **10.0 ETHICAL AND REGULATORY CONSIDERATIONS**

This study will be conducted in accordance with FDA's Good Clinical Practice regulations.

### **10.1 Informed Consent**

In accordance with the provision of 21 CFR Part 50, each subject will provide written informed consent for participation in this study prior to the use of the investigational device (Appendix B).

The study will be explained to the prospective subject by the investigator or his designee. The nature of the experimental product will be explained together with potential hazards of the surgical procedure, including any possible adverse reactions. The subject will be informed that he/she is free to terminate participation in the study for any reason. One copy of the signed consent form will be retained in the medical record.

### **10.2 Institutional Review Board**

This protocol and the informed consent form will be approved initially and reviewed annually by an Institutional Review Board (IRB) constituted according to FDA regulations. Progress reports will be submitted at the completion of the study or at least once yearly, whichever comes first, to the IRB. Serious adverse events will be reported to the IRB and the FDA in accordance with applicable FDA regulations for serious adverse events.

### **10.3 Complications and Adverse Events**

Throughout the course of the study, every effort will be made to remain alert to possible adverse events and complications. If adverse events occur, the first concern will be the safety of the patient. Appropriate medical intervention will be made. Any adverse event observed by the investigator or reported by the patient, regardless of severity and whether or not ascribed to the study materials, will be recorded in the appropriate section of the patient's data collection forms.

Serious adverse events will be documented until their medical outcome is stable and written reports will be provided to the Sponsor by the Investigator. The patient will be continued in the study until protocol visits are completed.

Serious and/or potentially vision-threatening adverse events include, but are not limited to, the following:

- Corneal infiltrate or ulcer,
- Persistent central corneal epithelial defect at 1 month or later post-treatment,
- Corneal edema at later than 1 month post-treatment,
- recurrent corneal erosion at 1m or later post-Treatment,
- corneal perforation,
- retinal detachment,

- retinal vascular accident,
- uncontrolled intraocular pressure (IOP) with increase of >5 mm Hg above baseline, and any IOP above 25 mm Hg,
- more than 10% endothelial cell loss as measured by specular microscopy at 3 months or later post-Treatment,
- decrease in BSCVA of greater or equal to 2 lines ( $\geq 10$  letters ETDRS) not due to irregular astigmatism as shown by rigid contact lens refraction at 3 months or later, and any other vision-threatening event.

Complications include, but are not limited to, the following:

- Corneal edema between 1 week and 1 month post-Treatment,
- Persistent peripheral corneal epithelial defect at 1 month or later post-Treatment,
- Keratitis (non-vision threatening),
- Conjunctivitis, and
- Pain, tearing, photophobia and/or foreign body sensation at 1 month or later post-Treatment.

All clinical findings (both serious adverse events and complications) are to be reported on Case Report Forms (CRFs). Complications should be reported on each CRF with clinical grading using a scale of Trace, Mild, Moderate or Severe to assess grade. Each of these grade scales is defined on the CRFs. Opacities in treatment spots should be individually graded on a scale of 1 to 4 (none, trace, mild, dense) and their depths graded on a scale of 1 to 4 ( $\leq 25\%$ , 26 to 50%, 51 to 75%,  $\geq 76\%$ ). Anterior chamber observations should be described and graded as indicated on each CRF.

Complications will be reported in routine reports to FDA and the IRB but individual reports are not required.

### 10.3.1 Serious and Unanticipated Adverse Device Effects

An unanticipated adverse device effect is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.”

#### *10.3.1.1 Sponsor Responsibilities*

In accordance with 21 CFR Part 812.150(a)(1) and (b)(1), the sponsor shall promptly report the results of an evaluation of any serious and unanticipated adverse device effect to FDA, all reviewing IRB’s and participating investigators (if any) as soon as possible, but not later than 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as the FDA requests. Complications and non-serious or anticipated adverse events should be documented and tabulated but need not be submitted by the sponsor to the FDA as individual reports. All vision threatening adverse events should also be reported to FDA, all reviewing IRB’s, and all participating investigators in the same manner as reporting a serious and unanticipated adverse device effect.

