Results of the US Phase III Clinical Study:

Corneal Cross-linking for Progressive Keratoconus and Ectasia Following Refractive Surgery

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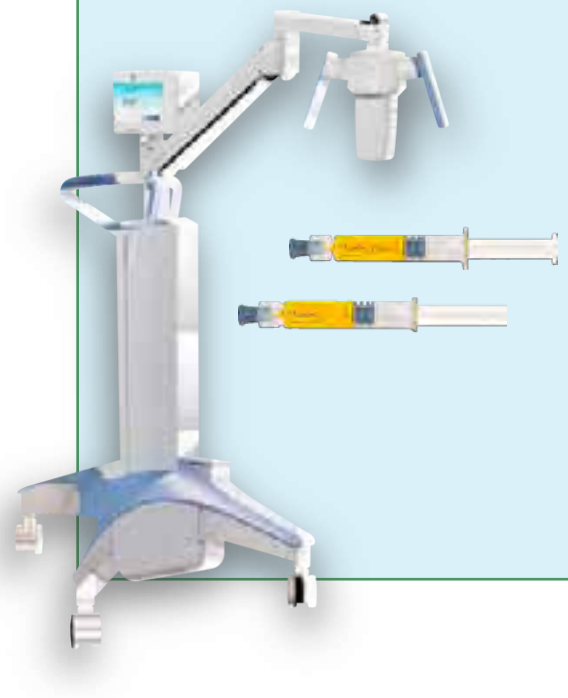
Financial Disclosures:

- **Employee of Avedro, Inc**

United States FDA Approval



- Avedro, Inc. received approval from the U.S. Food and Drug Administration (FDA) for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146%, and the KXL system for corneal cross-linking for the treatment of progressive keratoconus on April 15th 2016.
- **Photrexa Viscous, Photrexa and the KXL System are the first and only FDA-approved therapeutic treatment for progressive keratoconus and corneal ectasia following refractive surgery.**

Phase III Clinical Study Sites

UVX-001 (KC and Ectasia)

Site No.	Principal Investigator	Site
01	R. Doyle Stulting, M.D., Ph.D.	Emory Vision

UVX-002 (KC) & 003 (Ectasia)

Site No.	Principal Investigator	Site
01	Perry S. Binder, M.D.	Gordon, Binder & Weiss Vision Institute
02	Eric D. Donnenfeld, M.D.	Ophthalmic Consultants of Long Island
03	Peter Hersh, M.D.	Cornea and Laser Eye Institute
04	Francis Price, Jr. M.D.	Price Vision Group and Cornea Research
05	David Schanzlin, M.D.	UCSD, Shiley Eye Center
07	Steven Trokel, M.D.	Columbia University, Harkness Eye Institute
08	Daniel Durrie, M.D.	Overland Park, KS
09	William Trattler, M.D.	Center for Excellence in Eye Care
10	David Hardten, M.D., FACS	Minnesota Eye Consultants, P.A.
11	Walter Stark, M.D.	Wilmer Eye Institute, Johns Hopkins Hospital

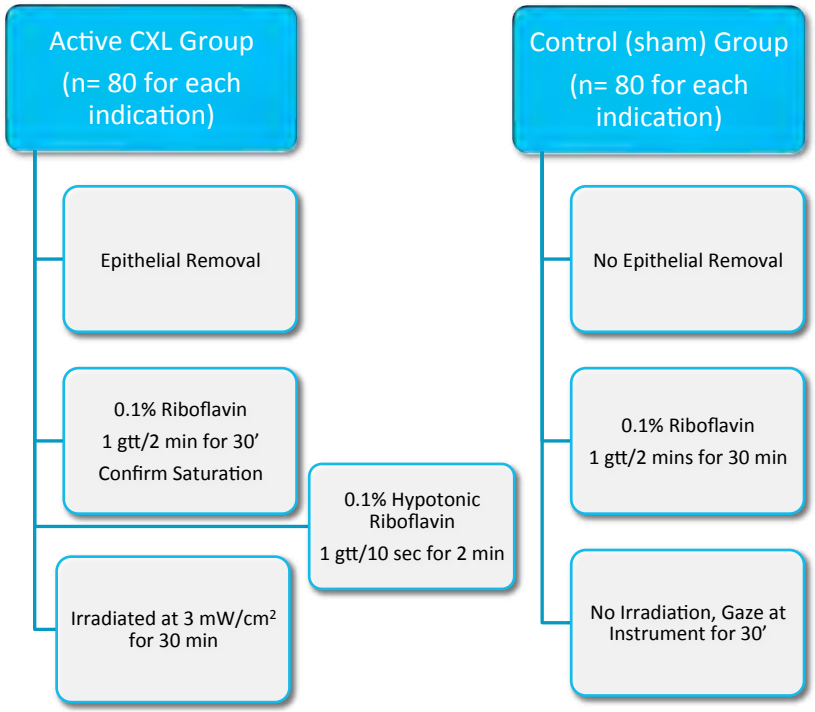
United States Phase III Studies

Avedro's NDA submission which encompassed data from three prospective, randomized, parallel-group, open-label, placebo-controlled, 12-month trials conducted in the United States to evaluate the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing corneal collagen cross-linking.

