Quantitative Analysis of Trans-Epithelial Corneal Riboflavin Loading

Roy Rubinfeld, MA, MD,
Jonathan Talamo, MD,
Doyle Stulting, MD, PhD

Affiliations

Dr. Rubinfeld: Re:Vision Private Practice and Department of Ophthalmology, Georgetown University Medical School/Washington Hospital Center, Washington, DC
Dr. Stulting: Stulting Research Center, Woolfson Eye Institute, Atlanta, GA, Professor of Ophthalmology Emeritus, Emory University
Dr. Talamo: Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, MA

Financial Interests

R. Rubinfeld

- CXL Ophthalmics
- CurveRight, LLC
- CXLUSA, LLC

J. Talamo

- Abbott Medical Optics
- Aura Biosciences
- Cowen and Company
- CXL Opthalmics
- Intersystems
- Optimedica Corporation
- Shire
- SV Life Sciences Advisors
- Wavetec Vision

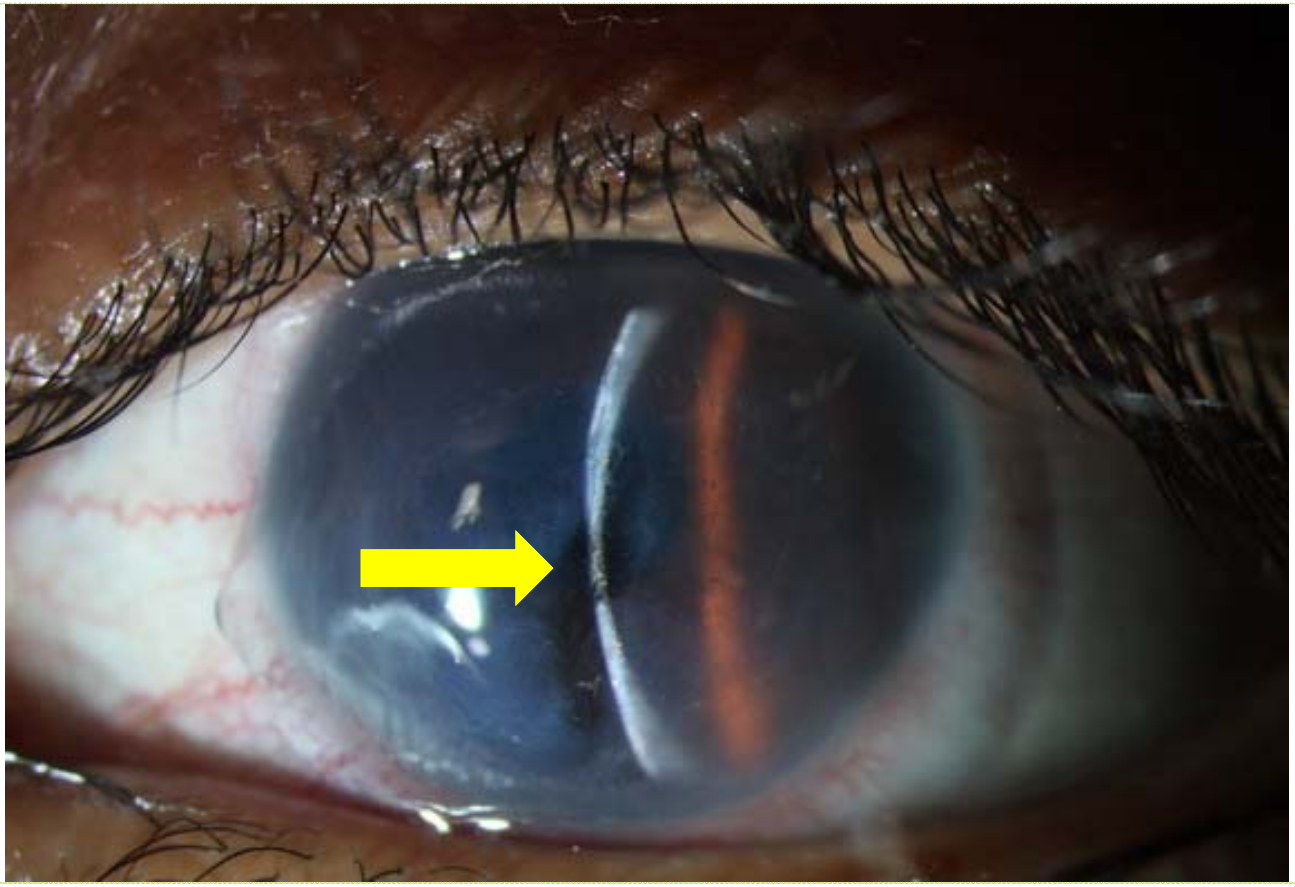
D. Stulting

- Abbott Medical Optics
- Alcon Laboratories
- Allergan
- Calhoun Vision
- Cambium Technologies
- Eye-Yon
- Ocumetrics
- Ophtec
- Optovue
- Shire
- TearLab

Background

- Dresden protocol effective, epi removal risks
- Advantages of less invasive transepi CXL
  - Return to preop vision, function POD 1
  - Log scale shift in safety and risk/benefit
  - Treat upon diagnosis

Perforation after Epi-Off CXL



SPECIAL SECTION: CROSSLINKING

Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results

Aldo Caporossi, MD, FRCS, Cosimo Mazzotta, MD, PhD, Anna Lucia Paradiso, MD, Stefano Baiocchi, MD, PhD, Davide Marigliani, MD, Tomaso Caporossi, MD

PURPOSE: To assess the clinical results of transepithelial collagen crosslinking (CXL) in patients 26 years and younger with progressive keratoconus suitable for epithelium-off (epi-off) CXL.

SETTING: Department of Ophthalmology, Siena University Hospital, Siena, Italy.

DESIGN: Prospective case series.

