PROTOCOL NUMBER CXL-005

Protocol Version: Revision 04.3

COLLAGEN CROSS-LINKING WITH ULTRAVIOLET-A IN ASYMMETRIC CORNEAS

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1.0 PROTOCOL SUMMARY

Protocol Number	CXL-005, Revision 04.1
Title	Collagen Cross-Linking with Ultraviolet-A in Asymmetric Corneas
Sponsor	CXLUSA, LLC
Regulatory Status	Phase 2 investigational new drug study
Objectives	Assess changes in visual acuity and corneal symmetry after corneal collagen cross-linking (CXL) of asymmetric corneas.
Study Design	Prospective, randomized, controlled, open label, multicenter trial
Study Population	A total of 3,000 males and females >= 8 years old. Inclusion Criteria A diagnosis of at least one of the following conditions: 1. Keratoconus 2. Forme fruste keratoconus 3. Post-LASIK ectasia 4. Pellucid marginal degeneration 5. Forme fruste pellucid marginal degeneration 6. Diurnal fluctuation post-radial keratotomy 7. Terrien's marginal degeneration Exclusion Criteria 1. Corneal thickness < 375 microns measured by ultrasound or Pentacam. 2. Contraindications or hypersensitivities to any study medications or their components. 3. Pregnancy or breastfeeding. 4. Any history of herpes simplex corneal disease in an eye to be treated. 5. Nystagmus or any other condition that would, in the judgement of the investigator, prevent a steady gaze during the treatment. 6. Inability to cooperate with diagnostic tests. 7. Enrollment in another ophthalmic clinical trial.
Number of Centers	21
Investigational Product	CXLO Corneal Strengthening Solution; ultraviolet-A illuminator.
Study Procedures	Pre-Procedure Screening Subjects will be instructed to remove contact lenses prior to screening – 2 weeks prior for rigid/gas permeable contact lenses and 3 days prior for soft or scleral lenses – unless subject has no suitable vision correction option. Mandatory screening procedures include medical, prior ophthalmic surgery, and contact lens history, refractive assessments for manifest refraction, uncorrected visual

Study Procedures (cont'd)	acuity (UCVA), corrected distance visual acuity (CDVA), corneal thickness (ultrasound pachymetry or other scanning device such as Pentacam), Pentacam corneal tomography, intraocular pressure (IOP), slit lamp examination, and dilated fundus exam. Optional screening procedures include quality of life and/or comfort survey questions such as VFQ-25, ophthalmic assessments including corneal wavefront measurement, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator, and previous ophthalmic history such as old eyeglass prescriptions and topographic maps. When eligibility has been established using the inclusion/exclusion criteria, the patient will be enrolled. Randomization Randomization will be stratified by indication and by investigational site among 3 UVA illumination groups consisting of: Group 1: 4 mW/cm^2 cycled On/Off at 15 second intervals for 20 minutes (total UVA corneal surface dose of 2.4 J/cm^2), or Group 2: 6 mW/cm^2 cycled On/Off at 15 second intervals for 20 minutes (total UVA corneal surface dose of 3.6 J/cm^2), or Group 3: 4 mW/cm^2 cycled On/Off at 15 second intervals for 30 minutes (total UVA corneal surface dose of 3.6 J/cm^2).
	Day of Cross-Linking Procedure One or both eligible eyes may be treated on the same day, or on different days. CXL Procedure A. Instill anesthetic eye drops. B. Insert lid speculum in each eye undergoing treatment. C. Use a sterile ophthalmic sponge hydrated with saline or anesthetic drops to gently swab the surface of the cornea to remove mucus and any other debris and to enhance riboflavin penetration into the cornea. The epithelium is not to be removed, as treatment with an intact epithelium has the potential to halt progression of the disease while reducing post-procedure pain, complications related to