Randomization	Primary (Study) Eye		Secondary Eyes		Total
	CXL	Sham	Fellow Eye CXL	Sham Eye CXL	
Keratoconus					
Subjects Randomized to CXL	102	---	56	---	---
Subjects Randomized to Sham	---	103	41	94	---
TOTAL CXL	102	---	97	94	293
Ectasia					
Subjects Randomized to CXL	91	---	26	---	---
Subjects Randomized to Sham	---	88	22	80	---
TOTAL CXL	91	---	48	80	219

US Phase III Studies

- Study eye randomized into one of two groups
  - CXL treatment
  - Sham Control
- At Month 3 or later:
  - Non-randomized fellow eyes could receive CXL treatment
  - Control eye could receive CXL treatment
- The primary efficacy parameter evaluated over time was corneal curvature, as measured by maximum keratometry (K_{max})
- Study success was defined as a difference of at least 1 diopter in the mean change in Kmax from baseline comparing the CXL treatment group and the control group



Progressive Keratoconus: Clinical Study Definition

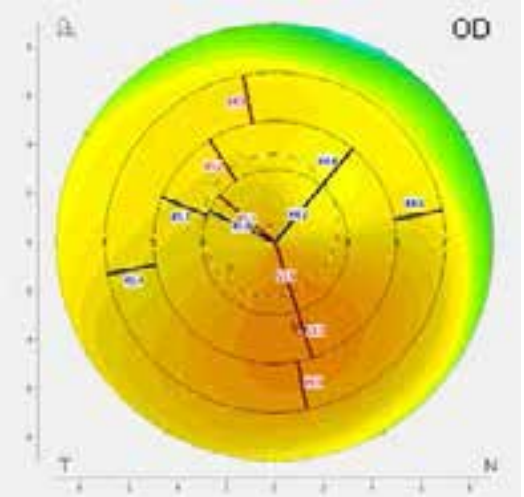
Progression of keratoconus was defined as one or more of the following changes over a period of 24 months or less:

a. An increase of ≥ 1.00 D in the steepest keratometry value (or simK)

b. An increase of ≥ 1.00 D in regular astigmatism evaluated by subjective manifest refraction

c. A myopic shift (decrease in the spherical equivalent) of ≥ 0.50 D on subjective manifest refraction

d. A decrease ≥ 0.1 mm in the BOZR (Back Optical Zone Radius) in rigid contact lens wearers where other information is not available.



Key Inclusion and Exclusion Criteria

Inclusion	Exclusion

• Had central or inferior steepening on the Pentacam map.
• For corneal ectasia patients only: Had axial topography consistent with corneal ectasia
• For progressive keratoconus only: presence of one or more findings associated with keratoconus, such as:
  • Fleischer ring
  • Vogt striae
  • Corneal thinning
  • Corneal scarring
  • Scissoring of the retinoscopic reflex
• Steepest keratometry (Kmax) value ≥ 47.00 D (progressive keratoconus only)
• Had a BSCVA worse than 20/20 (<55 letters on Early Treatment of Diabetic Retinopathy Study [ETDRS] chart)
	• Eyes classified as either normal, atypical normal (except corneal ectasia), or keratoconus suspect on the severity grading scheme.
	• For progressive keratoconus, a history of previous corneal surgery or the insertion of Intacs in the eye(s) to be treated.
	• Corneal pachymetry at the screening exam that was < 400 microns at the thinnest point measured by Pentacam in the eye(s) to be treated when the riboflavin with dextran solution alone was to be used or < 300 microns when the riboflavin without dextran was to be used.
	• A history of chemical injury or delayed epithelial healing in the eye(s) to be treated.
	• Subjects with nystagmus or any other condition that would have prevented a steady gaze during the CXL treatment or other diagnostic tests.

Progressive Keratoconus

Demographics

Parameter	Statistic	Pooled Studies		
		CXL Group	Control Group	Total
Received Randomized Treatment	N	102	103	**205**
Completed	n (%)	92 (90.2)	85 (82.5)	**177 (86.3)**
Age (yrs)	Mean	31.1	35.0	**33.0**
Gender	Female - n (%)	27 (26.5)	35 (34.0)	**62 (30.2%)**
	Male - n (%)	75 (73.5)	68 (66.0)	**143 (69.8%)**
Kmax	Mean (SD)	**60.9 D (+/- 9.14)**	**60.4 D (+/- 8.94)**	

Corneal Ectasia

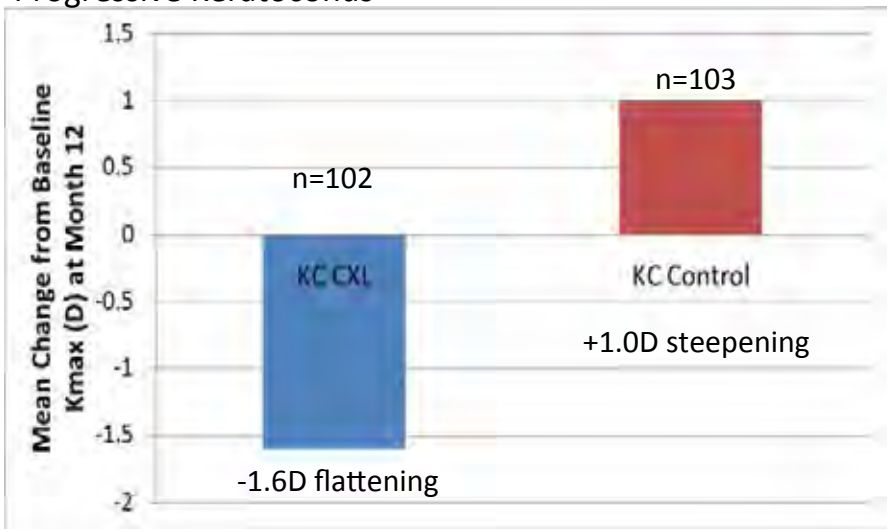
Demographics

Parameter	Statistic	Pooled Studies		
		CXL Group	Control Group	Total
Received Randomized Treatment	N	91	88	179
Completed	n (%)	78 (85.7)	72 (81.8)	**150 (83.8)**
Age (yrs)	Mean	43.5	41.8	42.7
Gender	Female - n (%)	33 (36.3)	24 (27.3)	57 (31.8)
	Male - n (%)	58 (63.7)	64 (72.7)	122 (68.2)
Kmax	Mean (SD)	**55.4 D (+/- 6.86)**	**54.8 D (+/- 6.40)**	

