Multicenter, Randomized, Sham-Controlled, Phase 3 Study to Evaluate Efficacy & Safety of Epithelium-On CXL in Keratoconus Subjects 8 to 45 Years

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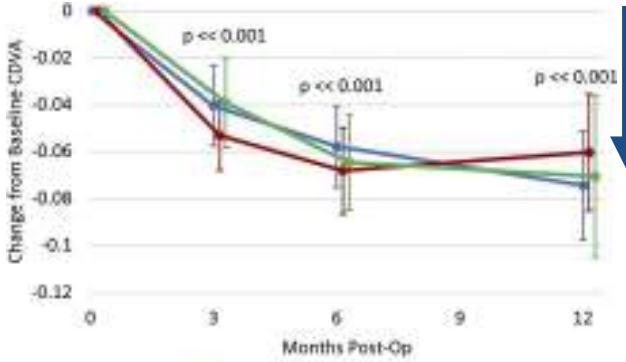
EpiSmart® Clinical Advantages

- True Epithelium-On
  - No need for supplemental Oxygen
  - No need for goggles
  - No need for epithelium “loosening” agents
- Excellent Full-Thickness, Limbus to Limbus Riboflavin saturation (***RiboStat®***)
- Ability to perform Simultaneous, Bilateral Treatments
- Rapid return to activities of daily living
  - 24-48 hours mild discomfort
    - No need for narcotics

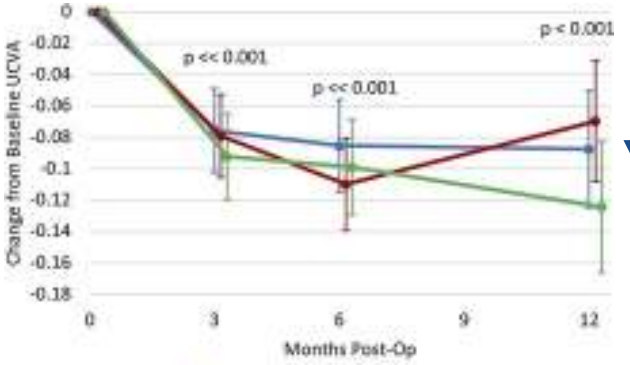
- Safety profile (Phase 2) similar to prescription dry eye medication

Summary of Phase 2 Results (n=1605)

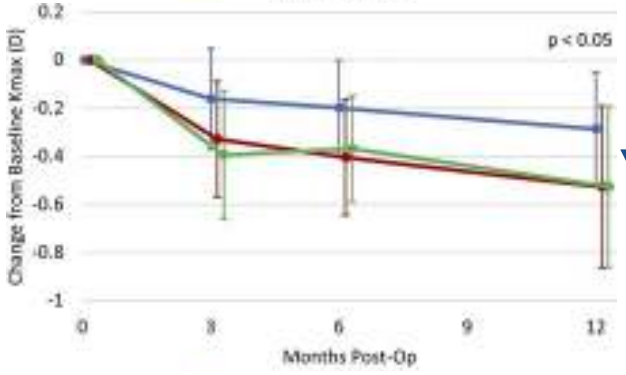
Robust improvement in VA, Kmax flattening, no corneal thinning