METHODS: The study included 26 eyes (26 patients) treated by transepithelial (epithelium-on) CXL. The mean age was 22 years (range 11 to 26 years) (10 younger than 18 years; 16 between 19 years and 26 years). Preoperative and postoperative examinations included uncorrected (UDVA) and corrected (CDVA) distance visual acuities, simulated maximum keratometry (K), coma and spherical aberration, and corneal optical coherence tomography optical pachymetry. The solution for transepithelial CXL (Ricrolin TE) comprised riboflavin 0.1%, dextran 15.0%, trometamol (Tris), and ethylenediaminetetraacetic acid. Ultraviolet-A treatment was performed with the Caporossi Baiocchi Mazzotta X Linker Vega at 3 mW/cm^2.

RESULTS: After relative improvement in the first 3 to 6 months, the UDVA and CDVA gradually returned to baseline preoperative values. After 12 months of stability, the simulated maximum K value worsened at 24 months. Coma aberration showed no statistically significant change. Spherical aberration increased at 24 months. Pachymetry showed a progressive, statistically significant decrease at 24 months. Fifty percent of pediatric patients were retreated with epi-off CXL due to significant deterioration of all parameters after 12 months of follow-up.

CONCLUSIONS: Functional results after transepithelial CXL showed keratoconus instability, in particular in pediatric patients 18 years old and younger; there was also functional regression in patients between 19 years and 26 years old after 24 months of follow-up.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2013; 39:1157–1163

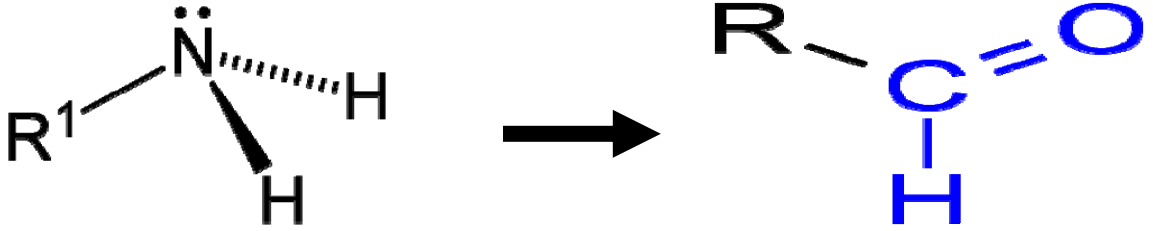
- Initial excitement
- Majority progressed @ 2 yr
- Published 2013

CXL Photochemistry

UVA Light
Energy
Source

Oxygen
Rate Limiting
Reagent

Riboflavin
Energy Transfer



Amide

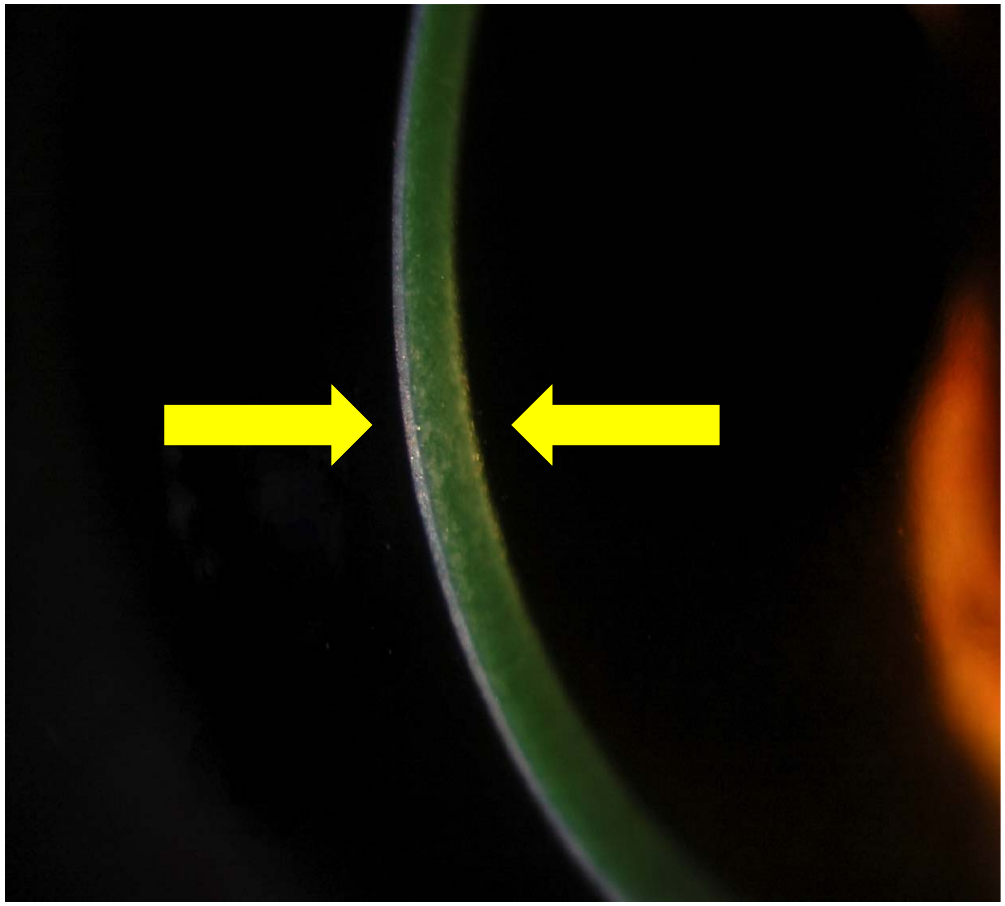
Aldehyde

Epi-On Success Requires

1. **Stroma**: Reliable, consistent riboflavin loading
2. **Epithelium:** Good UVA transmission, relatively clear of riboflavin, intact, non-edematous,
3. **Oxygen:** Rate limiting reagent if 1,2 present

Clear Epithelium, Loaded Stroma

No Visible Green Color in Epithelium



Well Loaded Green Stroma

CXL USA

Purpose

- Evaluate corneal penetration of riboflavin using a novel, proprietary, patent pending formulation and delivery system
- Compare results to those using a commercially available product
- Correlate slit lamp findings with quantitative measurements of corneal riboflavin concentration

Materials

- *Absorption Systems, Inc*., San Diego California
- 3-4.4 kg New Zealand white rabbits
- Group 1: ParaCel™ q90 sec x 4 min., then VibeX Xtra™ q90 sec x 6 min. (per label)[1]
- Group 2: Proprietary prep x 30-60 sec. then CXLUSA/CXLO riboflavin[2] via sponge with drops q1-3 min x 10 min.