### *10.3.1.2 Investigator Responsibilities*

Investigators should report all serious and unanticipated and all vision threatening adverse events to the sponsor within 10 working days of first learning of the event. Those that are determined to be serious and unanticipated after sponsor review should also be reported the IRB within 10 working days of first learning of the event. Should the IRB have more stringent time requirements, the reporting requirements of the IRB will be followed.

### *10.3.2 Non-serious or Anticipated Adverse Events*

Non-serious or anticipated adverse events and complications should be documented on the case report forms and tabulated for reporting but need not be submitted as individual reports by the investigator to the sponsor or IRB. Should the IRB have different reporting requirements, the requirements of the IRB will be followed.

## **10.4 Monitoring**

A monitor will be designated by the sponsor to oversee the progress of the investigation. The monitor may be an employee of the sponsor or a consultant to the sponsor. The monitor will meet with the investigator and staff before the study, during the study, and at other appropriate times to ensure compliance with the FDA's Good Clinical Practice requirements and with the protocol specifications. All records pertaining to the study will be made available to the monitor at each review.

## **10.5 Source Documents / Case Report Forms**

Adequate records will be maintained for the study including subject medical and surgical records, signed informed consent forms, and device use records. All original source documentation will remain at the investigative site. Study data that are stored at the investigator site in any electronic medical records system, including measurements that are obtained electronically (e.g., topography), will be printed and retained in the study files.

All study data will be recorded onto case report forms (electronic or paper) designed for the study. If paper case report forms are used, copies of the case report forms will be retained with the investigator's study files and the original forms will be filed with the sponsor.

## **10.6 Deviation from the Protocol**

The investigator will not deviate from the protocol without prior IRB and sponsor approval, unless such deviation is necessary to manage a medical emergency. The investigator will notify the IRB and the sponsor of any protocol deviation to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event any later than 5 working days after the emergency occurred. All other revisions and/or amendments to the protocol that affect subject

treatment, study outcome, or subject safety should be submitted in writing to the IRB and the sponsor for approval prior to implementation if the changes or deviations to the protocol affect the scientific soundness of the study or the rights, safety, or welfare of human subjects. In this case, the change should not be implemented until IRB and sponsor approvals are obtained. The investigator should maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

Changes that affect the scientific soundness of the study or the rights, safety, or welfare of human subjects may also require FDA approval, in addition to sponsor and IRB approval, prior to implementation. The sponsor and investigator will obtain such approvals, if required.



## APPENDIX A: STUDY FLOW CHART AND EXAMINATION SCHEDULE

Examination and/or Information	Screen	Tx	1D	1W	1M	3M	6M	9M	12M	18M	24M <sup>6</sup>
Demographics	X	X	X	X	X	X	X	X	X	X	X
Ocular, Medical & Medication History <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X
Opti-K™ Treatment		X									
Distance and near UCVA <sup>8</sup>	X	X	X	X	X	X	X	X	X	X	X
Distance and near BSCVA <sup>9</sup>	X	X	X	X	X	X	X	X	X	X	X
Binocular D- and N-UCVA	X	X	X	X	X	X	X	X	X	X	X
Contrast sensitivity <sup>10</sup>	X				X		X		X		X
Pupil diameter <sup>11</sup>	X				X		X		X		X
Manifest refraction <sup>12</sup>	X		X	X	X	X	X	X	X	X	X
Cycloplegic refraction <sup>13</sup>	X						X		X		X
Keratometry <sup>14</sup>	X				X		X		X		X

<sup>6</sup> The 24 Month examination is the final examination for the study. If the study is terminated early or a patient is withdrawn from the study before completion of the 24 Month examination, the 24 Month procedures should be completed as a Final Examination, whenever possible.

<sup>7</sup> Ocular history should include history of contact lens wear. Non-specific questioning should be used at each visit to determine other vision-related complaints, complications, or adverse events that are not otherwise captured on the case report forms. Medication history should include all prescribed medications and any non-prescription medications taken on a daily basis.