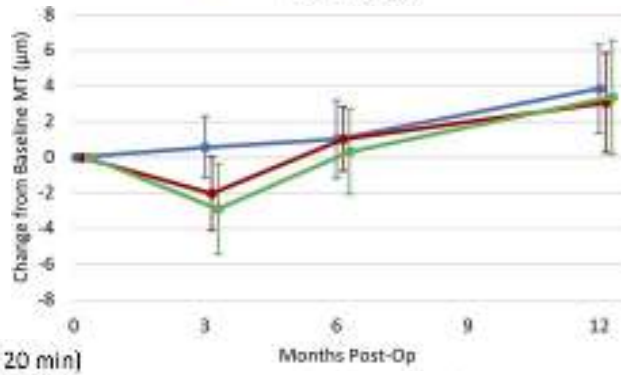
Corrected VA improved



Uncorrected VA improved



Kmax decreased



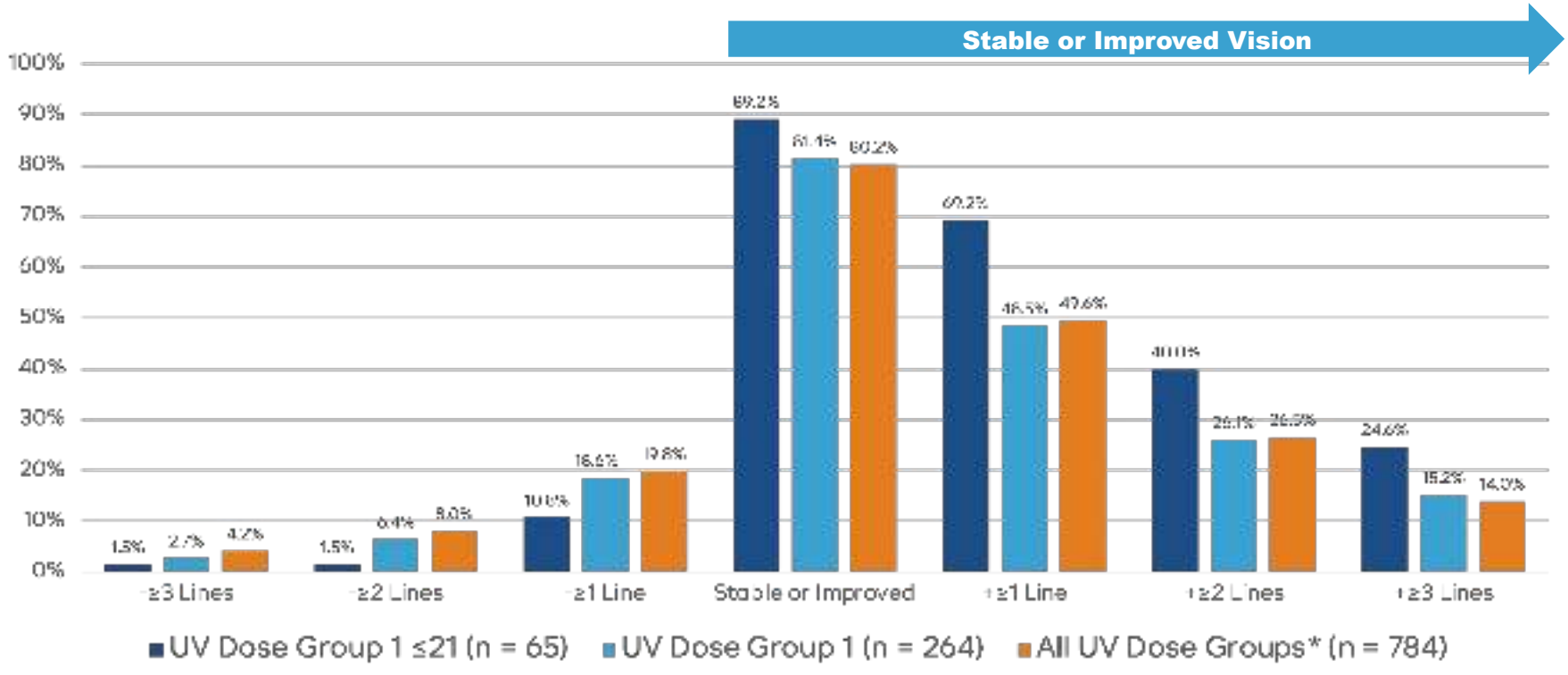
Corneal thickness: no change

Group 1 (2.4 J/cm2; 20 min)
Group 2 (3.6 J/cm2; 20 min)
Group 3 (3.6 J/cm2; 30 min)

Cornea 42(7):p 858-866, July 2023.

CXL-005: Responder Analysis

81% of patients stable or improved vision; 89% for those ≤21 years old



*Three UV dose groups were examined in Phase 2.

