

**Evaluation of two Riboflavin Dosing Regimens for Corneal  
Collagen Cross-Linking in Eyes with Progressive Keratoconus  
or Ectasia**

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PHYSICIAN SPONSOR: Francis W. Price, Jr. MD

CONFIDENTIAL

## Background

This clinical protocol is designed to evaluate two riboflavin-dosing regimens for treatment of patients with progressive keratoconus or corneal ectasia using investigational technology that increases the cross linking of the corneal stroma using the photochemical interaction of UVA light with the chromophore riboflavin.

In this treatment, the corneal stroma is saturated with riboflavin by irrigating the surface after removal of the corneal epithelium. The riboflavin-saturated cornea is then exposed to a uniform field of UVA light with a narrow bandwidth centered at 365 nm. The light is generated by an IROC UV-X irradiation system that creates a uniform 11 mm circle of UVA light. The device has a timer that allows a precise 30-minute exposure of the corneal tissues. The irradiation field of the UVX system produces UVA light with a uniform irradiance of 3 mj/cm<sup>2</sup> at the corneal surface.

The FDA has classified this technology as a combination product with two components. First is the UV-X light source, which has an LED source and is calibrated and rendered uniform by the use of an optical homogenizer. The second component is a riboflavin ophthalmic solution. This solution is used to saturate the corneal stroma prior to its photochemical activation.

This combination product has been studied in a FDA-approved, randomized, placebo-controlled, multi-center trial that has enrolled patients. Financial problems led to suspension of this trial (**IND 77882**). In addition, the system has been the subject of a prospective double blind study in Australia and the preliminary report on the first 66 randomized eyes indicated stabilization of the cornea after the treatment.<sup>1</sup>

Additional published literature has reported on extended clinical follow up of up to 6 years on 241 eyes.<sup>2</sup> These reports supply compelling evidence that this technology stabilizes the corneal structure, prevents further degradation of the corneal topography and improved visual function in some percentage of patients.

The clinical conditions to be treated in this protocol are characterized by a bulging or ectasia of the anterior corneal surface. The most common of these progressive conditions are keratoconus, post-LASIK ectasia, and pellucid marginal degeneration. Keratoconus and pellucid marginal degenerations are genetically based ocular conditions and post-surgical ectasia is an iatrogenic condition. All three of these syndromes are characterized by a weakening of the corneal stroma that produces progressive thinning and steepening of the central and inferior cornea. This distortion of the essential anterior optical element of the eye results in increasing steepening and unevenness of the optical surface. This produces a progressive myopia and progressive irregular astigmatism. The irregular astigmatism produces an attendant loss of vision when using spectacles. The next step in the management of these patients when spectacles are no longer effective is to use rigid contact lenses to create an artificial anterior corneal surface, a step that improves visual acuity in many patients. Eventually, contact lenses fail because they cannot be tolerated,

or the surface irregularity has become so severe that the contact lenses are rejected and fall off the eye. At this stage there is usually thinning and opacification within the cornea. The only treatment that has been shown to stabilize the cornea has been augmentation of the corneal strength by photochemically inducing cross linking. This technique has been studied over a ten-year period and is widely used throughout the world.

Together, keratoconus and post-refractive corneal ectasia are the second most frequent indication for corneal transplantation and accounted for 21% of the transplanted corneas supplied by the Eye Bank Association of America in 2008 (2008 Eye Banking Statistical Report, available at [www.restoresight.org](http://www.restoresight.org)). Corneal transplantation has inherent risks that could result in permanent loss of vision and significantly impact the patient's quality of life during the surgical recovery phase, with lost work time, and often permanent changes in lifestyle. Moreover, corneal transplantation permanently weakens the eye leading to a lifetime of increased risk of perforation from minor trauma and loss of the eye.<sup>3</sup> Some patients also require prolonged, even lifetime use of topical corticosteroids to prevent immunologic graft rejections. Long term topical corticosteroids can lead to increased intra-ocular pressure in at least a third of eyes and can lead to the need of glaucoma surgery to control intra-ocular pressure.<sup>4</sup> Filtration surgery, and to a lesser degree, the use of topical glaucoma medications appear to increase the risk of graft failure and immunologic graft reactions. African-Americans in particular, may be at increased risk of immunologic graft reactions based on the rejection rate encountered in a variation of corneal transplantation, Descemet's stripping and endothelial keratoplasty where just the endothelium and posterior stromal tissue are transplanted.<sup>5</sup> Clearly, any modality that can delay or prevent corneal transplantation in these patients is of great benefit. The evidence seems compelling that photochemically increased cross linking is the sole and unique treatment for these conditions.