<sup>8</sup> Distance and near visual acuity charts, chart luminance, ambient illumination, testing distances and testing procedures will be standardized for all clinical sites and investigators. For distance visual acuity measurements, Early Treatment of Diabetic Retinopathy Study (ETDRS logMAR) charts will be used at 4 meters optical distance, with chart background luminance in the range of 80 to 160 cd/m<sup>2</sup>, chart contrast 85% or greater, ambient illumination from dim to dark to maximize pupil size and with no surface within the patient's field-of-view that exceeds the chart's background in luminance. Testing will be done by counting correct letters read; reporting will be in both decimal and Snellen notations. For near visual acuity measurements, ETDRS-style near visual acuity charts will be used at 40 cm distance, with chart background luminance, chart contrast, ambient illumination, other surface luminance, testing and reporting the same as for distance visual acuity measurements listed above.

<sup>9</sup> BSCVA should be performed using an ETDRS eye chart and recording the total number of letters that are seen. If visual acuity with spectacle correction is > 2 lines below that obtained preoperatively at 3 months or later, a hard contact lens over refraction should be performed to determine the effect of higher order aberrations and to estimate the best possible corrected visual acuity.

<sup>10</sup> Contrast sensitivity with and without glare should be performed using the Functional Vision Analyzer according to the contrast sensitivity testing protocol. Contrast sensitivity testing may be performed at other times at the investigators discretion to assess contrast related adverse events, complications, or complaints. The contrast sensitivity substudy will be completed at one clinical site with an enrollment of 68 eyes (assuming a 10% loss to follow-up; more eyes will be enrolled if necessary so that the completed cases cohort comprises at least 61 eyes) as recommended in Section E.3.1 of ANSI Z80.11.

<sup>11</sup> Pupil size should be assessed under dim conditions at the preop exam and final exam. Mesopic pupil size should be measured at all contrast sensitivity testing visits under the same lighting conditions used to perform the contrast sensitivity testing. Pupil size may be measured using a pupillometer (e.g. NeurOptics; San Clemente, CA) that can be operated under mesopic lighting conditions.

<sup>12</sup> Manifest refractions may be recorded on the source documents in the investigator's usual notation (plus or minus cylinder format) and will be recorded onto the case report forms using the standard notation designated by the sponsor.

<sup>13</sup> One drop of 0.5% cyclopentolate HCl ophthalmic solution will be instilled into each eye for cycloplegia

<sup>14</sup> Keratometry data will be obtained using Simulated Keratometry outputs from corneal topography

Examination and/or Information	Screen	Tx	1D	1W	1M	3M	6M	9M	12M	18M	24M <sup>6</sup>
Corneal topography <sup>15</sup>	X		X	X	X	X	X	X	X	X	X
Aberrometry <sup>16</sup>	X		X	X	X	X	X	X	X	X	X
Intraocular pressure <sup>17</sup>	X			X	X	X	X	X	X	X	X
Specular microscopy <sup>18</sup>	X				X	X	X		X		X
Pachymetry <sup>19</sup>	X						X		X		X
Subjective questionnaire	X				X	X	X		X		X
NEI RQL-42 questionnaire	X				X	X	X		X		X
Slit-lamp exam <sup>20</sup>	X	X	X	X	X	X	X	X	X	X	X
Dilated fundus exam	X						X		X		X
Adverse events/complications		X	X	X	X	X	X	X	X	X	X

<sup>15</sup> Corneal topography measurements will be obtained using Orbscan II®, EyeSys® or equivalent instruments

<sup>16</sup> Aberrometry measurements will be obtained using a LADARWave CustomCornea Wavefront System (Alcon Laboratories, Irvine, CA).

<sup>17</sup> Intraocular pressure measurement will be measured with a Goldmann tonometer or equivalent.