Primary Endpoint Met

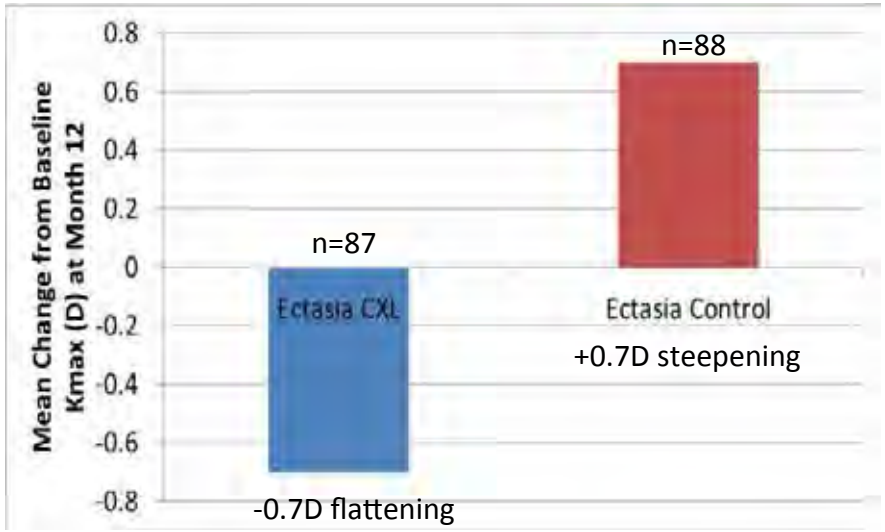
Mean Change K_{max} (D) – Month 12

Progressive Keratoconus



Mean Difference Kmax Change = 2.6 D
Meets definition of success, p<0.0001

Corneal Ectasia

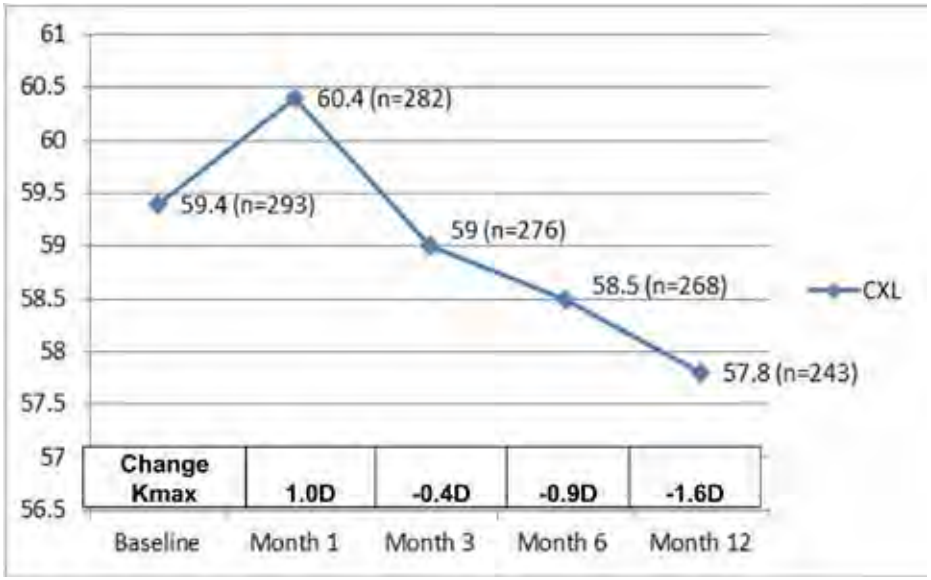


Mean Difference Kmax Change = 1.4 D
Meets definition of success, p<0.0001

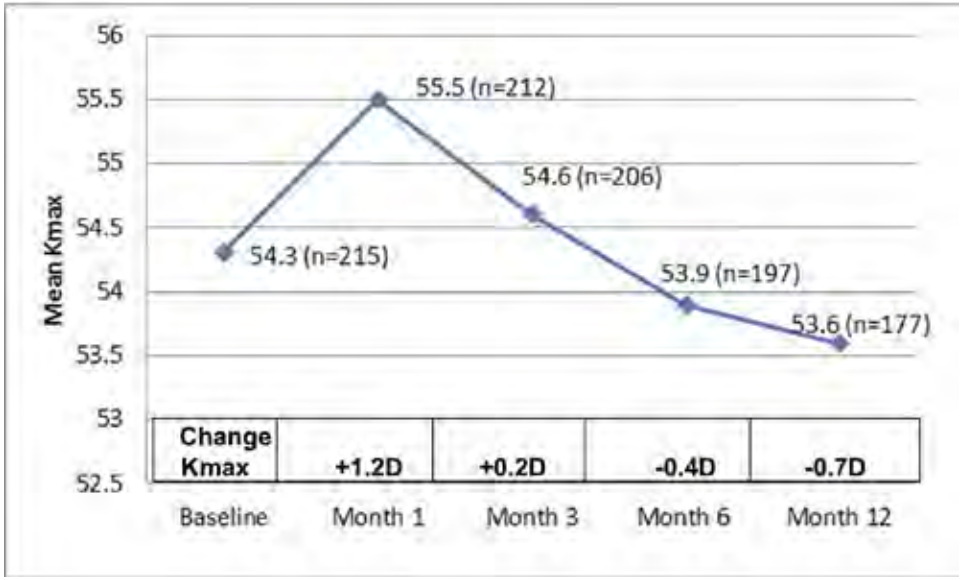
*Includes LOCF

Mean K_{max} – All CXL Eyes

Progressive Keratoconus

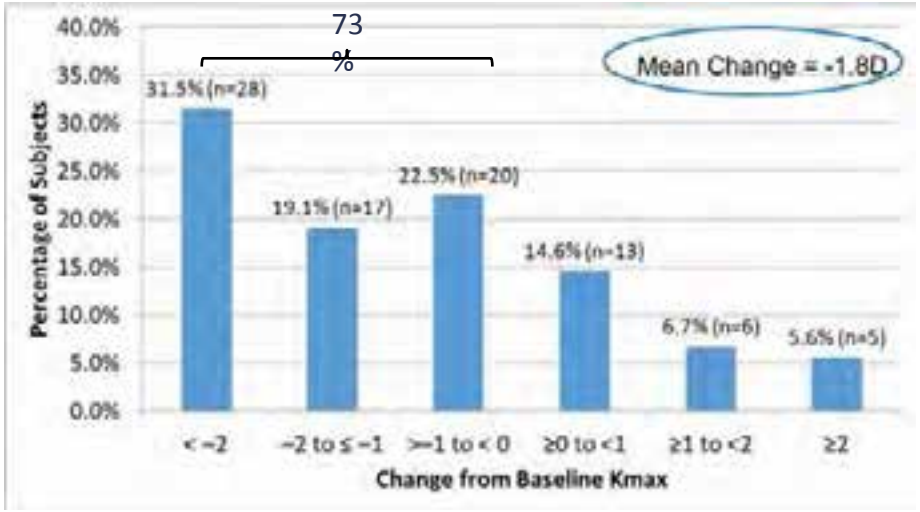


Corneal Ectasia



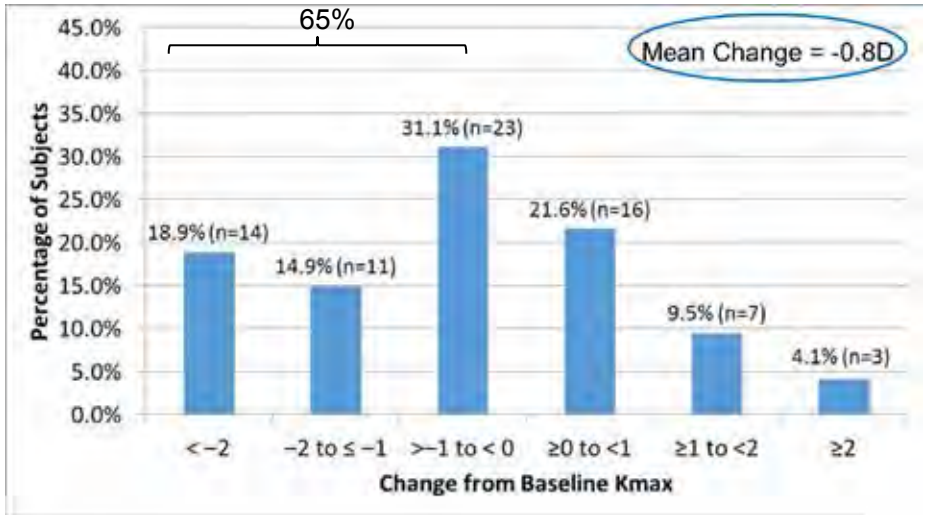
Distribution of Change – Observed Eyes

Progressive Keratoconus



N=89, Month 12

Corneal Ectasia



N=74, Month 12

Pediatric Efficacy Progressive Keratoconus (Pooled)

Visit	Statistic	Age 16 – 21 yrs		Age < 16 yrs	
