Safety and Effectiveness of the PXL-Platinum 330 System for Corneal Collagen Cross-Linking in Eyes with Corneal Thinning Conditions

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1.0 BACKGROUND

This study is being conducted to evaluate the safety and effectiveness of using the PXL Platinum 330 system for performing corneal collagen cross-linking (CXL) for the treatment of corneal thinning disorders. The PXL Platinum 330 system is a combination product consisting of a UVA 365 nm wavelength light source (PXL Platinum 330 Illumination System) and riboflavin (Peschke-TE 0.25% ophthalmic solution or Peschke-L 0.23% ophthalmic solution) administered in conjunction with the UVA light as a photosensitizer.

The PXL Platinum 330 treatment is intended to induce corneal collagen cross-linking to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma. Corneal collagen cross-linking is performed by pretreating the cornea with riboflavin 0.1% ophthalmic solution beginning 30 minutes before UVA light exposure to saturate the corneal tissue with the riboflavin photosensitizer. The cornea is then irradiated with UVA light (365 nm) at an irradiance of 3 mW/cm^2 for 30 minutes. Exposure of the cornea to this combination of UVA light (365 nm; 3 mW/cm^2 irradiation; 30 minutes duration) after topical administration of riboflavin has been shown to induce cross-linking of the corneal collagen fibrils with a resultant increase in tensile strength and diameter of the collagen fibrils. Clinically, cross-linking has been shown to stabilize the corneal curvature in eyes with progressive keratoconus with no significant change in the refractive index of the cornea.

1.1 Rationale

Clinical applications of corneal collagen cross-linking include treatment or prophylaxis of conditions distinguished by corneal thinning, such as post-LASIK/PRK/SMILE/INTACS ectasia, keratoconus, pellucid marginal degeneration, bacterial and fungal keratitis.

Keratoconus is a naturally occurring ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in increasing myopia, irregular astigmatism, and eventual loss of best spectacle-corrected visual acuity. Rigid contact lenses can be used to improve visual acuity in many patients, but keratoconus frequently progresses to the point that corneal transplantation is required to restore useful vision. Keratoconus may recur following corneal transplantation and require further transplant surgery.

Together, keratoconus and post-refractive corneal ectasia are the second most frequent indication for corneal transplantation, accounting for about 15% of the corneal transplants performed in the United States. 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. Any modality, such as corneal collagen cross-linking, that can delay or prevent corneal transplantation in patients with these conditions is of great benefit.

Corneal collagen cross-linking using UVA light with riboflavin photosensitizer to strengthen corneal tissue was recently approved in April 2016 with the Avedro KXL

system for slowing or stopping the progression of keratoconus and post-refractive surgery ectasia. However, patients with other corneal thinning disorders (pellucid marginal degeneration, immune-related corneal melts, bacterial or fungal keratitis, non-progressive keratoconus) were not included in the approved indication. Further, the Avedro KXL system is a significant burden on patients and clinics due to requirement for epithelial scraping (which increases pain, infection risk, and scarring risk), time necessary to perform the procedure, expense, and lack of reimbursement. Lastly, the approved system does not offer 30 mW energy (which lowers time required for the procedure) or pulsed wave light delivery, which seems to improve outcomes after crosslinking in keratoconus due to improve oxygen availability. [1,2,3]

1.2 Prior Experience

1.2.1 Preclinical Studies

Preclinical investigations have been performed to: (1) determine the optimal photosensitizing agent/dosage and irradiance/exposure time for cross-linking; (2) characterize the biomechanical and biochemical effects of cross-linking on corneal collagen tissue using rabbit, porcine, and human corneal tissue models; and, (3) determine toxicity to keratocytes and endothelial cells (see Section 2.9).

1.2.2 Clinical Experience

1.2.2.1 Conventional Crosslinking with Dresden Protocol

UVA/riboflavin corneal collagen cross-linking was first used clinically in 1998. (Unless specified otherwise, the treatments referenced below in this subsection all used UVA light (365 nm, 3 mW/cm^2, 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 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. [4] The mean preoperative maximum K-value (Kmax) was 50.93 D, and the mean preoperative progression of Kmax was 1.42 D (±1.18 D) in the 6 months 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 ±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,

[1] (Moramarco, Iovieno, Sartori, & Fontana, 2015)
[2] (Mazzotta, Traversi, Caragiuli, & Rechichi, 2014)
[3] (Mazzotta, Traversi, Paradiso, Latronico, & Rechichi, 2014)
[4] (Wollensak, Spoerl, & Seiler, 2003)

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 (±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. There were no changes in endothelial cell density or IOP. [5]

Patients treated in an ongoing clinical study at the University of Dresden (Dresden, Germany), have experienced outcomes similar to those reported by Wollensak. [6] 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 CXL treatment and the trend continues to be observed as long as 7 years after cross-linking.

Table 9.2.1-1: Change in Maximum Corneal Curvature (K-Max) in Eyes treated with CXL

Time	N	Baseline Mean K-Max (diopters)	Post-CXL 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 Refraktive Surgery with a

[5] (Caporossi, Baiocchi, Mazzotta, Traversi, & Caporossi, 2006)
[6] ("Data on File. IROC/University of Dresden," 2006)

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. [7] 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. [8] In this case, corneal topography remained stable for 18 months after cross-linking.

Fifty eyes in 36 patients have been enrolled in an Australian randomized study of observation-only control versus cross-linking in eyes with progressive keratoconus. [9]Maximum K-readings taken before and at 3 and 6 months after cross-linking showed a mean decrease of -1.10 diopters and -1.39 diopters in the treatment group. In contrast, the untreated control eyes show a statistically significant increase 0.70 D and 0.78 D increase in K-readings at 3 and 6 months after randomization. The treatment group also showed a mean 2.2-line improvement in BSCVA at three and six months, 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.

More recent studies confirm long-term improvement in eyes treated with crosslinking, including 10 year follow-up study as well as a crossover study, and 3 trials in pediatric populations. [10,11,12,13,14,15,16,17,18,19,20]

With respect to the use of the Dresden protocol with the Peschke system, the relevant papers include:

- **Corneal Cross-Linking and Safety Issues**

Open Ophthalmol J. 2011; 5: 14-16. Eberhard S Et al.
The authors analyzed the current treatment protocol regarding safety during CXL with the riboflavin/UVA (370 nm) approach. When the corneal stroma thickness is at least 400 microns, a homogenous irradiance of UV light of 3mW/cm2 for 30min at 370 nm with

[7] (Wollensak, 2006)
[8] (Kohlhaas et al., 2005)
[9] (Snibson, 2007)
[10] (Raiskup, Theuring, Pillunat, & Spoerl, 2015)
[11] (Kumar Kodavoor, Arsiwala, & Ramamurthy, 2014)
[12] (P. Vinciguerra, Albe, Frueh, Trazza, & Epstein, 2012)
[13] (R. Vinciguerra et al., 2013)
[14] (Mazzotta, Balestrazzi, Baiocchi, Traversi, & Caporossi, 2007)
[15] (Zamora & Males, 2009)
[16] (P. Vinciguerra et al., 2009)
[17] (Caporossi, Mazzotta, Baiocchi, & Caporossi, 2010)
[18] (Chatzis & Hafezi, 2012)
[19] (Zotta et al., 2012)
[20] (El Rami et al., 2015)

the application of 0.1% riboflavin didn't damage either corneal endothelium or deeper structures such as lens and retina.