[1]Trans-epithelial Cross-Linking Kit, Avedro, Inc.
[2]Proprietary system from CXL Ophthalmics utilized by CXLUSA investigators under a physician-sponsored IRB approved study.

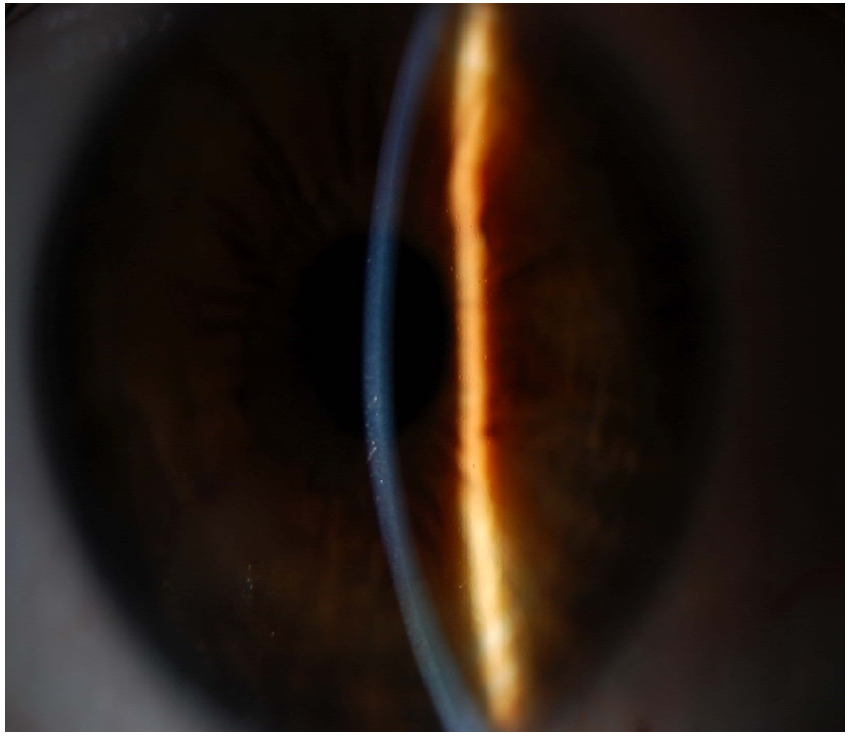
Methods

- Slit lamp photos at baseline
- Riboflavin application
- Masked grading and slit lamp photos at 10, 15, and 20 min. (2X labeling)
- Euthanasia, epithelial removal, and riboflavin assay by liquid chromatography/tandem mass spectrometry (LC-MS/MS) 22-25 min. after application

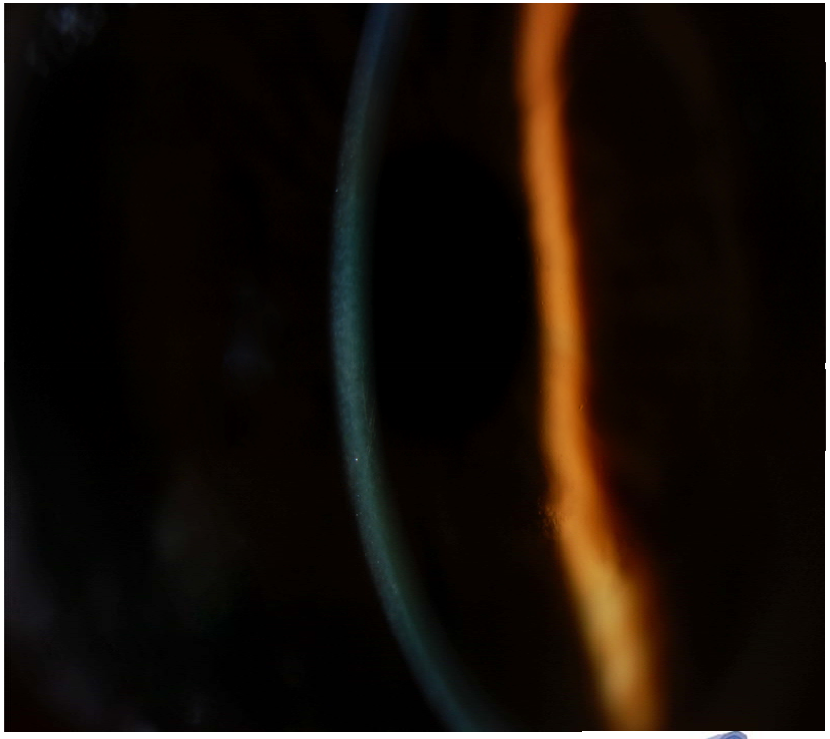
Slit Lamp Grading System

Grade	Findings
I	Mild green tint just visible
II	Substantial green visible
III	Obvious green color
IV	Bright green appearance
V	Strong, bright green color