Because this treatment is unique, many of our patients have been so desperate to mitigate their disease that a significant number of patients with progressive keratoconus and post-refractive ectasia have traveled to Europe or Canada to have this corneal collagen cross-linking procedure performed. They are subjectively aware that the disease has progressed and seek the treatment in an effort to avoid or delay corneal transplantation. This international treatment is not an entirely satisfactory solution to their problem. In addition there is a great expense involving travel, professional fees, increased risk, and the necessity to arrange follow by a local ophthalmologist.

Based on the available data, corneal collagen cross-linking offers the only alternative to the relentless progression of optical degradation that leads to vision loss and surgical corneal transplantation. The practice of having treatment overseas is not ideal. While the patient's immediate needs are met, their follow up is uneven and there is no attempt to capture the clinical data associated with their case.

We are experienced in the use of this technology, as we have been a part of the multi-center placebo-controlled trial. Furthermore, we are conducting an independent investigator-sponsored investigational plan for this technology that is being used to study the effect of this photochemical interaction on corneal infections (IND 104,456). Our

center is unique in that we perform approximately 1% of all corneal transplants in the United States, and many keratoconus patients are referred to our busy tertiary referral center for treatment.

## **Rationale**

Previous studies of corneal collagen cross-linking have employed riboflavin dosing regimens of 2 to 5 minutes. However, none have investigated whether the specific dosing regimen affects the efficacy or safety of the treatment. With each application, the riboflavin ophthalmic solution coats the corneal surface with a thick layer that absorbs much of the incident UVA light. With increasing length of time between subsequent doses, this layer thins from evaporation. This may affect the effective depth of the treatment. This study is a prospective randomized study to evaluate potential dosing effects.

## **Clinical Experience**

UVA/riboflavin corneal collagen cross-linking was first used clinically in 1998.<sup>6</sup> (Unless specified otherwise, the treatments referenced below all used UVA light (365-370 nm, 3 mw/cm<sup>2</sup>, 30 minutes) with photosensitizing riboflavin 0.1% (10 mg in 10 ml dextran-T-500 20% solution) applied after a central corneal abrasion, beginning at least 5 minutes before irradiation and continuing every 2-5 minutes during irradiation.)

Wollensak et al. treated 23 eyes of 22 patients to evaluate the effect of cross-linking on patients with moderate or advanced keratoconus. The mean preoperative maximum K-value (Kmax) was 50.93 D, and the mean preoperative progression of Kmax was 1.42 D ( $\pm 1.18$  D) in the before cross-linking. After cross-linking, there was a mean decrease in Kmax of 2.01 D ( $p=0.001$ ) with follow-up of 3 to 47 months (mean 23.2  $\pm 12.9$  months). In five of the untreated contralateral eye controls, the mean Kmax progressed an average of 1.48 D in the first year after cross-linking was performed in the contralateral eyes. Best spectacle corrected visual acuity (BSCVA) improved by an average of 1.26 lines ( $p=0.026$ ) and manifest refraction spherical equivalent (MRSE) improved by an average of 1.14 D ( $p=0.03$ ) in the treated eyes. No adverse events occurred. The postoperative healing process was unremarkable except for slight transient stromal edema during the first 3 postoperative days. Corneal and lens transparency, intraocular pressure (IOP), and endothelial cell density ( $p=0.45$ ) were unchanged after treatment compared to baseline.

Similarly, Caporossi et al. reported a 3.6 line increase in uncorrected visual acuity (UCVA), a 1.66 line improvement in BSCVA, a mean reduction in Kmax of 2.1 D ( $\pm 0.13$ ), and a 2.5 D reduction in MRSE at 3 months after cross-linking in a series of 10 eyes in 10 patients with progressive keratoconus.<sup>7</sup> There were no changes in endothelial cell density or IOP.

Patients treated in an ongoing clinical study at the University of Dresden (Dresden, Germany), have experienced outcomes similar to those reported by Wollensak. A preliminary analysis of the Dresden keratometry data shows a 1.25 D reduction in

maximum corneal curvature (K-max) in those eyes that have reached the 6-month evaluation timepoint. Progressively increasing corneal curvature is a hallmark of keratoconus and corneal ectasia. Based on the preliminary analysis of the Dresden data, corneal curvature progression is halted in this series of patients. The effect is significant through 5 years after the CCCL treatment and the trend continues to be observed as long as 7 years after cross-linking.