The EpiSmart System

Fully Patent-Protected **Drug** and **Device** Components

EpiPrep Applicators

- **Wand** enhances epithelial permeability without disruption

- **Loading sponge** maintains drug concentration during stromal loading

RiboStat Drug

Novel Fixed-Dose Combination:

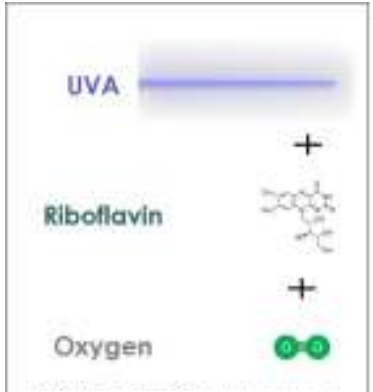
riboflavin-5'-phosphate and sodium iodide

UV-3000 Device

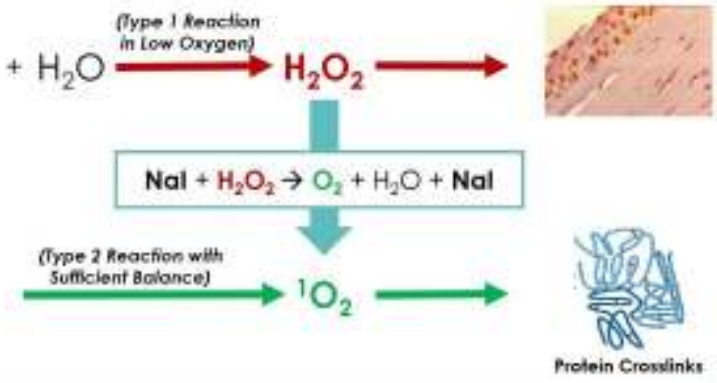
- **Optimal light cycling** for oxygen recovery
- Double head for **simultaneous bilateral treatment**

Key Features of RiboStat

- Highly concentrated Riboflavin (0.5%)
- Sodium Iodide (0.015%)
  - Enhances epithelial penetration
  - Stabilizes stromal Riboflavin
  - Breaks down hydrogen peroxide
    - Promotes desirable type 2 reaction