Grade 0/V

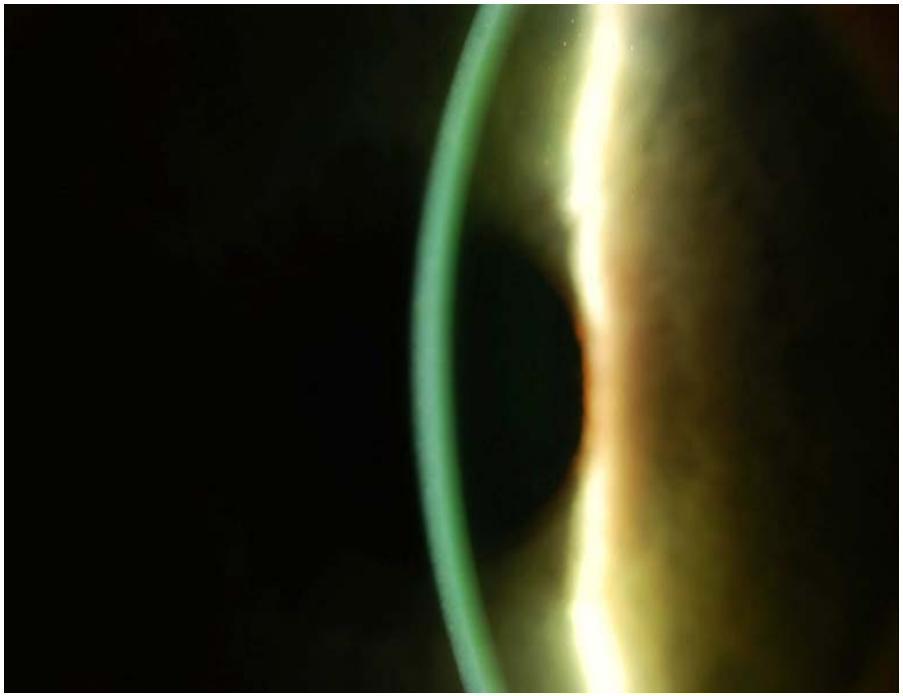


Grade I/V



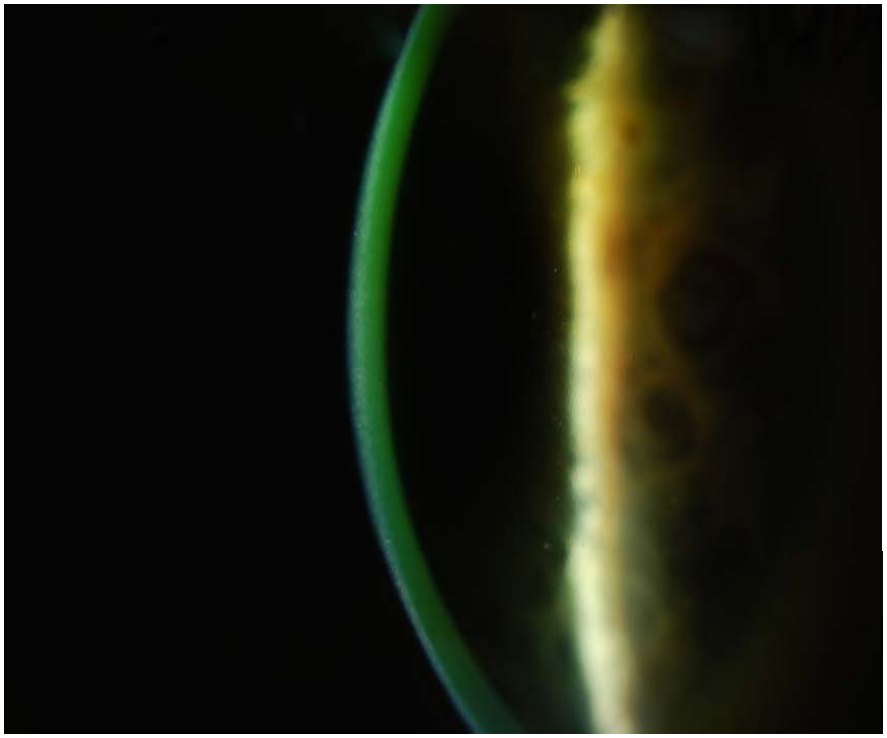
Grade II/V

Grade III/V

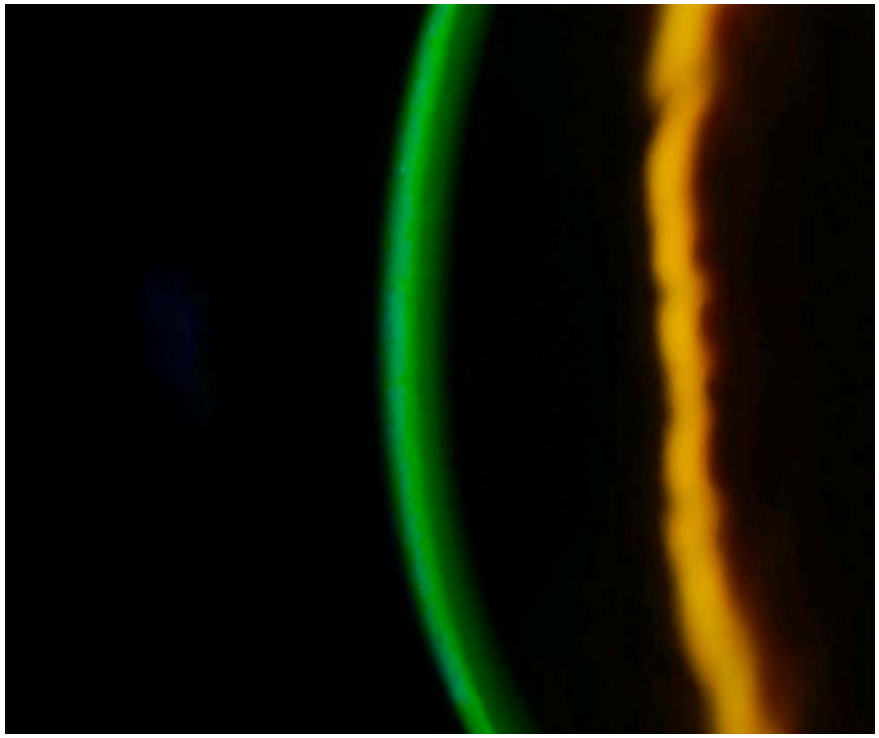


CXL USA

Grade IV/V



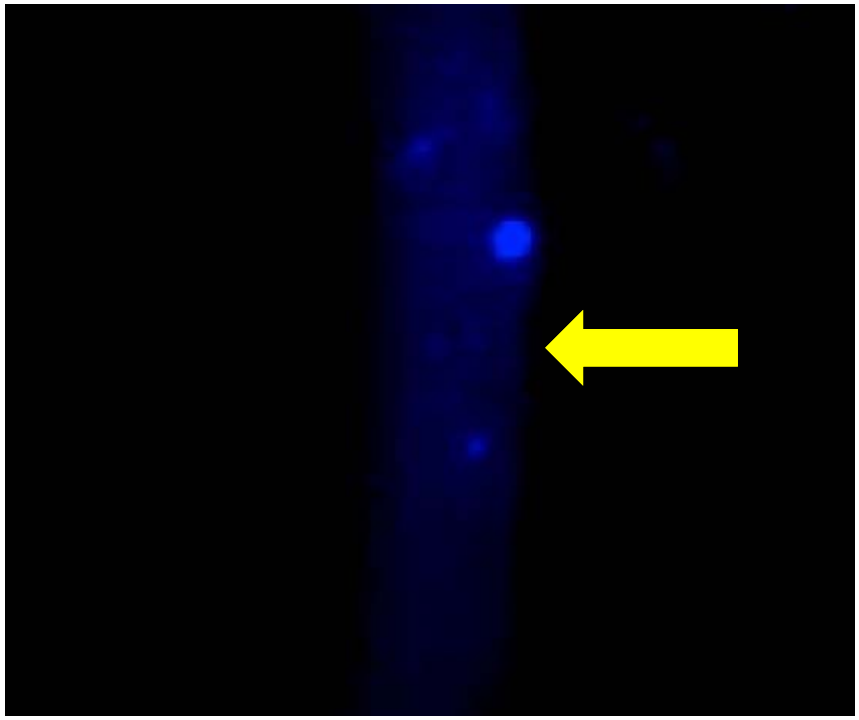
Grade V/V



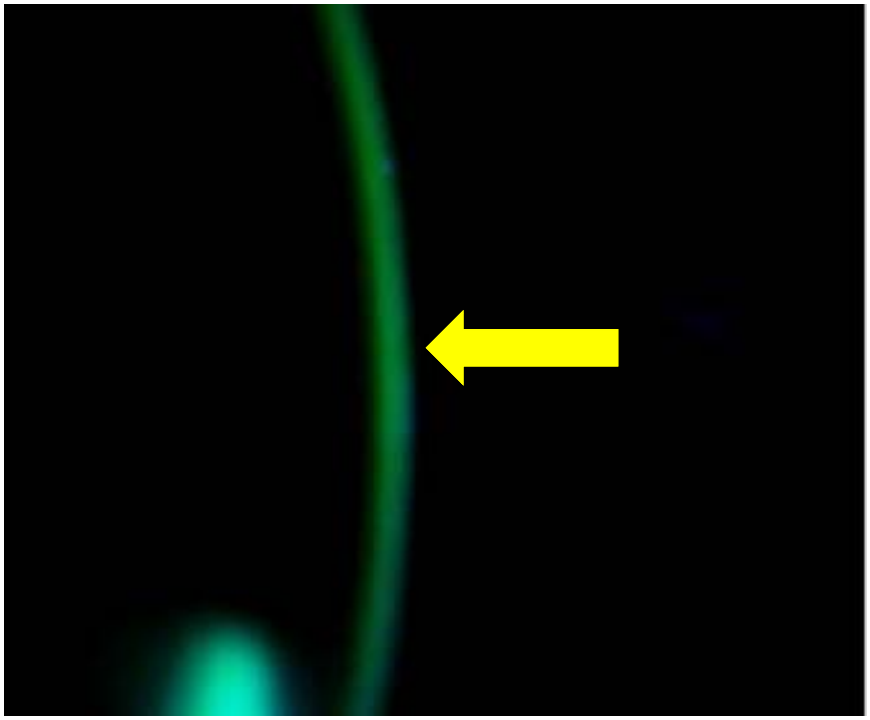
CXL USA

Ex Vivo Rabbit Cornea SL Photos

Paracel™-VibeX Xtra™
At 20 min