Table: Change in Maximum Corneal Curvature (K-Max) in Eyes treated with CCCL

Time	N	Baseline Mean K-Max (diopters)	Post-CCCL Mean K-Max (diopters)	Difference in K-Max (diopters)	K- Max Percent Difference (%)	K-Max Difference (p<0.05)	K-Max % Difference (p<0.05)
Baseline	365	53.6044				.	.
6 Months	196	53.9003	52.6523	-1.24801	-1.83121	0.001013	0.002256
1 Year	136	53.7790	52.3346	-1.44449	-2.35446	0.000025	0.000039
2 Years	60	54.0197	52.4340	-1.58567	-2.52731	0.001214	0.001250
4 Years	30	53.4627	50.7030	-2.75967	-4.58245	0.000396	0.000342
5 Years	13	52.2777	50.0723	-2.20538	-3.78418	0.020667	0.019656
6 Years	5	50.6400	48.1740	-2.46600	-4.81223	0.064549	0.067719
7 Years	4	52.3825	49.4500	-2.93250	-5.48322	0.057697	0.056259
8 Years	1	47.3400	47.1400	-0.20000	-0.42248	.	.

Kohlhaas presented results for 127 of these eyes at the 2005 Congress of the German-Language Society for Intrakularlinsen Implantation and Refractive Surgery with a follow-up of up to 60 months. Progression of keratoconus was stopped in all the eyes, and 81.7% of them showed a mean decrease of 2.87 D in Kmax. No opacification of the lens or change in endothelial cell density was seen in any patient. Long term follow-up results in a subset of 60 eyes in the Dresden Clinical Study that underwent cross-linking 3-5 years ago confirm the lasting effects of cross-linking in that there has been no progression of keratoconus in any of the eyes and 51.2% (31/60) of the eyes have a slight reversal and flattening of the Kmax. Kohlhaas et al. also reported a patient who developed bilateral keratectasia at 4 weeks after LASIK and underwent UVA/riboflavin cross-linking 6 months later. In this case, corneal topography remained stable for 18 months after cross-linking.

Sixty-six eyes in 49 patients have been enrolled in an Australian randomized study of observation-only control versus cross-linking in eyes with progressive keratoconus.<sup>1</sup> Maximum K-readings taken before and at 6 and 12 months after cross-linking showed a mean decrease of -0.92 diopters and -1.45 diopters in the treatment group (P=0.002).<sup>1</sup> In contrast, the untreated control eyes show a statistically significant increase of 0.60 D and 1.28 D in K-readings at 6 and 12 months after randomization.<sup>1</sup> The treatment group also showed an improvement in BSCVA, while BSCVA in the control group worsened.

Similar to the Dresden experience, these data lead to the conclusion that corneal cross-linking halts, and even reverses, the progression of keratoconus.

The only adverse event reported after epithelial healing was complete has been corneal edema in an eye with a pretreatment corneal thickness of approximately 300 microns, presumably caused by UV damage to the corneal endothelium. Subsequent experiments led to the conservative recommendation that corneas not be treated with UVA/riboflavin unless they are thicker than 375 microns after epithelial debridement. It has also been recommended that complete or partial epithelial removal be created prior to instillation of the riboflavin drops to promote penetration of the cornea by riboflavin and assure maximal absorption of UVA light in the anterior corneal stroma. The recommended epithelial debridement heals rapidly and is not affected by the cross-linking procedure.

To date, there have been no known reports of cataract formation as a result of UVA/riboflavin treatment. Most of the UVA light is absorbed within the first 300 microns of the cornea. By requiring 375-micron minimum corneal thickness, we stay well below the cytotoxic threshold for the corneal endothelium. A study by Jacob et al has shown that a riboflavin-soaked non-UV-blocking soft contact lens (approximately 100 microns thick) can be applied to the cornea when necessary to increase the minimum thickness.<sup>9</sup> Any UVA not absorbed in the cornea is absorbed as soon as it enters the anterior chamber, which is saturated with riboflavin, which has an absorption peak at the exact wavelength of UVA used. Therefore we do not anticipate any significant level of UVA light reaching the crystalline lens.