The EpiSmart system keeps these three components in balance

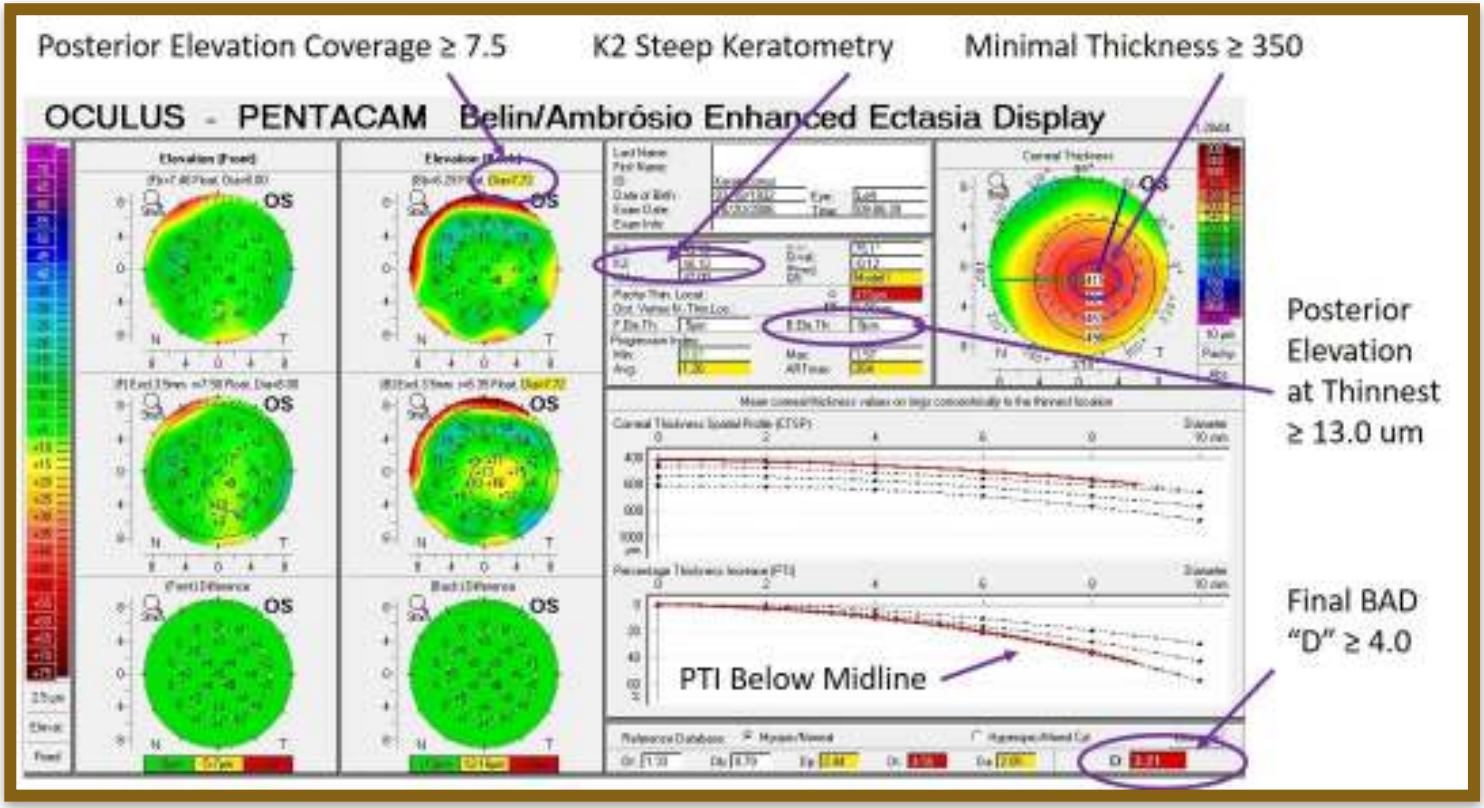


Iodide in Ribostat mediates an efficient CXL reaction, while preserving riboflavin and tissue

Unique Features of Phase III Trial

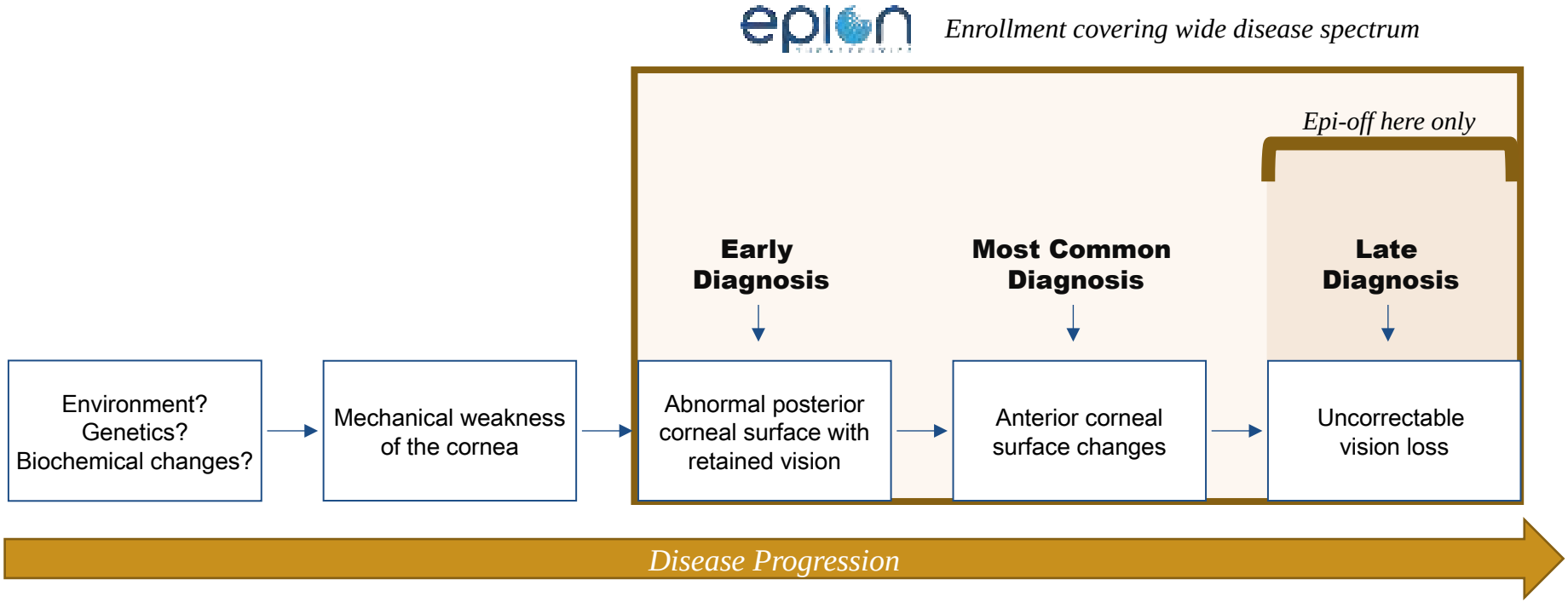
- Treatment on Initial Diagnosis
  - Dx confirmed by standardized Tomographic criteria
- Ability to treat both eyes simultaneously *(if both qualify)*
- 1:1 active *vs* sham randomization
  - Active "rescue" for documented progression
  - Active treatment (cross-over) at end of 12-month follow-up
- **Visual Acuity as the Primary Efficacy Endpoint**