		CXL Group (N=15)	Control Group (N=11)	CXL Group (N=4)	Control Group (N=3)
Baseline	n	15	11	4	3
	Mean	66.4	64.8	57.3	71.9
Change from Baseline					
Month 12 LOCF	n	15	11	4	3
	Mean	-4.4	2.0	-1.6	2.0
Month 12 Observed	n	15	0	3	0
	Mean	-4.4	--	-1.6	--

Treatment Emergent Adverse Events (TEAEs)

Safety assessed in 512 eyes undergoing crosslinking

The most common ocular adverse reactions in CXL-treated eyes were corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision

The majority of adverse events reported resolved during the first month.

Example of how haze can present over time on Scheimpflug imaging

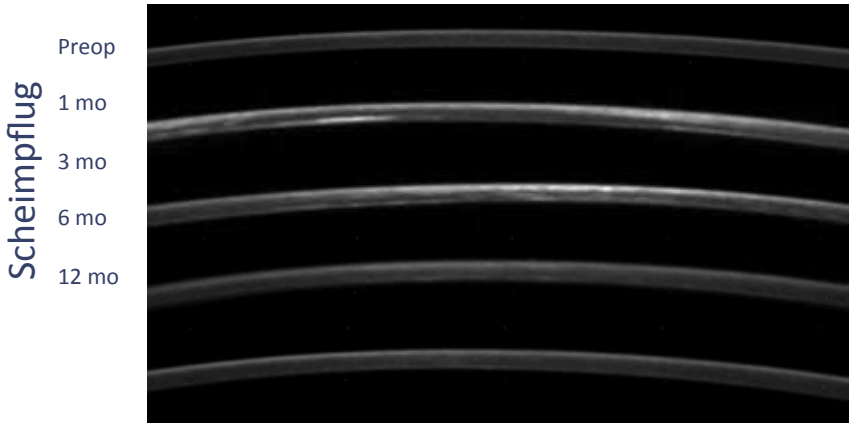


Image from Hersh Vision Group

Most Common (≥1%) Ocular Adverse Reactions in CXL-Treated Study Eye in the Pooled Randomized Safety Population – N (%) (Page 1/2)