Using confocal microscopy, Mazotta et al. evaluated 10 patients treated with UVA/riboflavin for progressive keratoconus and found normal epithelial morphology and an absence of subepithelial stromal nerve fibers in the central irradiated area at 5 days after cross-linking. Nerve regeneration was observed at 1 month and nerve fiber recolonization was complete at 6 months with restoration of corneal sensitivity. No changes were observed in the peripheral untreated area at any time. Recently, Seiler et al. described a thin corneal stromal demarcation line that was detectable by slit lamp microscopy at a depth of approximately 300 microns 2 weeks after cross-linking in 14 of 16 eyes evaluated. This demarcation line is believed to be due to a difference in the refractive index or reflection properties of untreated and cross-linked corneal stroma. When epithelial thickness (approximately 50 microns) is taken into account, the 300 micron demarcation line observed by Seiler et al. is consistent with the studies and theoretical principles that the selected parameters for UVA/riboflavin treatment produce maximal cross-linking to a depth of about 200 microns and that 94% of the UVA light is absorbed in the anterior 300 microns of corneal stroma without injury to the endothelium.

The above data showing a flattening of the steepest corneal meridian is identical to the findings reported from the FDA approved American multi center trial as summarized in data shown at professional meetings.

## Risks

Riboflavin, also known as Vitamin B2, is a naturally occurring photosensitizer. It is the precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), two coenzymes that are crucial for the metabolism of carbohydrates, fats and proteins into energy. Riboflavin is an essential constituent of all living cells. It is water-soluble and only a trace amount is found in the human body. Riboflavin is non-toxic and it is used as a coloring agent in food and pharmaceuticals. The intake of riboflavin from food and diet supplements ranges from 4 to 10 mg a day. No adverse effects have been associated with high intakes of riboflavin from food or supplements.

Pharmacokinetic studies have shown that the maximal amount of riboflavin that is absorbed after a single oral dose is 27 mg, regardless of the amount in excess of this that is ingested. Excess riboflavin is excreted in urine and, since it is not a fat-soluble vitamin, is not stored in fat or other body tissues. No upper limit for riboflavin uptake has been established by the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences due to insufficient human and animal data. A risk assessment performed by the UK government has determined that a total intake of 43 mg is not expected to result in any adverse effects.

The standard concentration of riboflavin used in the riboflavin/UVA treatment is 0.1%. The maximum amount of riboflavin to which a patient is exposed during treatment is estimated to be  $\leq 1.6$  mg based on the volume of one drop being 0.05 ml and 1 drop being instilled every 2 minutes during the 30-minute pre-treatment, and every 2 or 5 minutes for 30 minutes during the UVA light irradiation. This amount is below the 43 mg “safe” limit by an order of magnitude.

The potential cytotoxicity of UVA light and the UVA/riboflavin exposure on keratocytes and endothelial cell function have been characterized in a series of *in vitro* experiments. In each of these experiments, UVA exposure (370 nm, 30 minutes) and riboflavin (0.025% solution; equivalent to the corneal concentration after diffusion of a 0.1% solution) were administered to mimic conditions of clinical usage. Irradiance levels were varied to determine the irradiance threshold for cytotoxic effects. Keratocyte toxicity was evaluated in porcine keratocyte cell cultures after exposure to riboflavin alone, UVA light alone (irradiance range 2 to 9  $\text{mw}/\text{cm}^2$ ), and UVA light plus riboflavin (irradiance range 0.4 to 1  $\text{mw}/\text{cm}^2$ ). Riboflavin alone had no cytotoxic effect on keratocytes. The cytotoxic threshold for inducing cellular necrosis or apoptosis was 5  $\text{mw}/\text{cm}^2$  for UVA light alone and 0.5  $\text{mw}/\text{cm}^2$  for the UVA/riboflavin treatment. Using the Lambert-Beer equation, in human corneas the cytotoxic keratocyte UVA irradiance of 0.5  $\text{mw}/\text{cm}^2$  is reached at a stromal depth of 300 microns. The potential for endothelial cell toxicity was evaluated on endothelial cell cultures obtained from porcine cornea that were exposed to riboflavin alone and to various UVA irradiances (range 0.1 to 1.6  $\text{mw}/\text{cm}^2$ ) with and without riboflavin. An abrupt cytotoxic threshold was observed at an irradiance of 4  $\text{mw}/\text{cm}^2$  for UVA light alone and was ten-fold lower with an irradiance threshold of 0.35  $\text{mw}/\text{cm}^2$  for the UVA/riboflavin treatment. No endothelial cell damage was observed in the cells treated with riboflavin alone. Endothelial cell damage in the UVA groups is believed to

be due to oxidative damage caused by the oxygen reactive free radicals (singlet oxygen, superoxide anion, hydrogen peroxide) that are generated by the UV light.