- **Prospective, randomized, double-blind trial to investigate the efficacy and safety of corneal cross-linking to halt the progression of keratoconus.**

BMC Ophthalmology 2015; 15:78. Stefan Lang Et al.
The efficacy and safety of corneal cross-linking were investigated in a randomized, blinded, placebo controlled, multicentre trial. 15 eyes were randomized to the treatment troup (corneal epithelial removal, 0.1% riboflavin, UVA 370 nm at 3mW/cm2 for 30 min) and 14 to the control group (no epithelial removal, fluorescein drops, visible blue light for 30 min). Follow-up averaged 1098 days. The treatment group showed a decrease in corneal refractive power (on average 0.35 dioptres/year) while the controls showed an increase of 0.11 dioptres/year. However, some of the treated patients still progressed, whereas some controls improved. The change in visual acuity did not show a statistically significant difference between the two groups.

1.2.2.2 Accelerated or Pulsed Crosslinking

Pulsed crosslinking seems to be able to enhance functional and structural outcomes due to improved oxygen bioavailability during the crosslinking reaction. [21,22,23] The stromal demarcation line (commonly accepted as a marker of depth of biomechanical strengthening) was deeper with pulsed crosslinking in 2 studies (Moramarco et al. JRS 2015 and Mazzotta et al. Eye 2014). Mazzotta et al.'s 1 year results (J Ophthalmol 2014) show that pulsed crosslinking achieved a 1.2 diopter reduction in corneal keratometry, whereas continuous light crosslinking only resulted in a 0.13 diopter reduction.

With respect to the use of the accelerated or pulsed crosslinking using the Peschke system, the relevant studies include:

- **Accelerated (18mW/cm2) Corneal Collagen Cross-Linking for Progressive Keratoconus.**

Cornea. 2015 Nov;34(11):1427-31. Alnawaiseh M Et al.
The charts and anterior segment data of 20 patients (28 eyes) who were treated with accelerated corneal collagen cross-linking (18 mW/cm2; 5 minutes) were reviewed. The mean follow-up time was 21.7 months. It found a significant reduction (improvement) of Kmax (the steepest radius of curvature of the anterior corneal surface) and stabilization of corrected distance visual acuity (CDVA) with no reported complications.

- **Accelerated (9-mW/cm2) corneal collagen crosslinking for keratoconus-A 1-year follow-up.**

Cornea. 2014 Aug;33(8):769-73. Elbaz U Et al.

[21] (Moramarco et al., 2015)
[22] (Mazzotta, Traversi, Caragiuli, et al., 2014)
[23] (Mazzotta, Traversi, Paradiso, et al., 2014)

16 mild-moderate keratoconus-affected eyes (14 patients) underwent an accelerated crosslinking (irradiance of 9 mW/cm2; 10 minutes). At either 6 or 12 month follow-up, no statistically significant changes were found in the mean CDVA, mean refractive cylinder, or mean manifest refraction spherical equivalent. There was an improvement in the uncorrected distance visual acuity (UDVA); a gain of 0.13 logarithm of the minimum angle of resolution lines in the mean UDVA (P = 0.012). Ksteep, Kflat, average K (Km), corneal astigmatism (Kcyl), and maximal curvature reading at the corneal apex (Kmax) were stable.

- **Safety of high-intensity corneal collagen crosslinking**

J Cataract Refract Surg. 2014 Aug;40(8):1337-40. George Kymionis Et al.
10 eyes (9 patients) were treated underwent corneal cross-linking with 9mW/cm2 irradiance for 10 minutes. 3 months after procedure, endothelial cell density (ECD) did not change and CDVA improved but the improvement wasn't statistically significant. No eye lost lines of CDVA. The mean steep K readings decreased significantly.

- **One-year outcomes of conventional and accelerated collagen crosslinking in progressive keratoconus.**

Sci Rep. 2015 Sep 25;5:14425. Vanissa Chow Et al.
19 eyes each group underwent conventional (3 mW/cm2, 365-nm UVA, 30 minutes) or accelerated (18 mW/cm2, 365-nm UVA, 5 minutes) collagen crosslinking. One year postoperatively, there were no inter-group differences in keratometry, UCVA, and best corrected visual acuity (BCVA).

- **Evaluation of Corneal Stromal Demarcation Line Depth Following Standard and a Modified-Accelerated Collagen Cross-linking Protocol.**

Am J Ophthalmol. 2014 Oct;158(4):671-675. George Kymionis Et al.
26 eyes were treated for 30 minutes with 3 mW/cm2 UVA, while 26 eyes were treated for 14 minutes with 9 mW/cm2 UVA. One month postoperatively, corneal stromal demarcation line depth was assessed using AS-OCT with no significant difference between the two groups.

- **Safety profile of accelerated corneal cross-linking versus conventional cross-linking: a comparative study on ex vivo-cultured limbal epithelial cells.**

Br J Ophthalmol. 2015 Feb;99(2):272-80. Rohit Shetty Et al.
Day 14 cultured limbal epithelial cells (LECs) were either unexposed (control) or exposed to different intensities of UVA irradiance for different durations (3 mW for 30 min, 9 mW for 10 min, 18 mW for 5 min and 30 mW for 3 min) in the presence and absence of riboflavin. When the apoptotic status was evaluated through quantitative real-time PCR, vital staining, immunofluorescence staining and fluorescence-activated cell sorting, it was shownd that the 30 mW UVA irradiation used in accelerated corneal cross-linking appears to be safe on cultured LECs in comparison with 3 mW used in corneal cross-linking.

- **Corneal stroma demarcation line after standard and high-intensity collagen crosslinking determined with anterior segment optical coherence tomography.**

J Cataract Refract Surg. 2014 May;40(5):736-40. George Kymionis Et al.
9 eyes were treated for 30 minutes with 3 mW/cm2 UVA and 12 eyes were treated for 10 minutes with 9 mW/cm2 of UVA. One month after procedure, the corneal stroma demarcation line was significantly deeper after a 30-minute 3 mW/cm2 UVA treatment than after a 10-minute 9 mW/cm2 of UVA irradiation.

1.2.2.3. Transepithelial cross-linking: published literature
Use of epithelial-on, or transepithelial, cross-linking is emerging as an alternative for treatment of keratoconus and other corneal thinning disorders. This approach avoids the risks of epithelial debridement, including infection, haze, pain, and scarring. Published studies of transepithelial cross-linking with the Peschke system include:

- **Efficacy and safety of transepithelial corneal collagen crosslinking vs. standard corneal collagen crosslinking for keratoconus: a meta-analysis**
  BMC Ophthalmology 2017; 17: 262. Li W & Wang B.
  In a meta-analysis of trials evaluating standard vs. trans-epithelial CXL, the trans-epithelial CXL group gained more improvement in corrected distance visual acuity
- **Transepithelial corneal crosslinking in treatment of progressive keratoconus**
  Pak J Med Sci. 2017; 33: 570-5. Akbar B et al.
  In a series of 26 eyes of 26 patients, Kmax was reduced over 1 year, and no intra- or post-operative complications were noted.
- **Epi-off vs. transepithelial corneal collagen crosslinking for progressive corneal ectasia.**
  BJO 2017; 101: 503-8. Rush S & Rush R
  In a randomized control trial of 131 eyes followed over 2 years, there was no statistically significant difference in best spectacle corrected visual acuity between the 2 groups. There were 3 adverse events in the epi-off group, but none in the transepithelial group
- **Transepithelial accelerated vs. conventional crosslinking in patients with keratoconus.**
  Clin Ophthalmol 2019; 13: 445-52. Madeira C et al.
  In a study of 16 eyes with transepithelial vs. 10 eyes of conventional crosslinking, there were no significant differences in efficacy
- **Comparision of transepithelial vs. epi-off CXL in progressive keratoconus.**
  Taiwan J Ophthalmol 2017; 7: 185-90. Akbar B et al.
  In a comparison of 32 eyes each undergoing transepithelial vs. epi-off CXL, there were no differences in visual acuity outcomes between the 2 groups. In epi-off CXL, there were 3 eyes with stromal haze which required long-term steroid use, but there were no adverse events in the transepithelial CXL group

1.2.2.4. Our experience with transepithelial, pulsed, accelerated CXL

We initiated a single-site study at our practice in 2017 after approval of the Peace Health IRB. 15 patients consented to the study; 2 were screen failures, and 1 has not yet undergone treatment. Of the 12 patients who underwent crosslinking, none experienced any adverse events (e.g., haze, epithelial sloughing, infection, melt, or scarring). 16 eyes of 10 patients have had data collected out to 1 year. Average demarcation line observed has been 243 microns. Mean keratometry declined by 1.35 D in the CXL-only group and 2.24 D in the Intacs + CXL group. Patients undergoing concurrent CXL + Intacs have experienced 5 letter improvement in ETDRS BCVA, while patients undergoing CXL alone have had stabilization in BCVA.

1.2.2.5. Using corneal cross-linking to treat Infectious keratitis

Corneal cross-linking (CXL) therapy was used to treat a 68 year old patient with a central 2x2-mm corneal epithelial defect with deep stromal infiltration in one eye (OS) with a clinical appearance suggesting fungal infection. [24] The patient had visual acuity (VA) of CF at 2-ft. Initially, the patient was treated with topical voriconazole, amphotericin B and fluconazole drops for 10 days with no response. Then, he was treated with standard UVA-riboflavin CXL treatment. [25] After the removal of loose epithelium, riboflavin was topically administered for a period of 30 minutes at a 2-minute intervals. Then cornea was illuminated with UVA at 365nm wavelength, with an irradiance of 3.0 mW/cm^2 for 30 min. Riboflavin was administered throughout the UV illumination. However, patient had a reactivation of the infection 2 weeks post CXL treatment. Patient was given a second CXL treatment as described above with adjuvant antimicrobial therapy. The antimicrobial therapy was tapered and stopped 3 months post second CXL treatment. No reactivation of the corneal ulcer was noted and patient's VA was CF at 4 ft with complete scarring of the lesion.

CXL therapy was used to treat a 57 year old patient with a history of penetrating keratoplasty (PK) 12 months ago. [26] He presented with a central corneal ulcer at the graft measuring 3 to 3.5mm in one eye (OS). Patient's VA was CF at 1 ft due to optic nerve damage prior to PK. After the cultures came back positive for gram positive cocci (MRSA), patient was started on antimicrobial therapy including fortified 5% vancomycin topical drops. After 3 days of further deterioration of the clinical picture, CXL therapy was administered. After de-epithelization of the area surrounding the ulcer, a mixture of 0.1% riboflavin in 20% dextran solution was instilled over the cornea every 2 min for 14 min. Then the cornea was illuminated with UVA at 370nm with an irradiance of 3mW/ cm^2 for 30 min. Riboflavin drops were administered throughout the UV illumination. Topical vancomycin drops were switched to moxifloxacin topical drops five days after CXL treatment. Patient's corneal epithelium was completely re-epithelized five days after CXL treatment. Topical antibiotic treatment was stopped at one month post-CXL treatment. At the final post-operative examination, the patient's cornea had minor scarring at the ulcer site with strong connection between the graft and recipient cornea. No relapses occurred during the total post-operative period of 12 months.

[24] (Saglk, Ucakhan, & Kanpolat, 2013)
[25] (Wollensak, Spoerl, et al., 2003)
[26] (Labiris, Giarmoukakis, Larin, Sideroudi, & Kozobolis, 2014)

CXL therapy was used in 8 patients with severe corneal ulcers in 8 eyes that had corneal melting and were not responding to topical and systemic antimicrobial therapy. [27] After de-epithelization of the area around the ulcer, riboflavin drops were instilled over the corneas every 3 min for 30 min. Then the corneas were illuminated with UVA at 365nm for 30 min with an irradiance of 3.0 mW/cm^2. During irradiance, riboflavin drops were administered every 3-4 min. After CXL treatment, fortified antimicrobial topical drops, cycloplegics, artificial tear drops and systemic doxycycline were used. Topical antimicrobial therapy was tapered and stopped at 1 month after re-epithelization of the corneas of the patients. All patients had improvement in symptoms such as photophobia and pain 24-48hrs post CXL treatment. Hypopyon that was present in 6 eyes completely regressed after 2-4 days post CXL treatment in 5 eyes. The progression of corneal melting stopped rapidly in all 6 eyes with complete wound-healing at 2-5 weeks post CXL treatment. The VA of the patients that ranged from light perception to CF before CXL improved to hand motions and 20/100 post CXL treatment at the final post-operative examination. One eye developed corneal perforation six days after CXL treatment and immediate PK was performed.

Price at al did a systemic review in which they looked at 204 eyes diagnosed with infectious keratitis, which were treated with the standard UVA-riboflavin CXL therapy along with adjuvant microbial therapy. [28,29] Out of the 204 eyes, 109 eyes had mild to moderate bacterial keratitis and 73 eyes had completely healed with no complications. When the review compared 37 eyes with moderate to severe bacterial keratitis, which were treated with CXL and adjuvant antimicrobial therapy, to 35 eyes that were treated with topical antimicrobial therapy alone, no difference in visual outcomes were found. However, the eyes with moderate bacterial keratitis treated with CXL had shorter wound healing time of 17 days compared to the control eyes treated with antimicrobial therapy alone. The latter group had a wound healing time of 24 days and longer duration of anterior chamber inflammation.

The review looked at 52 eyes with infectious fungal keratitis treated with standard CXL treatment with adjuvant antimicrobial therapy. [30,31] 28 eyes successfully healed with the CXL and adjuvant microbial therapy. The other 20 eyes with fungal keratitis treated with CXL and adjuvant microbial therapy did not differ in visual outcomes or wound healing times compared to the 21 eyes with fungal keratitis that were treated with antimicrobial therapy alone. Four out of six eyes with deep stromal fungal keratitis that were treated with CXL along with adjuvant antimicrobial therapy had corneal perforations. However, the seven control eyes with deep stromal fungal keratitis, which were treated with topical antifungal therapy alone, did not have such complications.