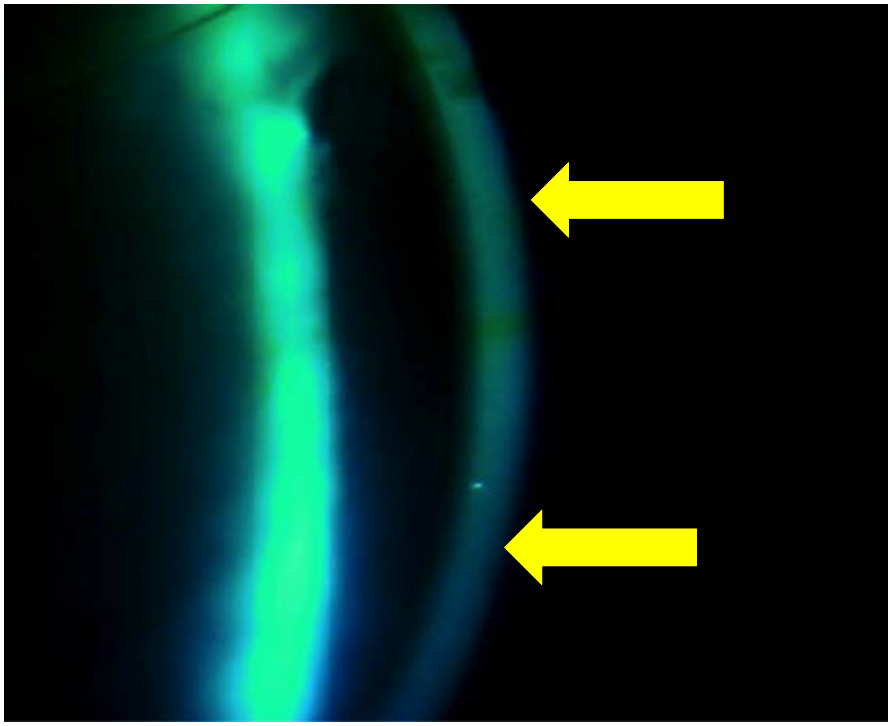


CXLUSA Formulation
At 10 Min

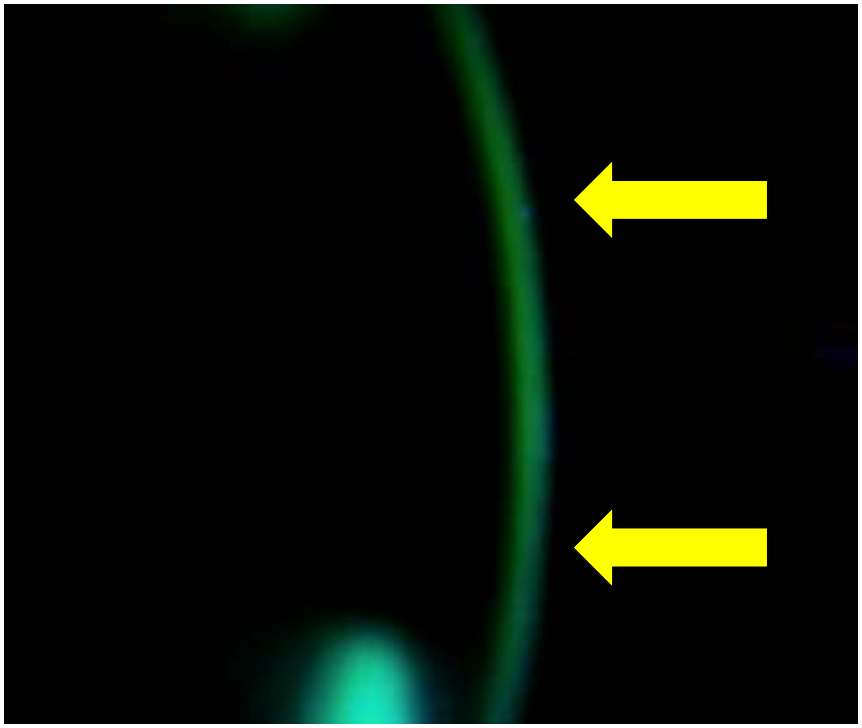


Ex Vivo Rabbit Cornea SL Photos

Paracel™-VibeX Xtra™
At 20 min

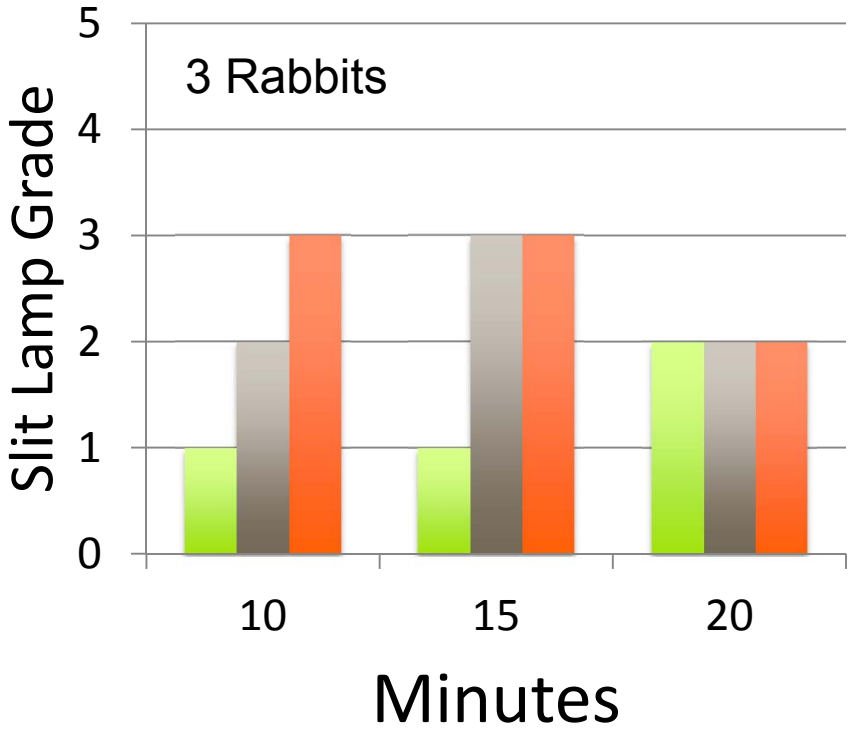


CXLUSA Formulation
At 10 Min

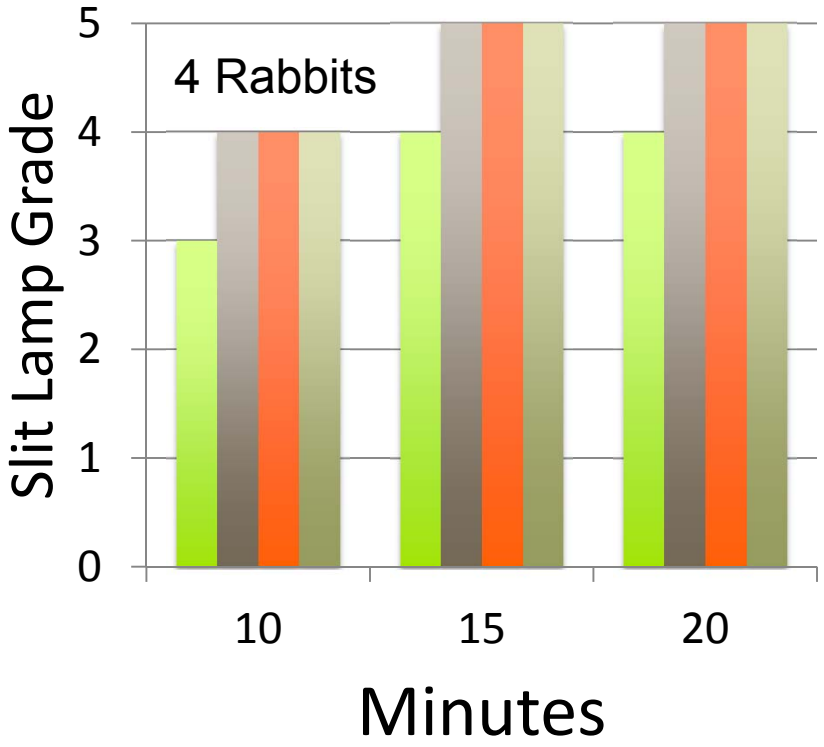


Slit Lamp Grade

Paracel™-VibeX Xtra™

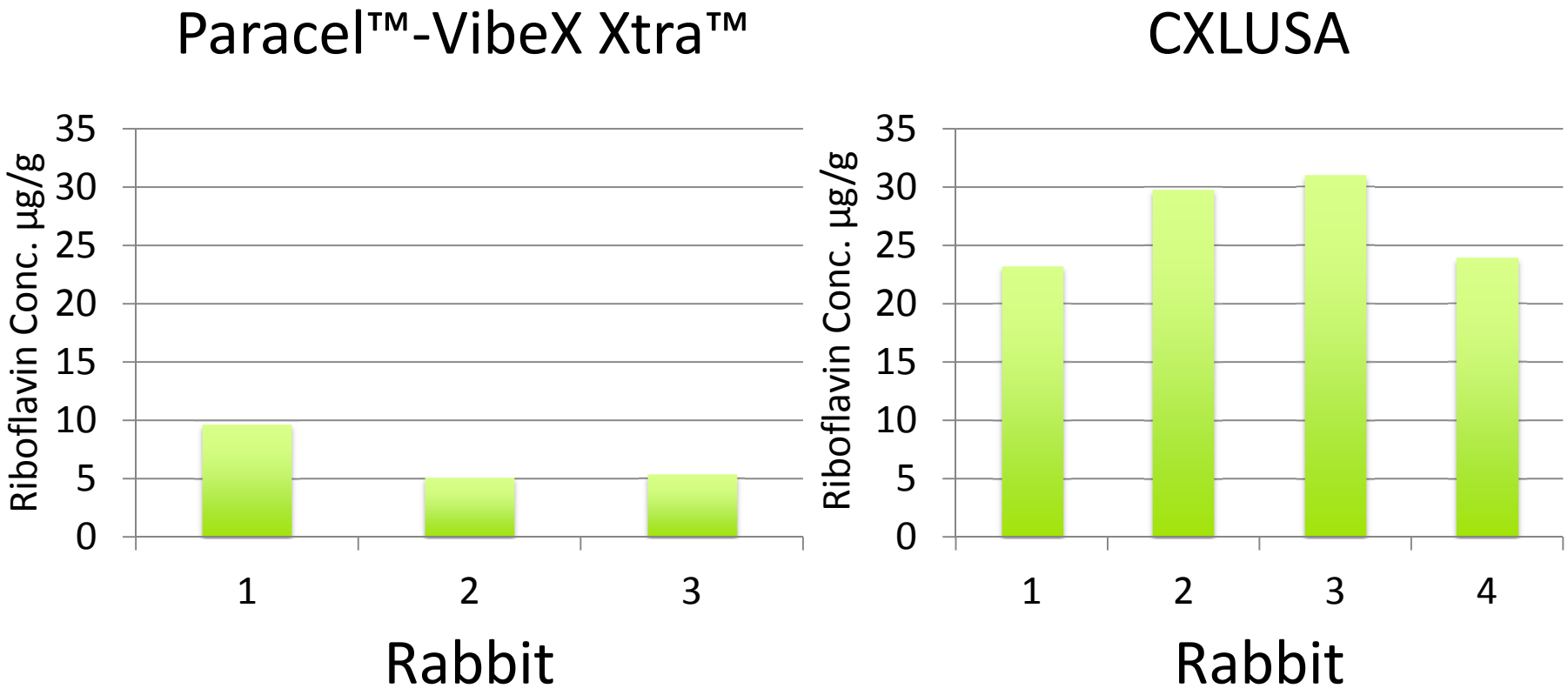


CXLUSA