The lower cytotoxic thresholds observed for the UVA/riboflavin combination in the keratocyte and endothelial cell toxicity studies are consistent with the increase in UVA absorption in the presence of riboflavin. For example, 94% of incident UVA light is absorbed in the anterior 400 microns of the corneal stroma in the presence of riboflavin, as depicted in the graph at the right, whereas only 32% is absorbed within that depth in the absence of riboflavin.

## UV-X™ Illumination System

The UV-X™ Illumination System is a portable electronic medical device. The device's light emitting diode (LED) is used to deliver a metered dose of UV-A light to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Components of the UV-X™ System include the LED light source, UV light detector, UV detector sensor probe and adapter, wall power supply with DC cord, transportation case, safety goggles (to be worn by user), mechanical stand (C-clamp, cross clamp, rods), and an instruction manual. System specifications are as follows:

Light Source	High Power UV-grade LED; LED Laser class 3R (EN 60825-1) (Mfg. Nichia Co. LTD; Tokyo, Japan)
Wavelength	365 nm ( $\pm$ 10 nm)
Optical Power	Maximum 10 mw
Beam Diameter	7.5 mm to 11.5 mm
Light Emission	Continuous wave
Intensity Setting	3.0 mw/cm <sup>2</sup> ( $\pm$ 0.3 mw/cm <sup>2</sup> )
Safety Class	Class II Equipment (EN 60601-1)
Medical Device Class	Class Ima according to MDD 93/42/EEC
EMI/EMC Class	Class B (EN 60601-1)
Power Supply	SELV (Safety Extra Low Voltage) 9V; max. 1.7A

The **Light Source** houses the UVA irradiation mechanism. The LED is preset by the manufacturer to emit UVA radiation at a wavelength of 365 nm at an intensity of 3 mw/cm<sup>2</sup> ( $\pm$ 0.3 mw/cm<sup>2</sup>). UVA light emission is controlled by an internal microprocessor, which controls the electrical current used to drive the UV-LED. No UV light will be emitted in case of processor or LED failure. The diameter of the Light Source beam aperture is 25 mm and the treatment plane is 50 mm from the beam aperture. An aperture wheel mounted in the UVA irradiation beam path is used to produce a circular area of irradiation at the treatment plane with an approximate diameter of 7.5 mm, 9.5 mm or 11.5 mm, which is controlled by selecting the corresponding aperture wheel setting on the device. An intensity of 3 mw/cm<sup>2</sup> and irradiance time of 30 minutes results in a standard surface dose of 5.4 J/cm<sup>2</sup> surface exposure. The Light Source has an integrated timer that automatically shuts off the light emission after 30 minutes of exposure. A **Power Supply** plugged into a main electrical wall outlet and into the Light Source via the DC cord powers the Light Source. The On/Off switch (On =

ready mode) powers the device; the Start/Stop button controls UVA emission; and, status display lights (Red- Internal error, yellow-UV emission, Green-Device is powered, but no UV emission) indicate the status of the UV-X™ device. A battery operated ***UV Light detector***, with a built-in low battery warning, is used to check the UV light irradiation in the treatment plane before patient treatment. The UV Light detector consists of a ***Sensor Probe and an indicator***. The ***Sensor Probe Adapter*** with a Sensor Probe is permanently mounted to the UV-light illumination system to shield the beam aperture and should only be removed for treatment.

## **Riboflavin Ophthalmic Solution**

The riboflavin ophthalmic solution is covered under IND (redacted).

## **Objectives**

The primary objective of this study is to evaluate two riboflavin-dosing regimens for corneal collagen cross-linking to slow the progressive changes in corneal curvature in eyes with progressive keratoconus or post refractive ectasia.

## **Efficacy and Safety**

The primary efficacy outcome measure is change in corneal curvature, as measured by maximum keratometry (Kmax). Secondary efficacy measurements will include: pachymetry, corrected distance acuity (CDA), and manifest refraction. Safety assessments will mean reporting any adverse events. All subjects will be evaluated at baseline, Day 1, Week 1 and 3 and 6 months after treatment with vision and intraocular pressure assessed at each visit.

Ophthalmic medical records after subjects exit the study will be retrospectively reviewed to assess visual changes and incidence of any subsequent ocular interventions.