	Progressive Keratoconus Studies		Other Clinical Experience	
Preferred Term	**CXL Group (N=102)[1]**	**Control Group (N=103)[1]**	**CXL Group (N=91)[1]**	**Control Group (N=88)[1]**
Anterior chamber cell	2 (2)	0	2 (2)	1 (1)
Anterior chamber flare	4 (4)	0	5 (6)	2 (2)
Asthenopia	1 (1)	1 (1)	2 (2)	0
Blepharitis	0	0	0	1 (1)
Corneal disorder	3 (3)	1 (1)	3 (3)	0
Corneal epithelium defect	24 (24)	1 (1)	26 (28)	3 (3)
Corneal oedema	3 (3)	0	3 (3)	0
Corneal opacity[2]	65 (64)	9 (9)	65 (71)	8 (9)
Corneal striae	24 (24)	12 (12)	8 (9)	6 (7)
Corneal thinning	1 (1)	2 (2)	0	0
Diplopia	2 (2)	1 (1)	1 (1)	0
Dry eye	6 (6)	2 (2)	13 (14)	4 (5)
Eye complication associated with device	2 (2)	0	1 (1)	0
Eye discharge	2 (2)	1 (1)	0	0
Eye oedema	7 (7)	0	0	0
Eye pain	17 (17)	3 (3)	24 (26)	0

1) Results are presented as the number (%) of subjects with an event from baseline to Month 3.
2) Almost all cases of corneal opacity were reported as haze.

Most Common (≥1%) Ocular Adverse Reactions in CXL-Treated Study Eye in the Pooled Randomized Safety Population – N (%) (Page 2/2)

	Progressive Keratoconus Studies		Other Clinical Experience	
Preferred Term	**CXL Group (N=102)[1]**	**Control Group (N=103)[1]**	**CXL Group (N=91)[1]**	**Control Group (N=88)[1]**
Eye pruritus	2 (2)	0	0	0
Eyelid oedema	5 (5)	0	5 (6)	1 (1)
Foreign body sensation in eyes	15 (15)	1 (1)	13 (14)	2 (2)
Glare	4 (4)	1 (1)	2 (2)	0
Halo vision	1 (1)	0	2 (2)	0
Keratitis	1 (1)	0	3 (3)	0
Lacrimation increased	5 (5)	0	9 (10)	1 (1)
Meibomian gland dysfunction	1 (1)	1 (1)	3 (3)	2 (2)
Ocular discomfort	0	0	8 (9)	0
Ocular hyperaemia	14 (14)	2 (2)	7 (8)	4 (5)
Photophobia	11 (11)	0	17 (19)	0
Punctate keratitis	25 (25)	8 (8)	18 (20)	3 (3)
Vision blurred	16 (16)	2 (2)	15 (17)	4 (5)
Visual acuity reduced	10 (10)	9 (9)	10 (11)	1 (1)
Visual impairment	3 (3)	2 (2)	4 (4)	1 (1)
Vitreous detachment	2 (2)	0	0	0

1) Results are presented as the number (%) of subjects with an event from baseline to Month 3.
Headache was reported in between 4 to 8% of treated patients.

Loss of BSCVA

Transient reduction in BSCVA ≥15 letters at Week 1 visit observed in higher proportion of treatment subjects for both indications

- Consistent with corneal debridement and expected time course of corneal healing