[27] (Zamani, Panahi-Bazaz, & Assadi, 2015)
[28] (Wollensak, Spoerl, et al., 2003)
[29] (Price & Price, 2016)
[30] (Wollensak, Spoerl, et al., 2003)
[31] (Price & Price, 2016)

The review looked at 12 eyes with acanthamoebic keratitis that were treated with the standard CXL therapy along with adjuvant antimicrobial therapy. [32,33] 11 out of 12 eyes healed completely with improved visual outcomes and symptoms. However, when the same CXL treatment was used to treat two eyes with Herpes keratitis, patients had corneal melting and needed to have tectonic keratoplasty. The review also looked at 16 eyes with infectious bacterial keratitis and 1 eye with infectious fungal keratitis that were treated with standard CXL therapy alone without adjuvant antimicrobial therapy. 15 eyes healed without any complications and 2 eyes (both eyes with bacterial keratitis) required adjuvant antimicrobial therapy. The review describes one case-report in which one eye with fungal keratitis (*Aureobasidium pullulans*) was treated with accelerated CXL therapy alone [6]. [34] In this procedure, after the removal of loose epithelium, riboflavin was topically administered for a period of 30 minutes at 2-minute intervals. Then cornea was illuminated with UVA at 365nm wavelength, with an irradiance of 9.0 mW/cm^2 for 10 min. Riboflavin drops were administered throughout the UV irradiation. The eye successfully healed in 3 days without any complications or recurrences.

1.2.3. Adverse Events

Adverse events have been reported after cross-linking. Corneal edema occurred in an eye with a pretreatment corneal thickness of ~400 microns, presumably caused by UV damage to the corneal endothelium. [35] 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. [36] 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 ~300 microns 2 weeks after cross-linking in 14 of 16 eyes evaluated. [37] 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 (~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.

Hafezi et al. recently published the results of corneal collagen cross-linking in 10 eyes of 10 patients who had ectasia after prior LASIK surgery. [38] Anterior stromal haze was observed in the early postoperative period in all 10 eyes, with the corneas completely clear at the 12 month evaluation. This anterior stromal haze is similar to the subepithelial haze that is seen with photorefractive keratectomy (PRK) procedures, but the haze after

[32] (Wollensak, Spoerl, et al., 2003)
[33] (Price & Price, 2016)
[34] (Tabibian, Richoz, Riat, Schrenzel, & Hafezi, 2014)
[35] (Seiler)
[36] (Mazzotta et al., 2006)
[37] (Seiler & Hafezi, 2006)
[38] (Hafezi, Kanellopoulos, Wiltfang, & Seiler, 2007)

cross-linking is not subepithelial in nature. The anterior stromal haze has also been reported anecdotally by the Australian investigators as a typical occurrence after cross-linking that disappears within 3 to 6 months after the procedure and is thought to be related to keratocyte apoptosis (as described in Section 1.3 below) and regeneration after cross-linking. [39]

Rare cases of persistent epithelial defect or corneal infection have been reported after crosslinking, typically after epithelium-off crosslinking which entails scraping of epithelium, allowing access for bacteria or other micro-organisms to invade the corneal stroma.

1.3 Risk Analysis

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. [40]

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 1.6 mg based on the volume of one drop being 0.05 ml and 1 drop being instilled every 2 minutes for 30 minutes before, and 30 minutes during, UVA light irradiation (32 drops). This 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 mW/cm^2), and UVA light plus riboflavin (irradiance range

[39] (Wittig & Snibson, 2007)
[40] www.food.gov.uk/multimedia/pdfs/evm.riboflavin.pdf

0.4 to 1 mW/cm^2). [41] Riboflavin alone had no cytotoxic effect on keratocytes. The cytotoxic threshold for inducing cellular necrosis or apoptosis was 5 mW/cm^2 for UVA light alone and 0.5 mW/cm^2 for the UVA/riboflavin treatment. Using the Lambert-Beer equation, in human corneas the cytotoxic keratocyte UVA irradiance of 0.5 mW/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 mW/cm^2) with and without riboflavin. [42] An abrupt cytotoxic threshold was observed at an irradiance of 4 mW/cm^2 for UVA light alone and was ten-fold lower with an irradiance threshold of 0.35 mW/cm^2 for the UVA/riboflavin treatment. No endothelial cell damage was observed in the cells treated with riboflavin alone. Endothelial cell damage 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. [43]

The lower cytotoxic thresholds observed for the UVA/riboflavin combination in the keratocyte and endothelial cell toxicity studies is consistent with the increase in UVA absorption in the anterior cornea 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 below, whereas only 32% is absorbed within that depth in the absence of riboflavin. [44]

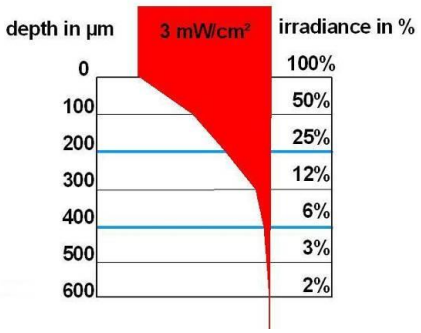

Fig. 7: Anterior stromal UVA absorption with riboflavin

2.0 COMBINATION PRODUCT DESCRIPTION

2.1 PXL Platinum 330 Illumination System

The PXL Platinum 330 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 PXL Platinum 330 System include the LED light source, UV light detector, UV detector sensor probe and adapter, wall power supply with DC cord,

[41] (Wollensak, Spoerl, Reber, & Seiler, 2004)
[42] (Wollensak, Sporl, Reber, Pillunat, & Funk, 2003)
[43] (Cho, Lee, Choi, & Joo, 1999)
[44] (Sporl, Schreiber, Hellmund, Seiler, & Knuschke, 2000)

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 (± 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^2 (±0.3 mW/cm^2)
Safety Class	Class II Equipment (EN 60601-1)
Medical Device Class	Class IIa 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 variable intensities of 3, 9, 18, or 30 mW/cm^2 (±0.3 mW/cm^2). 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 3 – 12 mm, which is controlled by selecting the corresponding aperture wheel setting on the device. An intensity of 30 mW/cm^2 and irradiance time of 3 minutes results in a standard surface dose of 5.4 J/cm^2 surface exposure. With pulsed mode (5 second on, 5 second off), the treatment time doubles. An eye tracker facilitates patient fixation on the light source. The Light Source has an integrated timer that automatically shuts off the light emission after the specified duration 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 PXL Platinum 330 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.

2.2 Riboflavin Solution

We obtain the riboflavin solutions from:

Peschke-MediTrade GmbH
Chaesigass 6a
6331 Huenenberg, Switzerland

Peschke-TE (Riboflavin 0.25% Transepithelial Solution): The riboflavin solution is an isotonic (0.9%) sodium chloride solution containing 0.25% riboflavin, 1% hydroxypropylmethylcellulose, and 0.007% benzalkonium chloride, adjusted to a pH of 7.0, and packaged in 3 mL sterile dropper bottles for topical ophthalmic use. Shelf life is 24 months.

Peschke-L (Riboflavin 0.23% Solution): This riboflavin solution is an isotonic (.9%) sodium chloride solution containing disodium hydrogenphosphate, sodium dihydrogenphosphate, and water for injection. It is adjusted to a pH of 7.0, and packaged in 2 mL sterile pre-filled syringes, sealed and sterilized for ophthalmic use. Shelf life is 24 months.

3.0 OBJECTIVES

The primary objective of this study is to evaluate the safety and effectiveness of corneal collagen cross-linking (performed using the PXL-Platinum 330 system) for treating corneal curvature and biomechanical anomalies associated with corneal thinning conditions, e.g., progressive or nonprogressive keratoconus, pellucid marginal degeneration, and treatment of patients with bacterial or fungal keratitis.