<sup>18</sup> A noncontact specular microscope (CellCheck XL, Konan Medical USA, Torrance, CA) will be used in a substudy on 40 eyes. Test conditions include use of images with at least 100 countable (i.e., not in shadow, washed out or blurred) cells grouped in a uniform area. Images will be obtained centrally and at two peripheral locations (12 and 6 o'clock at 3 mm from center). Automated image analysis will be used to measure endothelial cell density (ECD). Post-Tx vs. pre-Tx ECD will be used to calculate endothelial cell loss.

<sup>19</sup> Pachymetry measurements of central corneal thickness will be obtained using an ultrasonic pachymeter, Pentacam, or Orbscan II®. Optionally, additional pachymetry measurements of pericentral and peripheral corneal thickness will be obtained using an Orbscan II® system, Pentacam, or equivalent.

<sup>20</sup> Slit lamp will include a complete survey of the anterior segment, with detailed examination of the cornea and recording and grading of overall corneal clarity and any preoperative abnormalities. Post-treatment assessments will include the opacity (graded as absent, detectable, or moderately dense) of treated spots, together with the status of the corneal epithelium examined after instillation of sodium (Na) fluorescein and lissamine green B to visualize possible epithelial damage to cornea and/or conjunctiva.

## **APPENDIX B: CFR 50.25 - ELEMENTS OF INFORMED CONSENT**

**BASIC ELEMENTS OF INFORMED CONSENT:** In seeking informed consent, the following information shall be provided to each subject.

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the U.S. Food and Drug Administration may inspect records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

## APPENDIX C: TEST METHODS

**Visual Acuity (VA) assessment** – Distance and near visual acuity charts, chart luminance, ambient illumination, testing distances and testing procedures will be standardized for all clinical sites and investigators.

For distance visual acuity measurements, Early Treatment of Diabetic Retinopathy Study (ETDRS logMAR) charts will be used at 4 meters optical distance, with chart background luminance in the range of 80 to 160 cd/m<sup>2</sup>, chart contrast 85% or greater, ambient illumination from dim to dark to maximize pupil size and with no surface within the patient's field-of-view that exceeds the chart's background in luminance. Testing will be done by counting correct letters read on different eye charts for the two eyes and in a randomized testing order; reporting will be in both decimal and Snellen notations. The subject will be adequately masked by testing UDVA through a phoropter with a plano correction in the test eye and an occluder over the other eye. The subject will be instructed to close his/her eyes while the occluder is being switched from one eye to the other.

For near visual acuity measurements, ETDRS-style near visual acuity charts will be used at 40 cm distance, with chart background luminance, chart contrast, ambient illumination, other surface luminance, testing and reporting the same as for distance visual acuity measurements listed above.

### **Contrast Sensitivity**

Contrast sensitivity will be evaluated in a substudy at one clinical site according to the manufacturer's instructions using the Functional Vision Analyzer (StereoOptical; Chicago, IL). The Functional Vision Analyzer is a precision vision testing device that can be used as a clinical testing device or for research related to vision testing and clinical trials. The Functional Vision Analyzer's precision illumination is continually controlled by a microprocessor for accuracy and repeatability of the tests. The exclusive LED (Light Emitting Diode) system allows complete homogenous illumination that eliminates hot spots on testing slides, which can create inaccuracies of test results. This instrument is designed to do quick, accurate, reliable and confidential testing.

The instrument automatically monitors and calibrates the light level to 3.0 cd/m<sup>2</sup> for night or 85 cd/m<sup>2</sup> for day. It is equipped with the FACT™ sine-wave contrast sensitivity slide package. VSRC's patented Functional Acuity Contrast Test (FACT) Chart is an accurate and comprehensive sine-wave grating chart that tests functional visual acuity. Developed by Dr. Arthur Ginsburg, the FACT sine-wave grating chart tests five spatial frequencies (1.5, 3, 6, 12, and 18 cycles/degree) and nine levels of contrast. The luminance and gratings satisfy the ANSI IOL and laser standards for contrast sensitivity testing. The patient determines the last grating seen for each row (A, B, C, D and E) and reports the orientation of the grating: right, up or left. Results are recorded using EyeView Software or data collection sheets that are designed for use with the FACT charts.