Improved at Month 1

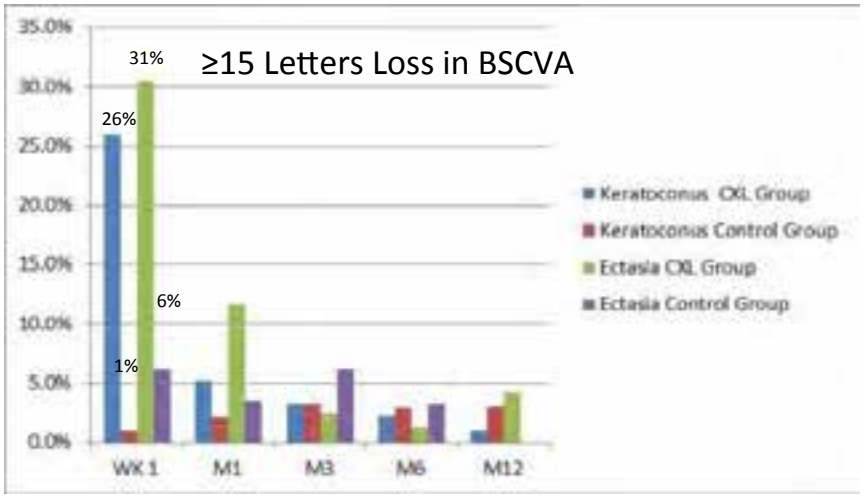
Month 12

- 4 CXL subjects lost

  ≥15 letters BSCVA

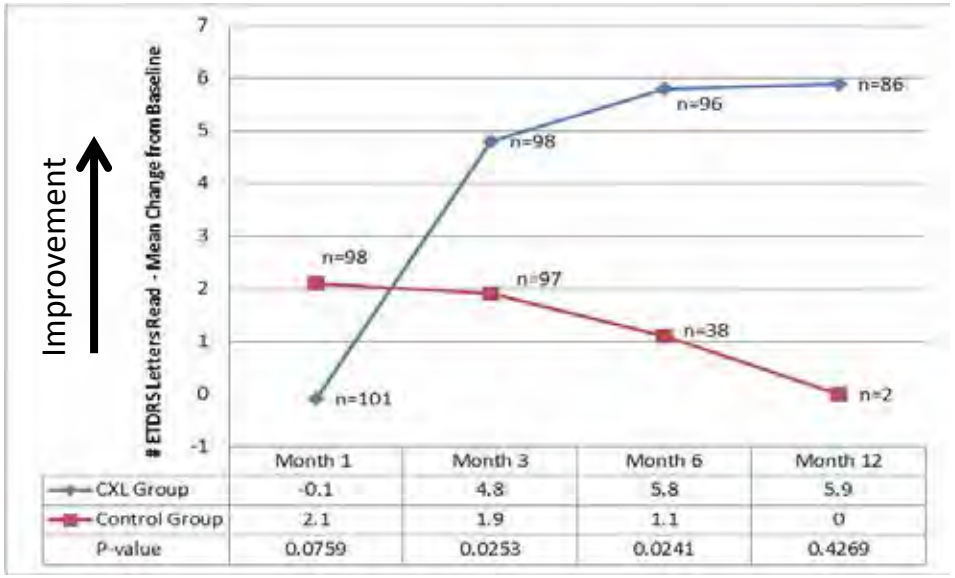
  - 1/83 Keratoconus
  - 3/72 Ectasia

No predictive preoperative characteristics



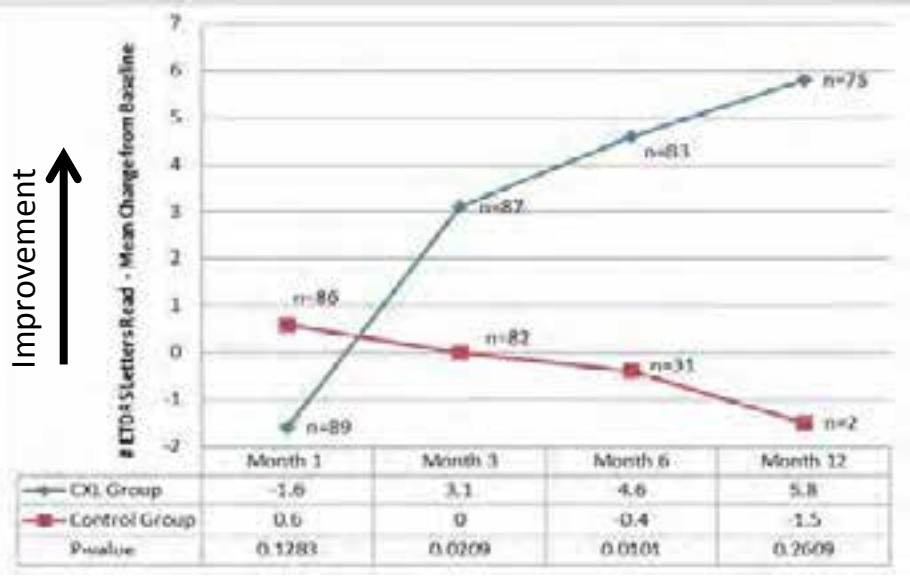
BSCVA - #ETDRS Letters Read

Progressive Keratoconus



	Month 1	Month 3	Month 6	Month 12
CXL Group	-0.1	4.8	5.8	5.9
Control Group	2.1	1.9	1.1	0
P-value	0.0759	0.0253	0.0241	0.4269

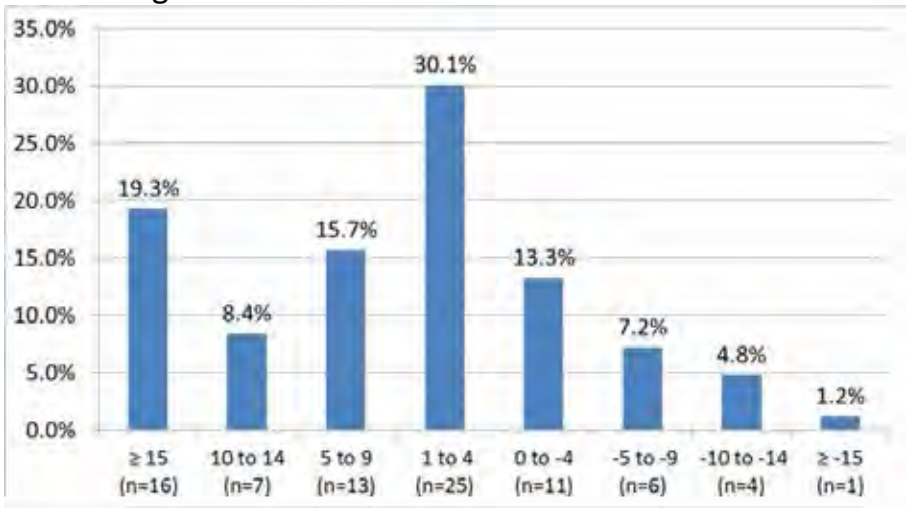
Corneal Ectasia



	Month 1	Month 3	Month 6	Month 12
CXL Group	-1.6	3.1	4.6	5.8
Control Group	0.6	0	-0.4	-1.5
P-value	0.1283	0.0209	0.0101	0.2609