Study Procedures (cont'd)	epithelial debridement, and promoting faster vision recovery to baseline CDVA. D. Apply a CXLO round loading sponge to the surface of the cornea to serve as a reservoir for CXLO Corneal Strengthening Solution. E. Saturate the sponge with several drops of CXLO Corneal Strengthening Solution. Instill 1-2 drops of CXLO solution every 1-3 minutes for 10-90 minutes (this range is required as different corneas load at different rates and the surgeon will visually confirm sufficient stromal loading later in the procedure). Topical anesthetic drops may be used infrequently as needed (generally every 10 -15 minutes) to maintain patient comfort. E. After 10-20 minutes of saturation, remove the lid speculum. Examine the eye using a slit lamp or a slit light to confirm uniform saturation of the cornea, referencing a "flip chart" of slit-lamp images, a copy of which is provided in Appendix 1. If the cornea is not adequately saturated, repeat the CXLO solution application instructions above, and re-assess corneal saturation via slit-lamp or slit light examination every 5-10 minutes until adequate, uniform corneal saturation is confirmed. F. After confirming adequate stromal saturation, irrigate the corneal epithelium with artificial tears for approximately 30 seconds prior to UVA illumination to avoid the "sunscreen" effect of riboflavin in the epithelium. G. Place the lid speculum(s) prior to UV light application. H. Apply artificial tears every 30 to 60 seconds during UVA light application to avoid corneal drying. These artificial tear solutions may be stored overnight at room pressure under different atmospheric oxygen levels to test the effects of dissolved oxygen variations due to storage and altitude on cross-linking. I. The total cumulative UVA dose will not exceed 3.6 Joules/cm^2. UV Irradiance will not exceed 6mW/cm^2 and the UVA light will illuminate a 12 mm diameter area on one or both corneas for 10-30 minutes. The irradiance and duration of UV exposure will be recorded. J. After completion of the procedure: 1. The lid speculum is removed. 2. Polytrim™ (or Floraquinolone or other appropriate broad spectrum antibiotic if the subject is hypersensitive) and anti-inflammatory drops are instilled. These may include Ciprofloxacin or Vigamox (or similar) and a nonsteroidal such as Voltaren, Acular or Xibrom. A topical steroid may also be instilled.

Clinical Parameters	The following clinical parameters will be evaluated: 1. Corrected distance visual acuity 2. Uncorrected distance visual acuity 3. Slit lamp assessment 4. Corneal topography/tomography 5. Manifest refraction 6. Pachymetry 7. Intraocular pressure (IOP) 8. Maximum corneal curvature (K_{max}) A schedule of assessment procedures is provided in Appendix 2.
Efficacy Endpoints	Primary: Change in corrected distance visual acuity (CDVA) at 6 months, compared to baseline. Secondary: Change at 6 months as compared to baseline in: 1. Uncorrected distance visual acuity 2. K_{Max}
Statistical Methods	Change from baseline will be calculated as follow-up visit – baseline. The baseline visit will be defined as Visit 1 (Pre-procedure visit). In general, continuous variables will be analyzed with two-sample t-tests for changes from baseline in normally distributed variables. For non-parametric data sets, Wilcoxon Signed Rank tests will be utilized. Patient demographics will be summarized using descriptive statistics (means, medians, standard deviations, etc.). Subject demographic characteristics and background variables will be summarized. Treatment differences with respect to baseline characteristics will be discussed in the final study report and assessed. All subjects enrolled in the study will be included as part of the safety analysis. All eyes treated (single or both eyes of an individual subject) will be included in the analysis of safety and efficacy. To determine efficacy, standard statistical methods such as p value analyses of continuous variables will be used along with newer artificial intelligence algorithms such as *Logitboost* or *Random Forest* to detect groupings and correlations of various outcome variables [1]. Large data sets will be analyzed and in these analyses stratification by UVA irradiance and total dose, age, diagnosis, severity of disease, gender, tomography,

Statistical Methods (cont'd)	topography metrics and other such criteria will be used to answer key questions related to the science and effects of treatments. Reference: [1]***Statistical Learning for Biomedical Data*** JD Malley, KG Malley, S Pajevic Cambridge University Press, 2011)

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2.0 BACKGROUND AND INTRODUCTION

Asymmetric corneas involved in this study are those caused by a number of "orphan" diseases that markedly impair vision due to progressive corneal thinning, steepening, and/or irregular astigmatism. These diseases include keratoconus, forme fruste keratoconus, post-LASIK ectasia, pellucid marginal degeneration, forme fruste pellucid marginal degeneration, diurnal fluctuation post-radial keratotomy, and Terrien's marginal degeneration.