*Contrast Sensitivity testing without Glare*

Dim the room lights to the level at which the test will be conducted. Do not turn on the contrast sensitivity testing apparatus until you are ready to perform the test. Only the study eye is required to undergo contrast sensitivity testing. If both eyes are tested, the suggested test order is to first test the right eye, the left eye, then both eyes. The order of testing should be consistent throughout the study. The recommended test strategy is as follows:

- If the patient has come in from bright light conditions, allow the subject to dark adapt by having them sit for at least five minutes in the room where contrast sensitivity testing will be performed.
- Complete photopic testing ( $85 \text{ cd/m}^2$ ) in the following order:
  - Photopic no glare (photopic  $85 \text{ cd/m}^2$ )
  - Photopic with high glare (Level 2)
- Allow the subject to dark adapt for approximately 5 minutes.
- Complete mesopic testing ( $3 \text{ cd/m}^2$ ) in the following order:
  - Mesopic no glare
  - Mesopic with low and high glare (Levels 1 and 2 for the first 10 patients; either Level 1 or Level 2 will be used for additional patients)

Always perform contrast sensitivity testing without glare prior to contrast sensitivity with glare testing.

All subjects are to be tested with best spectacle-corrected visual acuity preoperatively and at 1 and 6 months after the treatment. At each testing session, contrast sensitivity will be measured for five spatial frequencies: 1.5, 3, 6, 12, and 18 cycles/degree (cpd). The subject will be asked to perform the test monocularly with the other eye completely occluded and in a dimly illuminated room. The subject will be asked to identify the sine-wave gratings for each spatial frequency until he or she cannot recognize further patch gratings. The last patch grating that is observed will be recorded for each spatial frequency.

**Pupil Size (PS) measurement** – Mesopic pupil size measurement will be completed using a pupillometer (NeuroOptics, San Clemente, CA) operated under mesopic illumination conditions. The substudy will be completed with the same patient cohort that receives contrast sensitivity evaluation.

**Manifest refraction and cycloplegic refraction** will be obtained; one drop of 0.5% cyclopentolate HCl ophthalmic solution will be instilled into each eye for cycloplegia.

**Intraocular pressure (IOP)** will be measured with a Goldmann tonometer or equivalent.

**Slit-lamp biomicroscopy** will include a complete survey of the anterior segment, with detailed examination of the cornea and recording and grading of overall corneal clarity and any preoperative abnormalities. Post-Tx assessments will include the opacity (graded as absent, detectable, or moderately dense) of treated spots, together with the status of the corneal epithelium examined after instillation of sodium (Na) fluorescein and/or lissamine green B to visualize possible epithelial damage to cornea and/or conjunctiva.

**Pachymetry** measurements of central corneal thickness will be obtained using an ultrasonic pachymeter. Optionally, additional pachymetry measurements of pericentral

and peripheral corneal thickness will be obtained using an Orbscan II® system or equivalent.

**Keratometry** data will be obtained using Simulated Keratometry outputs from corneal topography - see below.

**Corneal topography** measurements will be obtained using Orbscan II®, EyeSys® or equivalent instruments.

**Aberrometry** measurements will be obtained using a LADARWave CustomCornea Wavefront System (Alcon Laboratories, Irvine, CA).

**Specular Microscopy (SM) assessment** – A noncontact specular microscope (CellCheck XL, Konan Medical USA, Torrance, CA) will be used in a substudy on 40. Test conditions include use of images with at least 100 countable (*i.e.*, not in shadow, washed out or blurred) cells grouped in a uniform area. Images will be obtained centrally and at two peripheral locations (12 and 6 o'clock at 3 mm from center). Automated image analysis will be used to measure endothelial cell density (ECD). Post-Tx *vs.* pre-Tx ECD will be used to calculate endothelial cell loss.

**Subjective questionnaires** will be obtained using the National Eye Institute Refractive Error Quality of Life questionnaire (see Appendix V).

All other examinations and test procedures will be conducted according to accepted ophthalmic examination standards.