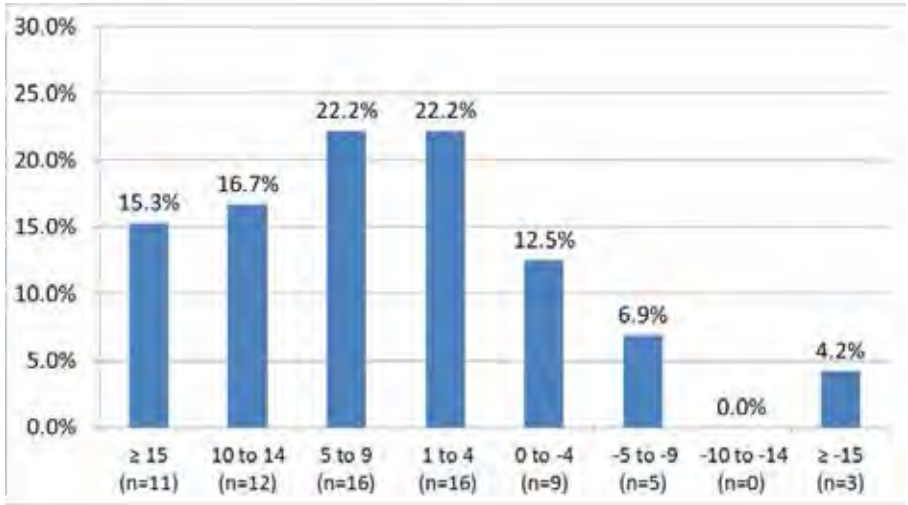
BSCVA Categorical Change Month 12

Progressive Keratoconus



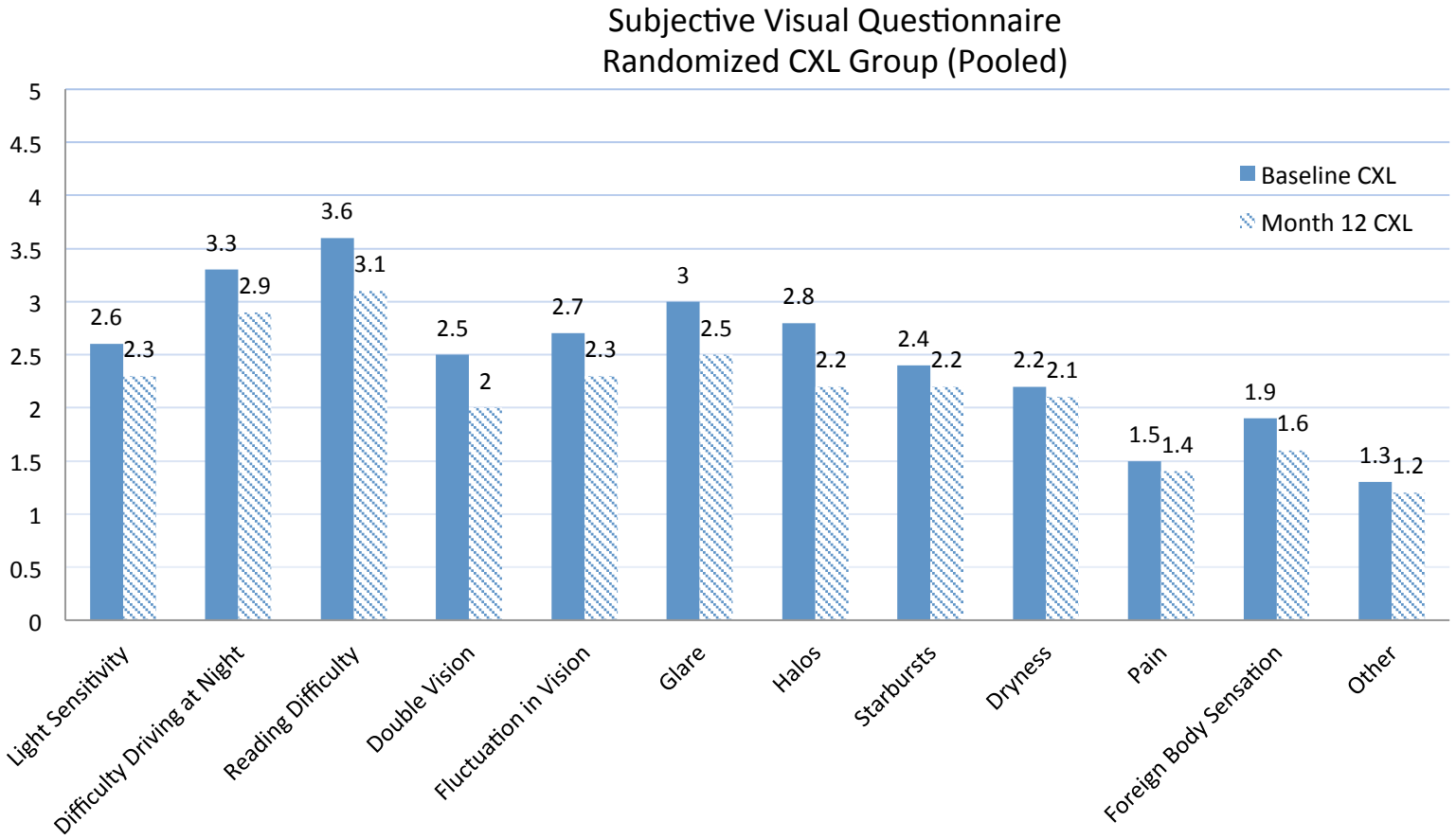
Mean Change = +5.9 Letters
Observed Subjects (n=83)