Tomographic Inclusion Criteria



Treat on Diagnosis, Not Progression

Early diagnosis and treatment may prevent vision loss



Vision as Primary Efficacy Endpoints

- **PRIMARY EFFICACY ENDPOINT** - Proportion of subjects who *gain* 15 letters of BSCDVA measured with high-contrast ETDRS letters in primary active-treated eyes between baseline and Month 12, compared to sham-treated control eyes.
- **KEY SECONDARY ENDPOINT** – Average (mean) change from baseline to Month 12 in BSCDVA measured using high-contrast ETDRS letters in primary active-treated eyes, compared to sham-treated control eyes.
- **SECONDARY ENDPOINTS**:
  - Proportion who maintain or gain letters of BSCDVA
  - Average change from baseline in BSCDVA
  - Change from baseline to Month 12 in anterior radius of curvature from a 3.0 mm optical zone centered on the thinnest point (“A” parameter from Pentacam ABCD classification)

Why Vision as an Endpoint ?

Flattening is not always desirable

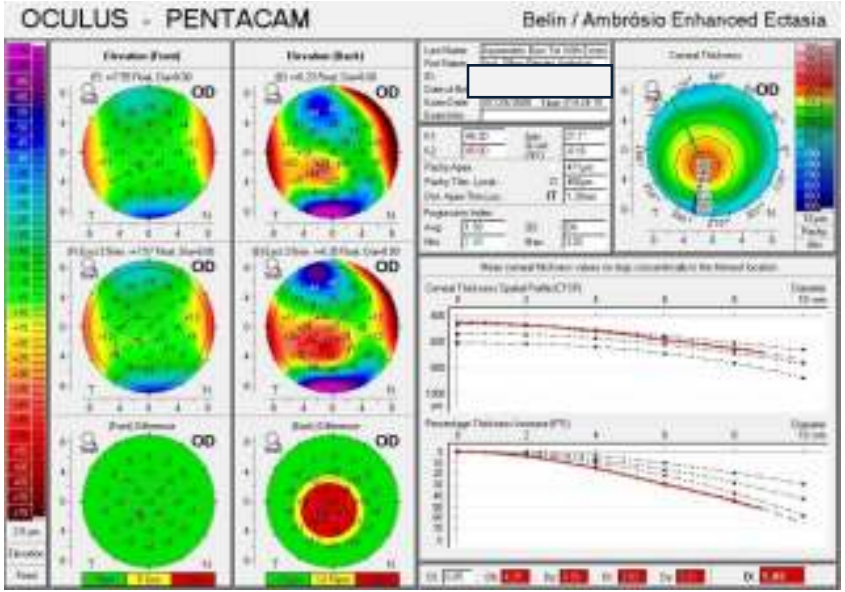
- Excessive flattening is associated with stromal haze, continued thinning and loss of BSCDVA
  - Henriquez MA, et. al. Long term corneal flattening after CXL in patients with progressive keratoconus. Clin Ophthalmol 2023; 17:1865-1875
    - Extreme flattening observed in 15.5% (7/45)
  - Padmanabhan P, Belin MW, Padmanaban V. Extreme corneal flattening following Collagen Crosslinking for previous Keratoconus. Euro J Ophthalmol 2021; 31:1546-1552
    - 7.85% of (43/548) eyes showed excessive flattening > 5.0 D
      - Duration of time after CXL was a significant predictor

Why Vision as an Endpoint ?