## **Patient Population**

Six hundred patients will be enrolled in the study.

### **Inclusion Criteria:**

Subjects who have one or both eyes that meet all of the following criteria will be considered candidates for this treatment:

1. 10 years of age or older
2. Having documented ectasia on topography or tomography after previous refractive surgery OR documented keratoconus on topography or tomography. Subjects > 32 years old who have not had prior refractive surgery must have a diagnosis of progressive keratoconus defined as one or more of the following changes over a period of 36 months or less before randomization:

- a. An increase of  $\geq 1.00$  D in the steepest keratometry value (or sim K)
  - b. An increase of  $\geq 1.00$  D in regular astigmatism evaluated by subjective manifest refraction
  - c. A myopic shift (decrease in the spherical equivalent) of  $\geq 0.50$  D on subjective manifest refraction
  - d. Documented decrease in visual acuity associated with irregular astigmatism and topographic features of ectasia.
3. Subjects with keratoconus diagnosis only:
- a. Axial topography consistent with keratoconus
  - b. Presence of central or inferior steepening on the Pentacam map.
  - c. Presence of one or more slit lamp findings associated with keratoconus, such as:
    - i. Fleischer ring
    - ii. Vogt striae
    - iii. Corneal thinning
    - iv. Corneal scarring
4. Contact Lens Wearers Only: Removal of contact lenses for the required period of time prior to the screening refraction:
- | <b>Contact Lens Type</b> | <b>Minimum Discontinuation Time</b> |
|--------------------------|-------------------------------------|
| Soft                     | 3 Days                              |
| Soft Extended Wear       | 1 Week                              |
| Soft Toric               | 2 Weeks                             |
| Rigid gas permeable      | 2 Weeks                             |
5. Signed written informed consent

**Exclusion Criteria:**

All subjects meeting any of the following criteria will be excluded from this treatment:

- 1. Any keratoconus patient over the age of 32 years without evidence of progression of the corneal deformity within the past 36 months.
- 2. Patients with excessively thin corneas based off of Pentacam map and Optical coherence tomography images.
- 3. Previous ocular condition in the eyes to be treated that may predispose the eye for future complications, for example:
  - a. History of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.)
  - b. Clinically significant corneal scarring in the proposed treatment zone
- 4. A history of chemical injury or delayed epithelial healing in the eye(s) to be treated.
- 5. A known sensitivity to treatment medications.
- 6. Patients with a current condition that, in the treating physician's opinion, would interfere with or prolong epithelial healing.
- 7. Pregnancy (including plan to become pregnant) or lactation during the course of the study

**Vulnerable Populations:**

### Non-English Speaking

This study plans to exclude any person who does not speak English as this is an unfunded study and there are no available funds to provide for a translator at each study visit or to translate the consent form in the patient's native language.

### Minors:

If a person not of age of legal consent (18), but who is at least 10 years of age meets all inclusion/exclusion criteria for the study, parents will be given a copy of the consent form and will be given time to read it, ask any questions of the investigator and staff, and explain it to the underage subject. The parent will then determine whether the subject voluntarily decides to participate in the research. The minor will sign the consent with the parent providing assent.

### Decisionally Impaired:

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 answer all questions satisfactorily will be permitted to provide informed consent. If the enrolling physician or designated staff member determines that a potential subject is not competent to provide a research informed consent, it will be determined whether or not the subject has a Legally Authorized Representative (LAR). If the subject does not have a LAR, they will not be permitted to enter the study. If the potential subject has a LAR, both the subject and LAR will be given a copy of the consent form and will be given time to read it and ask any questions of the investigator and staff. The LAR will then be given time to explain it to the subject. The subject will sign the consent with the LAR providing assent.

### Pregnant Women:

Pregnant women will not be enrolled into this study because hormonal changes during pregnancy can sometimes temporarily alter the shape of the cornea.