Corneal Ectasia



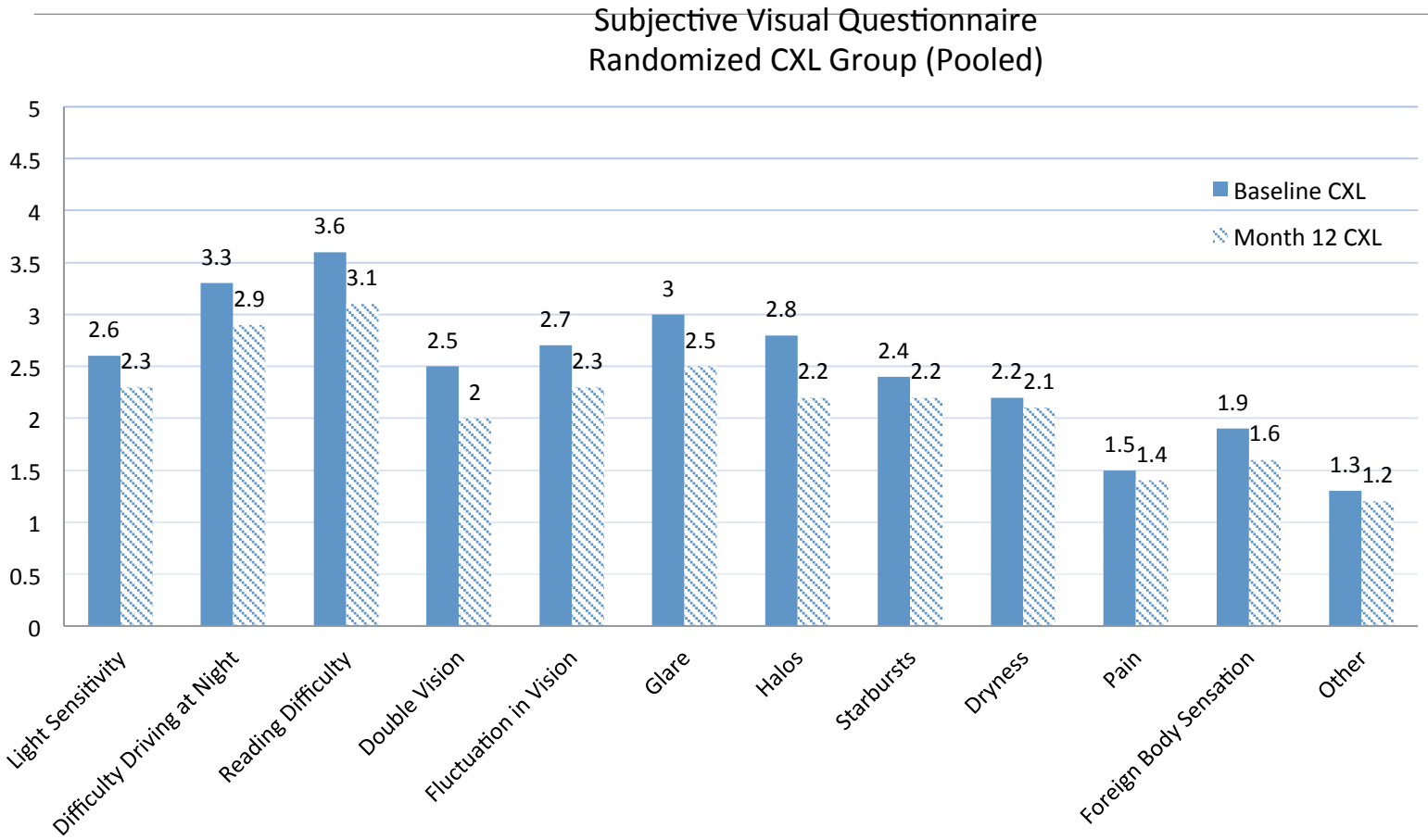
Mean Change = +5.8 Letters
Observed Subjects (n=72)

Subjective Vision Questionnaire Keratoconus



observed data

Subjective Vision Questionnaire Keratoconus



observed data

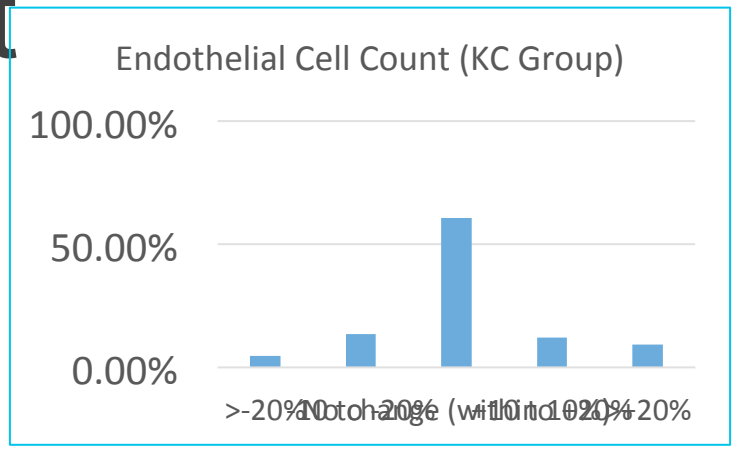
Endothelial Cell Count

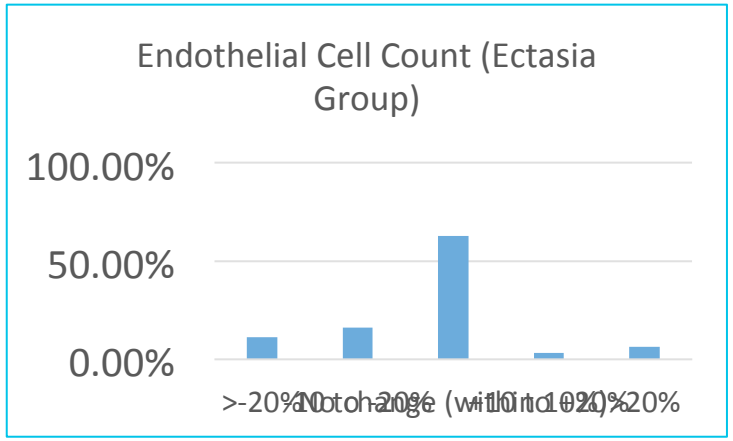
Keratoconus (Pooled)	Baseline (ECD)	3mo (ECD)	Change from Baseline 3mo	12 mo (ECD)	Change from Baseline 12 mo
Treatment (n=66)	2622 +/- 370	2551 +/- 343	**-72 (-2.7%)**	2653 +/- 348	**+31 (+1.2%)**
Control (n=86)	2575 +/- 410	2598 +/- 424	**+24 (+0.9%)**		**na**

Ectasia (Pooled)	Baseline (ECD)	3mo (ECD)	Change from Baseline 3mo	12 mo (ECD)	Change from Baseline 12 mo
Treatment (n=62)	2469 +/- 437	2418 +/- 340	**-51 (-2.1%)**	2357 +/- 364	**-112 (-4.5%)**
Control (n=71)	2594 +/- 431	2541 +/- 395	**-53 (-2.1%)**		**na**

*Safety population, observed data

Note: scatter in data likely secondary to difficulty obtaining specular microscopy in population





Conclusions

- CXL treatment decreases the progression of keratoconus that naturally occurs in KC and which may necessitate corneal transplantation
- CXL procedure with riboflavin provided statistically significant and clinically meaningful effects
- CXL treatment was safe and well tolerated in subjects
- Based on Avedro's data, Photrexa® Viscous, Photrexa ® and KXL ® System for use in corneal cross-linking offers a safe and clinically meaningful treatment for progressive keratoconus