Flattening is not always desirable

- With earlier intervention and treating on diagnosis (*i.e. subclinical keratoconus*) significant flattening a “normal” or “near-normal” anterior corneal surface may not be desirable

- Improving or stabilizing visual function is always desirable and a patient-centric endpoint



Advanced subclinical KCN with normal visual acuity

EpiSmart Treatment Overview

Preparation

<1 Minute

Riboflavin Saturation

30 Minutes

Slit Lamp Check

~1 Minute

Photoreaction

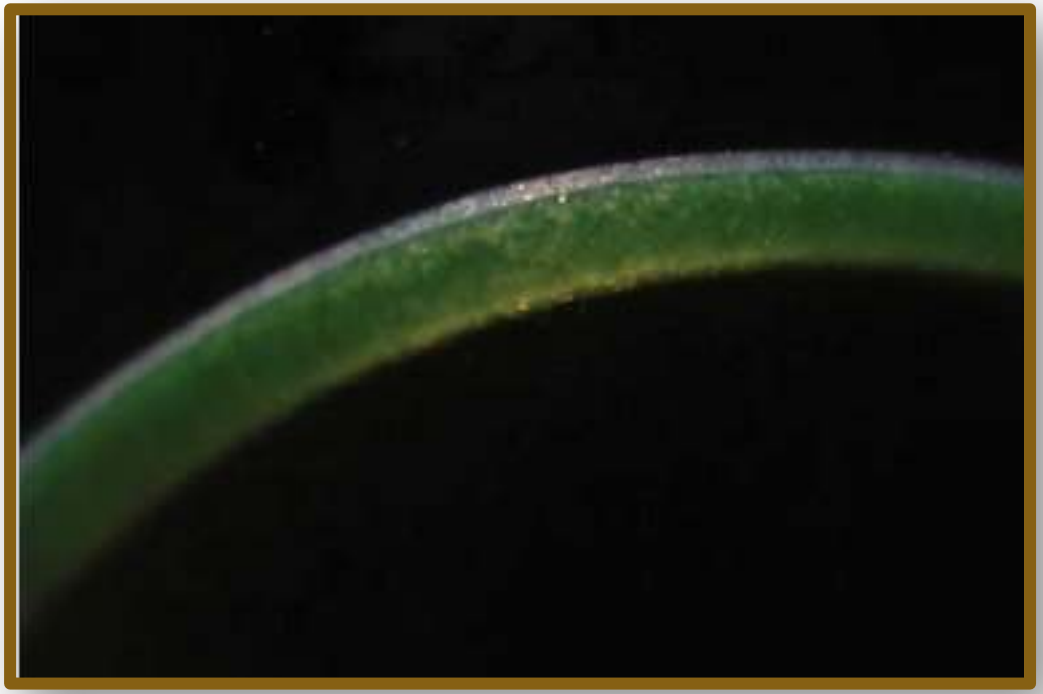
20 Minutes

- ~ 50 minutes average procedure time from start to finish **for both eyes**

Procedure - Loading

- **SATURATE** loading sponge with several drops of study drug and apply to cornea(s)
  - A saturated sponge should have a visible meniscus visible
  - Continue to apply study drug at a rate of 1 – 2 gtts every 2 minutes for 30 minutes
    - More frequently if needed to keep sponge visibly saturated

RiboStat Clinical Application



- 30 minutes of drug application every 2 minutes
  - To date, no subject needed supplemental application
  - All subjects to date at least 3.5 grading (1 – 5)
- Drops NOT applied during UVA treatment

Investigational Sites

Current Status of Phase III Trial

- Initiation date Oct, 2023
- 2 Trials
  - 400 subjects each
- Current enrollment *(as of Dec 31, 2025)*
  - **901 screened / 795 enrolled & treated subjects @ 26 sites**
  - Enrollment completed
  - Last 12-month follow up anticipated 2nd quarter 2026

Future Goals

- To offer a Cost-Effective, Physician and Patient “Friendly” procedure to address impediments to patient care
  - Enhanced Risk/Benefit ratio
  - Ability to treat on initial diagnosis to prevent further vision loss
    - Not waiting for further progression
  - Improved patient comfort
  - Rapid return to activities of daily living
    - Bilateral, Simultaneous treatments
- Simple, safe procedure ideally suited to LMIC

eplon THERAPEUTICS

Thank You