### **Examination Schedule:**

The patients will be followed to 6 months. The following examination schedule will be followed:

- Preoperative (-60 to day 0; any routine exam procedures that we performed within 60 days of study enrollment do not have to be repeated at the screening visit)
- Operative (Day 0)
- Day 1 (1-3 days)
- Week 1 or duration to healing of epithelium
- Month 3 (7 to 16 weeks)
- Month 6 (16 to 40 weeks)

### **Screening Eye Examination:**

Potential candidates will undergo a complete eye examination to determine their eligibility for treatment. A complete ocular history, medical history and medication history will be obtained. The complete eye examination and ocular history will include:

- History of contact lens wear

- Family history of keratoconus
- History of eye rubbing
- History of refractive surgery
- UCVA (distance)
- BSCVA (distance)
- Manifest refraction
- Pentacam analysis
- Optical coherence tomography (OCT)
- Corneal topography
- Intraocular pressure (by Goldmann applanation tonometry)
- Slit lamp examination of the cornea, anterior chamber and lens
- Dilated fundus examination

### **Randomization**

Subjects will be classified as having keratoconus, post-refractive ectasia, or pellucid marginal degeneration. In addition those with keratoconus will be classified as mild (flat keratometry reading < 51.00D), moderate (flat keratometry reading of 51.25 to 56D or astigmatism  $\geq$  8D), or severe (flat keratometry reading >56D). Block randomization will be employed to ensure representation of each classification in both treatment groups. If a subject has both eyes affected by the condition, the first eye treated will be randomized and the fellow eye will not. Fellow eyes will not be included in the efficacy analysis and will be dosed at 5 minute intervals during irradiation.

### **Subjects who elect to be treated will undergo the following procedure:**

#### **Treatment:**

Subjects will be prepared for treatment in accordance with the instructions for use in the UV-X™ Illumination System Operator's Manual, including the administration of the riboflavin and preoperative medications (e.g. topical anesthetics).

Prior to the treatment, the presence of an informed consent for it will be confirmed. Patients will receive a therapeutic contact lens after the treatment is complete. An operative report or chart note will be placed in the subject's medical records documenting the procedures used for each patient. Selected treatment information, including the riboflavin administration, irradiance settings, and duration of irradiation exposure will be documented.

The subject will lie on a surgical table or chair with the head supported in a headrest. The bed will be adjusted so the subject can lie flat or recline comfortably for the duration of the procedure without moving. The skin around the eye and the conjunctival surfaces will receive a surgical cleansing. Topical anesthesia will be applied and a lid speculum will be placed between the lids of the eye to be treated. The surgeon will remove the epithelium from a circular area approximately 6 mm in diameter centered on the maximum of the posterior float on the corneal tomography assessment performed at the screening visit. Additional local anesthetics will be applied as needed.

After the epithelium has been removed, Riboflavin ophthalmic solution will be instilled topically to the stromal surface every 2 minutes for 30 minutes. The corneal thickness will be measured and if the minimum thickness is at least 375 microns the irradiation will be started. If the minimum thickness is between 275 and 375 microns, balanced salt solution may be applied to swell the cornea or a riboflavin-soaked non-UV-blocking soft contact lens (approximately 100 microns in thickness) may be applied to increase the minimum thickness to at least 375 microns before starting the irradiation.

During irradiation, instillation of riboflavin will be continued every 2 minutes or every 5 minutes, depending on the group to which the patient was randomized.

Prior to use, the UV-X™ illumination system will be assembled and tested according to the manufacturer's instructions. The UV irradiance dose is the product of the irradiance intensity and the exposure time. The intensity is a fixed parameter of the device. It is checked during the light test and cannot be changed by the user.

The eye will be aligned under the UV-X™ light with the treatment plane at a working distance that is 50 mm from the UV-X™ beam aperture. The correct aperture setting will be selected for the size of the eye (7.5, 9.5, or 11 mm), and the eye will be irradiated for 30 minutes, during which time instillation of riboflavin will continue (1 drop every 2 minutes or every 5 minutes, depending upon the randomization). At the end of 30 minutes, the UV light source will automatically switch to the off position. The operator will keep track of irradiation time independently to confirm the actual treatment time.

The eye will be examined at a slit lamp, a drop of antibiotic and a bandage contact lens will be placed. The lens will be removed after the epithelial defect has closed.

### **Postoperative Care**

Prescriptions for postoperative medications and written postoperative instructions will be given to each subject and reviewed prior to discharge. The following postoperative eye drops will be prescribed:

1. antibiotic drops gtt 1 qid until; 24 hours after epithelialization is complete.
2. Prednisolone 1% ophthalmic suspension (PredForte® or generic equivalent) 1 drop qid X 2 weeks
3. Preservative-free artificial tears for dryness

All postoperative eye drop usage will be recorded in the subject's chart. Other prescription or nonprescription medications may be taken as needed throughout the treatment.