4.0 SAFETY AND EFFICACY ENDPOINTS

The primary efficacy parameter that will be evaluated over time is corneal curvature, as measured by maximum keratometry (Kmax) and mean keratometry (Kmean) in the randomized eyes. Study success is defined as a difference of at least 1 diopter in the mean change in Kmax or Kmean from baseline to 12 months in the treated eyes. Secondary efficacy measurements will include: pachymetry, diopters of astigmatism as measured by keratometric cylinder, posterior corneal elevation, best spectacle-corrected visual acuity (BSCVA) or contact-lens best-corrected visual acuity, manifest refraction, corneal resistance factor, and corneal hysteresis.

Safety assessments will include a tabulation of adverse events, patient symptoms, loss of visual acuity, slit lamp examination of the cornea and lens, and contact lens tolerance for contact lens wearers. Quality of vision will be assessed using the Refractive Status Vision Profile questionnaire. [45] Specific methods of analysis are provided in Section 9.0, Data Analysis.

5.0 STUDY DESIGN

This is a prospective, double-arm, randomized single-site study to determine the safety and effectiveness of the PXL Platinum 330 system for performing corneal collagen cross-

[45] (Schein, Vitale, Cassard, & Steinberg, 2001)

linking (CXL) in eyes with corneal thinning. Subjects with a history of keratoconus, pellucid marginal degeneration, or non-resolving bacterial or fungal keratitis will be evaluated initially for suitability as a candidate for CXL. Subjects that are candidates for CXL will be asked to participate in this study and will undergo the required screening procedures to determine study eligibility. Informed consent will be obtained from each subject before performance of any required study procedures that are not part of the investigator's routine examination. After completing screening procedures, the diagnosis for each eligible eye will be confirmed, and diagnosis classified as mild, moderate or severe. [46]

Eyes undergoing CXL will have topical anesthetic administered and then have topical riboflavin instilled onto the cornea and, after the riboflavin pre-treatment regimen is complete, eyes in the treatment group will be exposed to UVA pulsed light 30 mW/cm2 for 10 minutes (5 seconds, on, 5 seconds off) while eyes in the control group will be exposed to UVA continuous light at 9 mW/cm2 for 10 minutes, with topical riboflavin continuing to be administered during the illumination time for each group.

The CXL procedures will be performed on an outpatient basis using the PXL Platinum 330 System (UVA light source and riboflavin solution). All use of the PXL Platinum 330 System will be in accordance with this protocol and the general instructions provided by the manufacturer (IROC) in the PXL Platinum 330 operator's manual.

All subjects will be evaluated at screening/baseline, Day 0 (randomization/treatment day), and 1 day, 1 week, and 1, 3, 6 and 12 months after treatment. Topographic keratometry, posterior corneal measurements (with Pentacam/Galilei/Orbscan/Cassini), corneal topography, manifest refraction, and measurements of best spectacle or contact - corrected visual acuity, and intraocular pressure will be obtained at baseline and at appropriate times after the CXL treatment. Safety monitoring throughout the study will include observations at appropriate times for subjective complaints, complications, adverse events, clinically significant findings on ophthalmic examination, dilated fundus examination, and slit lamp examination. Quality of vision and subjective visual complaints will be evaluated preoperatively and postoperatively with a vision related quality of life questionnaire.

6.0 SUBJECT POPULATION

This study is a single-center study that will be conducted over 10 years. Up to 300 patients with corneal thinning conditions will be enrolled.

6.1 Inclusion Criteria

Subjects who have one or both eyes that meet criteria 1 and 1 or more of the following criteria will be considered candidates for this study:

1. 12 years of age or older

[46] (McMahon et al., 2006)

2. Presence of central or inferior steepening.
3. Axial topography consistent with keratoconus, post-surgical ectasia, or pellucid marginal degeneration
4. Presence of one or more findings associated with keratoconus or pellucid marginal degeneration, such as:
    a. Fleischer ring
    b. Vogt's striae
    c. Decentered corneal apex
    d. Munson's sign
    e. Rizzutti's sign
    f. Apical Corneal scarring consistent with Bowman's breaks
    g. Scissoring of the retinoscopic reflex
    h. Crab-claw appearance on topography
5. Steepest keratometry (Kmax) value ≥ 47.20 D
6. I-S keratometry difference > 1.5 D on the Pentacam/Galilei/Orbscan/Cassini map or topography map
7. Posterior corneal elevation >16 microns
8. Thinnest corneal point <485 microns
9. Predicted Post LASIK/PRK stromal ablation depth <350 microns or expected keratometry >47.2 D, or patients undergoing PRK/SMILE in keratoconus suspect eyes
10. Bacterial or fungal corneal keratitis persistent and not responding despite > 2 weeks of standard antimicrobial therapy or with rapid progression of corneal thinning, with loss of >25% corneal thickness
11. Contact Lens Wearers Only:
    a. Removal of contact lenses for the required period of time prior to the screening refraction:

Contact Lens Type	**Minimum Discontinuation Time**
Soft	1 Week
Soft Extended Wear	2 Weeks
Soft Toric	3 Weeks
Rigid gas permeable	2 Weeks per decade of wear

12. Signed written informed consent
13. Willingness and ability to comply with schedule for follow-up visits

6.2 Exclusion Criteria

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

1. Eyes classified as either normal or atypical normal on the severity grading scheme.
2. Corneal pachymetry at the screening exam that is <300 microns at the thinnest point in the eye(s) to be treated.
3. Previous ocular condition (other than refractive error) in the eye(s) to be treated that may predispose the eye for future complications, for example:

a. History of or active corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, acanthomeoeba, etc.)
b. Clinically significant corneal scarring in the CXL treatment zone that is not related to keratoconus or, in the investigator's opinion, will interfere with the cross-linking procedure.

4. Pregnancy (including plan to become pregnant) or lactation during the course of the study
5. A known sensitivity to study medications
6. Patients with nystagmus or any other condition that would prevent a steady gaze during the CXL treatment or other diagnostic tests.
7. Patients with a current condition that, in the physician's opinion, would interfere with or prolong epithelial healing.

7.0 SCREENING FOR CXL ELIGIBILITY

A flow chart of study procedures is provided in Appendix A.

7.1 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 the study personnel. Screening data from referring doctors will not be used as the screening data for the study, except to document the progression of keratoconus, ectasia, pellucid marginal degeneration or corneal infection. Procedures or evaluations that were performed by study personnel during their routine clinic evaluation may be used for the screening examination if the testing was completed: (1) within 30 days of randomization; (2) in accordance with the protocol requirements; (3) all screening tests performed are known to be included in the investigator's usual and customary examination procedures. Subjects will sign a consent form before any clinical protocol procedures or tests specific to the study protocol are performed.