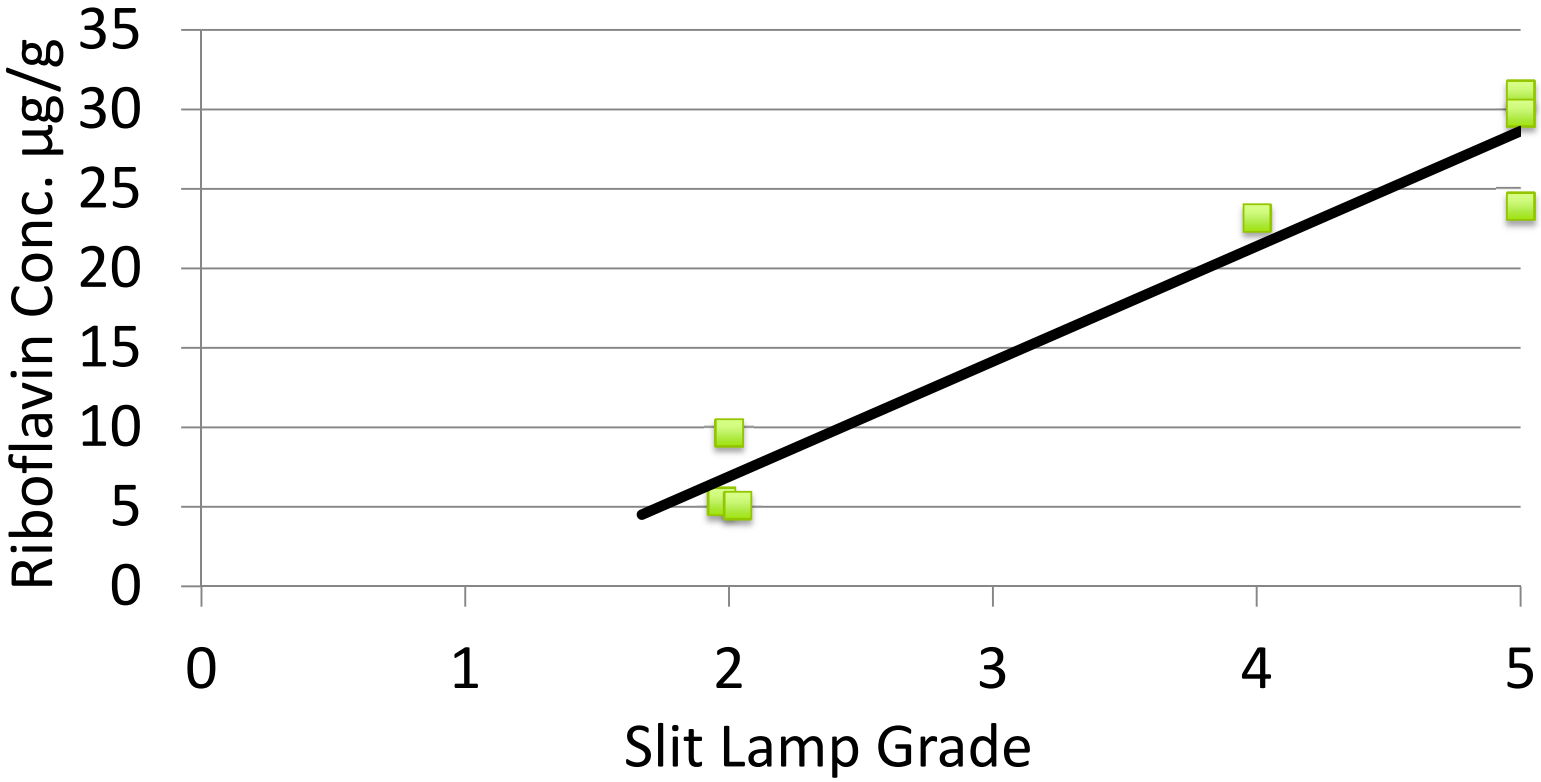


Riboflavin Concentration

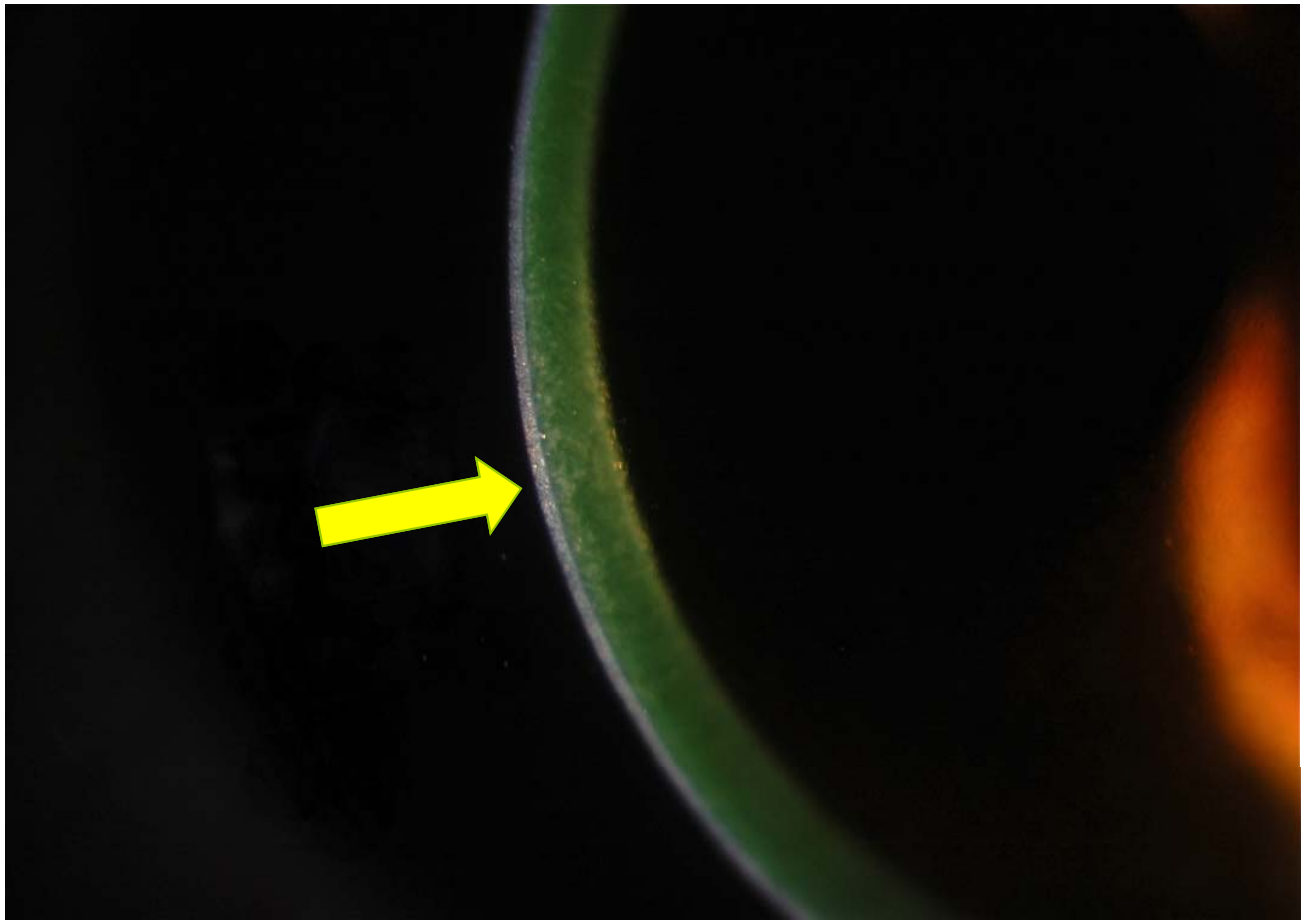
(µg/g at 20-25 min.)



Correlation Between SLE and LC-MS/MS



15 Min Epi-On Human CXLUSA



Conclusions

- CXLUSA Riboflavin system produces a 4.0-fold greater corneal stromal concentration in the rabbit than commercially available system
- This correlates well with the 4.3-fold greater concentration of stromal riboflavin produced in the human by the epi-off technique [Gore et. al., 2015; IOVS 56:5006] compared to the same commercially available system used in this study

Conclusions

- Failure of previous epi-on protocols to halt progression of ectatic corneal disease may, in part, be due to inadequate corneal riboflavin concentration
- Slit lamp exam provides a valid estimate of stromal riboflavin concentration that can be used to assure adequate corneal loading prior to UVA exposure

Conclusions

- The CXL technique used by CXLUSA may achieve corneal stiffening similar to that achieved by the classical Dresden epi-off technique without the risk of epithelial removal
- Early 2-year clinical data suggest this is a valid hypothesis


Thank You