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

A treatment flow chart summarizing the follow-up examination schedule and required procedures to be performed at each treatment visit is provided in Appendix A. All subjects will be seen at 1 day, 1 week, 3, and 6 months. If a study participant is unable to return to the study site for the 1-week exam, they may see a local doctor and efforts will be made to obtain copies of this exam.

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

- UCVA distance
- BSCVA distance (omit on Day 1 and Week 1)
- Manifest refraction (omit on Day 1 and Week 1)
- Pentacam measurements (omit on Day 1 and Week 1) , including
  - Pachymetry
  - Scheimpflug photography
- Corneal topography (omit on Day 1 and Week 1)
- Intraocular pressure (by Goldmann applanation tonometry (omit on Day 1)
- Slit lamp examination of the cornea, anterior chamber and lens
- Optical coherence tomography (OCT, omit on Day 1)

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

### **Retreatment**

Any subject who is at least 1-year post- cross-linking treatment and who shows signs of progression at two visits will be considered for retreatment. Retreated eyes will not be included in the efficacy analysis and will be dosed at 5 minute intervals during irradiation.

### **Fellow Eyes**

Patients who, at the discretion of the investigator, could benefit from the study treatment in both eyes may have both eyes treated; however, only the first treated eye per patient will be considered for the efficacy analysis. All treated eyes will be included in the safety analysis. Fellow eyes can be treated on the same or a different day as the randomized eye; this decision will be made by the patient and the principal investigator.

### **Safety Monitoring**

During the CXL treatment procedure, subjects will be observed closely to detect the occurrence of any adverse events or complications. On the day of treatment and at each follow-up visit, the subjects will be questioned to determine whether any adverse events might have occurred since the last examination. 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, measurements of refraction, and measurement of visual acuity. In the case of an adverse event or complication, the frequency of the examinations will be increased until the problem is resolved. Any complications or visual adverse events will be recorded in the medical record and reported to the FDA.

### **UV-X and Riboflavin Accountability**

All use of the UV-X™ Illumination System and Riboflavin Ophthalmic Solution will be under the direct supervision of the designated study coordinator. The use of the Riboflavin solution will be maintained in a clinical treatment program log.

## **Data Analysis**

Statistical analyses will be performed using SAS<sup>®</sup> software. All enrolled subjects will be included in the safety analysis. Testing will be 2-sided and P-values < 0.05 will be considered significant. To preclude confounding effects between fellow eyes, only the first treated eye per subject will be included in the efficacy analysis.

## **Ethical and Regulatory Considerations**

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

### **Informed Consent**

In accordance with the provision of 21 CFR Part 50, each subject will provide written informed consent for participation in this treatment prior to the use of the investigational device. The treatment will be explained to the patients, or guardian, by the surgeon. The alternatives to this treatment will be discussed together with the potential hazards of the proposed treatment. The potential patients will be informed that they are free to not treat their condition or to obtain treatment outside the United States. We will emphasize the fact that this treatment has not been approved by the FDA, and just because their disease has progressed in the past does not mean that it will continue to progress.

### **Institutional Review Board**

This proposal and the informed consent form will be approved initially and reviewed annually by the Institutional Review Board.

### **Adverse Events**

For all adverse events, a description of the event, date first observed, action taken, and its resolution will be reported.

### **Non-serious or Anticipated Drug or Device Adverse Events**

Non-serious or anticipated drug or device adverse events and complications will be documented on the case report forms and tabulated for reporting in the annual reports to FDA.

### **Serious and Unanticipated Adverse Device Effects**

Any adverse experience associated with the use of the drug that is both serious and unexpected shall be reported to the FDA and IRB. 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 drug or 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 drug or device that relates to the rights, safety or welfare of subjects." Since CDER has primary jurisdiction for the regulation of this combination product, serious and unanticipated

adverse device effects will be reported to FDA and the IRB in accordance with the reporting requirements described above.

## References

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**Table 1. Procedure schedule**

	Screening	Treatment	Day 1	Week 1	Month 3	Month 6
Informed Consent	x					
Inclusion/Exclusion	x					
Medical & Ophthalmic History	x					
Urine pregnancy testing (females of child-bearing age)	x					x
Adverse Events	x	x	x	x	x	x
Uncorrected distance acuity	x		x	x	x	x
Manifest refraction	x				x	x
Corrected distance acuity	x				x	x
Corneal tomography (Pentacam)	x				x	x
Corneal topography	x				x	x
Intraocular pressure	x			x	x	x
Slit lamp examination of cornea, anterior chamber and lens	x		x	x	x	x
Dilated fundus exam	x					x