7.1.1 Screening Eye Examination

Potential CXL candidates will undergo a complete eye examination to determine their eligibility for study participation. 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 or corneal infection
- History of risk factors for keratoconus
- UCVA (distance)
- BSCVA or best-contacted corrected visual acuity (distance)
- Manifest refraction
- Pentacam/Galilei/Orbscan/Cassini measurements, including
  - Pachymetry
  - Keratometry
  - Posterior corneal mapping

- Corneal topography
- Intraocular pressure (by Goldmann applanation tonometry)
- Slit lamp examination of the cornea, anterior chamber and lens
- Dilated fundus examination
- RSVP/ Subjective complaint questionnaire

For eyes undergoing CXL treatment, if the CXL treatment is performed more than one month after the screening examination, the following measurements will be repeated on the day of treatment:

- Topography
- Pentacam/Galilei/Orbsca/Cassini
- UCVA (distance)
- BSCVA (distance)
- Manifest refraction

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Manifest refractions will be recorded on the source documents in the investigator's usual notation (plus or minus cylinder format). All manifest refractions will be recorded on the case report forms in the study using plus cylinder format. Additional instructions for these test procedures are provided in Appendix A.

7.1.2 Contact Lens Discontinuation

Contact lens wearers should discontinue contact lenses at schedule noted above in inclusion criteria. Contact lens wearers should exhibit a stable refraction at the two most recent consecutive exams before cross-linking. A stable refraction is first determined as one in which the manifest refraction measurement and the topography (i.e., average SIM K readings from the topography) taken at the first visit do not differ by more than 0.75 D MRSE from the respective measurements taken at the second exam. If one or more of the measurements exhibit a difference greater than 0.75 D MRSE, the subject should either: (1) be declared a screening failure; or, (2) additional visits should be completed until stability ($\leq$0.75D MRSE difference) is attained for each of the three parameters. All exam dates for these measurements should be at least 7 days apart.

7.2 Keratoconus Severity

Eyes that meet the eligibility criteria for progressive keratoconus will be classified according to severity using the grading scheme below adapted from McMahon et al.[47] If the criteria fall into more than one severity category, the severity rating will be based on the keratometry reading. Eyes that are classified as being normal or atypical normal are ineligible for the study and will be recorded as screening failures.

- Normal

[47] McMahon TT, Szcotka-Flynn L, Barr JT, et al. A new method for grading the severity of keratoconus. Cornea. 25(7):794-800; August 2006

  - Regular axial topography pattern (round, oval, symmetric bow tie, etc.)
  - Normal slit lamp exam
  - Spectacle corrected acuity 20/20 or better
- Atypical Normal
  - Unusual axial topography explained by slit-lamp exam or history (contact lens warpage, cortical scars not typical of keratoconus, history of refractive surgery)
  - Normal or diminished spectacle acuity
- Keratoconus Suspect
  - Suspicious axial topography for keratoconus (isolated area of steepening, central steepening > 48 D) but I-S value less than 1.4
  - Normal slit lamp exam
  - BSCVA 20/20 or better
- Mild Keratoconus
  - Axial topography consistent with keratoconus
  - Flat keratometry reading < 51.00 D
  - Fleischer ring or Vogt striae
  - No corneal scarring
  - BSCVA worse than 20/20
- Moderate Keratoconus
  - Axial topography consistent with keratoconus
  - Flat keratometry reading between 51.25 D and 56.00 D or astigmatism ≥ 8.00 D
  - Fleischer ring or Vogt striae
  - May have corneal scarring up to and including CLEK grade 3.0 (any scarring up to well-defined stromal scarring consistent with keratoconus)
  - BSCVA 20/30 or worse
- Severe Keratoconus
  - Axial topography consistent with keratoconus with marked areas of steepening
  - Flat keratometry reading > 56.01 D
  - Fleischer ring or Vogt striae
  - May have corneal scarring up to and including CLEK grade 4.0 (any scarring up to a dense/opaque stromal scar consistent with keratoconus)
  - BSCVA worse than 20/40

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.

8.1 Examination Schedule

The study duration is 12 months following the crosslinking treatment, unless extended due to retreatment. The following examination schedule will be followed:

- Preoperative (-30 to -1 days)
- Operative (Day 0)
- Day 1 (1 to 3 days)
- Week 1 (5 to 14 days)
- Month 1 (3 to 6 weeks)
- Month 3 (10 to 14 weeks)
- Month 6 (20 to 28 weeks)
- Month 12 (40 to 60 weeks)

8.2 Outpatient CXL Treatment (Treatment Group)

An interim medical history, ocular history, and medication history will be obtained to determine whether any events or changes in health status have occurred that would preclude the subject from undergoing CXL treatment at the scheduled time or from participating in the study. Measurements from the complete eye examination that were performed during screening may be repeated, at the discretion of the investigator, to provide accurate baseline measurements.

Subjects will be prepared for CXL treatment in accordance with the instructions for use in the PXL Platinum 330 Illumination System Operator's Manual.

Prior to the CXL treatment, the staff will confirm that the informed consent form for the study has been signed. If the results of any repeat measurements performed on the CXL treatment day fail to meet eligibility criteria, the CXL treatment will be postponed or the subject will be dropped from the study.

Subjects will remain in the clinic until the CXL treatment has been completed and the investigator determines that it is safe for the subject to be discharged from the clinic. Generally, the average time from arrival to discharge will be approximately 2 hours.

8.2.1 Surgical Procedure for CXL

CXL will be performed according to the Instructions for Use provided in the PXL Platinum 330 Operator's Manual. A summary of the general technique for performing CXL is summarized below. CXL procedures used for each subject will be documented on the source documents. Selected treatment information, including the riboflavin administration, irradiance settings, and duration of irradiation exposure will be documented.

8.2.2 Subject Preparation

After topical anesthesia, the surgeon or trained designee will apply topical riboflavin (1 drop every 2 minutes for 40 minutes with transepithelial treatment). Local anesthetics will be administered as needed to maintain patient comfort during the CXL procedure.

8.2.3 Riboflavin

Riboflavin will be administered according to the instructions provided by the manufacturer. 1 drop of Riboflavin 0.25% ophthalmic solution or 0.23% ophthalmic solution will be instilled topically in the eye every 2 minutes for 40 minutes, or instilled under a scleral contact lens reservoir for 5 to 10 minutes. At the end of this pre-treatment period, the eye will be examined at the slit lamp for the presence of a yellow flare in the anterior chamber, indicating adequate riboflavin saturation of the corneal tissue. If the yellow flare is not detected, riboflavin will continue to be instilled 1 drop every 2 minutes for an additional 10 to 20 minutes, and the anterior chamber will be rechecked for yellow flare. This process will be repeated as necessary.

During irradiation, instillation of riboflavin will be continued every 2 minutes. For a 40-minute pre-treatment and 5-minute irradiation, the total dose of riboflavin solution is approximately 22 drops, or 1.1 ml (1 drop = 0.05 ml; 1.1 mL = 4.4 mg riboflavin).

8.2.4 UVA Light

Prior to the first treatment of the day, the PXL Platinum 330 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.

When the yellow flare in the anterior chamber is confirmed, the eye will be aligned under the PXL Platinum 330 light (the treatment plane will be at the correct working distance from the PXL Platinum 330 beam aperture when the border of the projected beam is in sharp focus). The correct aperture setting (3-12 mm) will be selected for the size of the eye and area needing to be treated, and the eye will be irradiated at 30 mW/cm2, with pulsed mode (5 second on, 5 second off) for 10 minutes (for standalone crosslinking procedures) or continuous mode for 2 minutes (2 (in concurrent refractive procedures), during which time instillation of riboflavin will continue (1 drop every 2 minutes). During the treatment, there will be 4 L blow-by oxygen via cannula. At the end of the treatment, 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 (4^{th} generation fluoroquinolone), and a drop of steroid (prednisolone 1%) will be placed. If the physician notes an epithelial defect, a bandage contact lens can be placed.

8.2.5 Concurrent Procedures

If Intacs are indicated based on patient's condition and status, the physician may perform those according to customary procedures. In this case, the crosslinking with riboflavin would be performed after Intacs with the UVA light of the PXL Platinum 330 system as per section 8.2.4.

8.2.6 Postoperative Care

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

- Gatifloxacin 0.5% drops for 2 weeks
- Pred-Forte 1% drops for 2 months on a tapering schedule
- Preservative-free artificial tears as needed

All postoperative eye drop usage will be recorded in the subject's chart. The dosage and/or frequency of any of the above medications may be altered at the discretion of the investigator. Other prescription or nonprescription medications, including pain medication, may be taken as needed throughout the study.

8.3 Follow-Up Visits (1 Day, 1 Week, 1, 3, 6 and 12 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, 1, 3, 6 and 12 months after CXL.

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

- Topography (omit on Day 1 and Week 1)
- UCVA distance
- BSCVA distance (omit on Day 1 and week 1)
- Manifest refraction (omit on Day 1 and week 1)
- Pentacam/Galilei/Orbscan/Cassini measurements (omit on Day 1 and Week 1), including
    - Pachymetry
    - Keratometry
    - Posterior corneal evaluation
- Intraocular pressure (by Goldmann applanation tonometry -- omit on Day 1)
- Slit lamp examination of the cornea, anterior chamber and lens
- Dilated fundus exam (Month 12 only)
- RSVP/subjective complaint questionnaire (omit on Day 1 and Week 1)
- Documentation of interim medical, medication, and ocular histories.

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

8.4 Retreatment

The CXL treatment is intended to be a one time treatment. If progression is observed at 3, 6, or 12 months, patient will be offered retreatment with the study device or referral to a center with the approved Avedro KXL system.

If a patient receives crosslinking retreatment with the study device, the duration of the study will be extended for 6 months after the retreatment. The patient will receive additional study visits according to the following schedule:

- Retreatment Operative (Day 0)
- Retreatment Day 1 (1 to 3 days)
- Retreatment Week 1 (5 to 14 days)
- Retreatment Month 1 (3 to 6 weeks)
- Retreatment Month 3 (10 to 14 weeks)
- Retreatment Month 6 (20 to 28 weeks)

The procedures and assessments at the retreatment visits are the same as those which take place at the original post-op visits at the same time points. If a patient is retreated and the timing of the visit windows allows, the retreatment visits may be combined with the post-op visits from the original crosslinking procedure (e.g. if a patient is retreated shortly after their 6 month post-op, their 6 month retreatment post-op can be combined with their 12 month post-op from the original procedure).

In prior ophthalmic experience with retreatment cases, it has been described that there can be insufficient or minimal penetration of riboflavin into the cornea. Sufficient penetration of riboflavin into the cornea is crucial for the success of the procedure and to reduce the risk of keratoconic progression. For retreatment cases, the investigator will follow the crosslinking procedure described in section 8.2 unless there is insufficient penetration of riboflavin upon slit lamp exam. If riboflavin penetration is insufficient, the following alterations to the surgical technique may be made at the investigator's discretion:

1) Central corneal epithelial cells can be removed followed by additional riboflavin solution soak
2) Using 9 mw/cm2 intensity and 10 minutes continuous illumination time

8.5 Safety Monitoring

During the CXL treatment procedure, subjects will be observed closely to detect the occurrence of any adverse events or complications that may have occurred. On the day of treatment and at each follow-up visit, it is suggested that the subjects be asked a non-leading question, such as “How are you seeing?,” 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, measurements of refraction, and measurement of visual acuity. In the case of an adverse event or complication, these tests may be repeated before the next scheduled visit at the investigator’s discretion. Any complications or visual adverse events will be recorded in the medical record/case report form.

8.6 Post-Study Procedures

Subjects will be discharged from the study after the 12-month follow-up examination is complete. Clinically significant abnormalities will be followed until the abnormality returns to acceptable limits or there is an adequate explanation for the abnormality.

8.8 PXL Platinum 330 and Riboflavin Accountability

All use of the PXL Platinum 330 Illumination System, Riboflavin 0.25% Ophthalmic Solution, and Riboflavin .23% Ophthalmic Solution will be under the direct supervision of the principal investigator or his designee.

8.9 Early Withdrawal from Study

Subjects will be advised that they are free to withdraw from the study at any time. Subjects experiencing adverse safety events will be followed until the reaction has resolved. Appropriate supportive and/or definitive therapy will be administered as required. 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.

8.10 Study Duration

The study duration is a total of 12 months for all study subjects following the CXL treatment. The duration of the study will also be extended for those patients who have received retreatment or for subjects who elect to have CXL treatment in an untreated fellow eye.

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%. The superiority hypotheses will be tested at a significance level o 2.5%.

9.1 Sample Size

9.1.1 Keratoconus, Ectasia, or Pellucid Marginal Degeneration

The primary efficacy hypothesis for the treatment of keratoconus, ectasia, or pellucid marginal degeneration is to determine whether there is a difference in the mean change

from baseline in the maximal or mean keratometry readings before or after CXL treatment at 3, 6, or 12 months. Since this hypothesis will be tested using a two sample t-test, Table 9.1-1 presents sample sizes per treatment group for various values of the difference between the two means δ, and the standard deviation, σ with the significance level = 0.025 and the power =80%. Previous studies have indicated that at the 12 months time period there is a decrease in the K-readings for the CXL group of about 1.2 to 2.0 diopters. From previous studies, the standard deviations for the differences in K-readings have ranged from 1.5 to 2.5. Thus these values are used in the following table.

Table 9.1-1 Sample Size Calculations for Keratoconus, Ectasia, or PMD Groups

δ	σ	sample size (per group)
1.2	1.5	39
	2.0	69
	2.5	108
2.0	1.5	14
	2.0	25
	2.5	39

Enrolling 108 patients in each treatment group will enable the detection of a 1.2 diopter difference between the treatment groups with a coefficient of variability of 2.5 D. We would aim to have 108 patients per group complete the study from both genders.

Since historically there is a 10% discontinuation rate, the sample size is adjusted for a 10% rate of discontinued and lost-to-follow-up eyes:

Adjusted Sample Size (n') = n/(1-0.10) = n/0.90
where: n is the initial estimated sample size
(n') = 108/0.90
(n') = 120

120 eyes per treatment group (KCN,) X 2 genders = 240 patients

9.1.2. Corneal keratitis or Thin Corneas Undergoing Refractive Surgery

Bacterial or fungal keratitis, and patients with thin corneas undergoing LASIK/PRK/SMILE are much rarer conditions. We would perform descriptive statistics only on these groups of patients. We would like to recruit up to 60 patients in any of these groups.

9.2 Accountability

Accountability by postoperative visit will be calculated as illustrated in Table 9.2-1 below.

Table 9.2-1: Accountability by Postoperative Visit

		1 Month	3 Months
Available for Analysis[2]	n/N[1](%)		
Missed Visit[3]	n/N[1] (%)		
Discontinued[4]	n/N[1] (%)		
Active[5]	n/N[1] (%)		
Lost to follow-up[6]	n/N[1] (%)		
% Accountability = Available for Analysis (Enrolled - Discontinued - Active)			

Where,

[1] Enrolled (N) = total number of subject eyes enrolled in the study.

[2] Available for analysis = total number of eyes for whom data is available at each postoperative interval.

[3] 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.

[4] Discontinued = total number of eyes that discontinued follow-up prior to completion of the study for any reason (e.g., retreatment, moved away).

[5] Active (not yet eligible for the interval) = total number of eyes that have not yet reached the visit interval.

[6] 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.

9.3 Screening

The screening data for all subjects who were screened but did not meet eligibility criteria will not be analyzed or tabulated.

9.4 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.

Risk factors will be tabulated by eye and summarized using descriptive statistics.

9.5 Primary Efficacy Criteria

9.5.1 Keratometry

The change in maximum and mean keratometry (Kmax and Kmean) from baseline will be evaluated at 3 months and 12 for all eyes. Data will be summarized using descriptive statistics, and the differences in mean changes between the CXL treatment group and the control group at 3 months will be evaluated using a two sample t-test to test the following hypothesis:

$H_0: \mu_{CXL} - \mu_C = 0$ versus $H_A: \mu_{CXL} - \mu_C > 0$

where μ_C is the baseline reading (Kmax or Kmean) and μ_{CXL} is the 3 or 12 month Kmax or Kmean reading.

If it assumed the data from both treatment groups are normally distributed, then the test statistic from the ANOVA for testing the above hypothesis is a t-test.

9.6 Secondary Efficacy Criteria

9.6.1 Manifest Refraction

The change in manifest refraction spherical equivalent from baseline will be evaluated at 3 months. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test at each time point.

As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.

9.6.2 Visual Acuity

Change in BSCVA or best-contact corrected visual acuity and UCVA compared to the baseline examination will be evaluated at 3 months postoperatively. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test.

As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.

9.6.3 Central Pachymetry

The change in central pachymetry from baseline will be evaluated at 3 months postoperatively. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test.

As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.

9.7 Clinical Safety Endpoint Criteria

9.7.1 Adverse Events and Complications

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

9.7.2 Key Safety Parameters

For each time point, the following key safety parameters will be estimated for the entire cohort.

1) Percentage of eyes that had a loss of 2 or more lines in BSCVA
2) Percentage of eyes that had a BSCVA worse than 20/40
3) Percentage of eyes that had a greater than 2D increase in Kmax or Kmean

9.8 Refractive Status Vision Profile

The RSVP will be administered pre-treatment at screening to establish the subject's baseline and at 1, 3, 6 and 12 months after CXL. The change in RSVP from baseline will also be evaluated at 1, 3, 6 and 12 months postoperatively. Data will be summarized using descriptive statistics. A lower RSVP score indicates less dysfunction.

The secondary safety endpoint will be the difference in the composite score for the RSVP administered at 3 months after CXL and the pre-treatment or baseline composite score. Therefore, it is desired to determine if the composite score for the RSVP has decreased significantly from the preoperative assessment by the 3 month time point. Published literature indicates that a difference of 6 points or more on the composite scores is a clinically significant change. [48]

9.9 Dropouts/Lost-to-Follow-up

Patients may drop out at any time during the study. All treated patients/eyes will be included in the safety analysis.

The primary analysis population for the primary analysis will be based on an Intent-to-Treat population in which missing differences at 3 months for the CXL treated group will be replaced by the smallest maximum difference observed. A per protocol analysis will also be conducted where the missing values are dropped from the analysis.

[48] (Schein et al., 2001)

9.10 Interim Analysis

An interim analysis will be performed after all eyes complete the 3-month post-CXL visit. All relevant data summaries will be made according to the regulatory process, using appropriate statistical methods.

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

Adverse events that are observed by the investigator or reported by the subject will be recorded on the study source documents/case report forms. For all adverse events, a description of the event, date first observed, any action taken, and its resolution will be recorded.

10.3.1 Serious and Unexpected Drug Adverse Events

The sponsor and investigator must comply with the applicable sections of 21CFR312.32 and 21CFR312.64(b) for IND safety reports. In accordance with these regulations, the following definitions apply:

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

Any adverse experience associated with the use of the drug that is both serious and unexpected shall be reported by the sponsor to FDA as soon as possible and in no event later than 15 calendar days after the sponsor’s initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA

determines that additional data are needed, the agency may require further data to be submitted.

The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

In addition to notifying FDA, the sponsor will also notify each investigator of any serious and unexpected, fatal, or life-threatening experiences associated with the use of the drug. The investigators will promptly report these experiences to the IRB. If the IRB has different or specific reporting deadlines, reports should be made to the IRB in accordance with the IRB's requirements.

10.3.2 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." 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 in Section 10.3.1 above.

10.3.3 Non-serious Drug or Device or Anticipated Device Adverse Events

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

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 annually, 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, test reports, work sheets, nursing notes, signed informed consent forms, drug and device use records, adverse experience reports and information regarding subject discontinuation and reasons for discontinuation. 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., Pentacam, 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. 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 approval from the IRB and the sponsor, 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, ocular health, 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 will 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 will not be implemented until IRB approval is obtained. The investigator will 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 and IRB approval prior to implementation. The sponsor and investigator will obtain such approvals, if required.

APPENDIX A: STUDY FLOW CHART

Procedure	Screen	Surgery[49]	POSTOPERATIVE VISITS					
			1 DAY	1 WK	1 MO	3 MO	6 MO	12 MO
Medical History	X	X	X	X	X	X	X	X
Ocular History[50]	X	X	X	X	X	X	X	X
Medication History	X	X	X	X	X	X	X	X
Demographics	X							
BCVA[51]	X			X	X	X	X	X
UCVA[52]	X		X	X	X	X	X	X
Manifest Refraction	X				X	X	X	X
Confocal microscopy (optional)	X							X
Intraocular Pressure Measurement[53]	X			X	X	X	X	X
Slit Lamp Exam[54]	X		X	X	X	X	X	X
Dilated Fundus Examination	X							X
Pentacam/Orbscan/Galilei/Cassini[55]	X				X	X	X	X
Corneal Topography	X				X	X	X	X
RSVP Subjective Complaint Questionnaire	X				X	X	X	X
Sign Consent	X							
Complications		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
CXL Treatment		X						

Notes for the Examination Schedule (See footnotes below)

[49] Repeat measurements from the screening exam prior to surgery if needed to provide accurate baseline measurements before CXL treatment.
[50] Ocular history should include history of contact lens wear, risk factors for keratoconus, and history of refractive surgery. Non-specific questioning should be used at each visit to determine other vision-related complaints, complications, or adverse events
[51] Distance BSCVA should be performed using an ETDRS eye chart and recording the total number of letters that are seen.
[52] Distance BSCVA should be performed using an ETDRS eye chart and recording the total number of letters that are seen
[53] Intraocular pressure measurement by Goldmann applanation tonometry at the slit lamp or by tonopen.
[54] The slit lamp exam should include a complete survey of the anterior segment. The cornea should be examined in detail with specific recordings and gradings (0 to 4+ scale, 0=clear) of the following information: overall corneal clarity, any abnormalities such as corneal infiltrates.
[55] Pentacam measurements are performed using the Pentacam HR (high resolution).

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: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory

requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX D: REFERENCES

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