Current non-surgical treatment alternatives include soft or rigid contact lenses or spectacles. However, as the disease progresses, these treatment modalities may not provide functional vision. Implantable intracorneal ring segments have been shown to improve visual acuity, but they do not affect the underlying disease and are associated with several possible complications. As a result, a significant number of these patients have had no treatment alternatives other than corneal transplantation.

Corneal collagen cross-linking has been shown to halt the progression of keratoconus (Raiskup-Wolf et. al., 2008; Wittig-Silva et. al., 2008; Coskunseven et. al., 2009, Grewel et. al., 2009; Vinciguerra et. al., 2009, Agrawal 2009, Kymionis et. al., 2009; Caporossi et. al., 2010; Greenstein et. al., 2011; Mazzotta et. al., 2012; Pinelli and Marzouky 2009; Stojanovic et. al., 2012; Rubinfeld et. al., 2013), as well as post-LASIK ectasia (Kymionis et. al., 2009, Greenstein et. al., 2011, Hovakimyan et. al., 2012), pellucid marginal degeneration (Spadea 2010), diurnal fluctuation post-radial keratotomy (Elbaz et.al 2014), and Terrien's marginal degeneration (Hafezi 2014).

The recent approval of the Avedro, Inc. system for corneal collagen cross-linking provides a method of stiffening the cornea to prevent progression of ectatic disease. This procedure, however, requires the surgical debridement of the corneal epithelium, saturation of the cornea with riboflavin ophthalmic solution, and illumination with ultra-violet A (365 nm) radiation. Side effects of surgical epithelial debridement include prolonged pain, epithelial healing, and vision recovery. In contrast, the procedure described in this application will not require epithelial debridement, and has the potential to halt progression of the disease while reducing post-procedure pain, and promoting faster vision recovery to baseline CDVA.

2.1 DESCRIPTION OF INDICATION FOR USE

The indications for use during this study will be the treatment of asymmetric corneas diagnosed with one of the following conditions: keratoconus, forme fruste keratoconus, post-LASIK ectasia, pellucid marginal degeneration, forme fruste pellucid marginal degeneration, diurnal fluctuation post-radial keratotomy, or Terrien's marginal degeneration.

2.2 CURRENT TREATMENT AND LIMITATIONS

There is currently no medical therapy in the United States that preserves the corneal epithelium for the treatment of corneal ectasia associated with keratoconus, forme fruste keratoconus, post-LASIK ectasia, pellucid marginal degeneration, forme fruste pellucid marginal degeneration, diurnal fluctuation post-radial keratotomy, or Terrien's marginal degeneration. As a result, subjects who progress to severe disease must have more invasive procedures involving surgical removal of the epithelium, implantation of corneal rings, or penetrating keratoplasty.

3.0 STUDY DESIGN

3.1 OBJECTIVE

The objective of this study is to assess changes in visual acuity after corneal collagen cross-linking of asymmetric corneas.

3.2 DESCRIPTION OF THE STUDY

Approximately 3,000 eligible subjects presenting with asymmetric corneas will be enrolled at 21 clinical sites.

The primary effectiveness analysis will be based on 6-month post-procedure assessments. Subjects will be assessed post-procedure day 1, at 3 months and at 6 months. Visual acuity measurements and full ocular assessments (manifest refraction with CDVA, UCVA, slit lamp biomicroscopy including a rating of corneal haze, pachymetry, Pentacam corneal tomography, IOP) will be performed during that period.

Optional 1 week, 1-2 month, 12-month, 24-month, and 36-month assessments will also be performed, at the discretion of the physician. The 1-2 month visit may occur if the subject experiences changes in refractive error, and requires a new prescription for spectacles or contact lenses.

Optional assessments including corneal wavefront measurement, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, or other non-invasive diagnostic tests that may be available to an investigator, as well as quality of life and/or comfort survey questions may be performed during the study period.

3.3 OUTCOME MEASURES

Effectiveness Outcome Measures
The following will be evaluated 6 months after the cross-linking procedure:

Primary effectiveness measure:
Change in CDVA

Secondary effectiveness measures:
Change in UCVA
Change in K_{max}

Safety Outcome Measures
Safety will be evaluated by assessing the following:

Adverse events (AEs)
Serious adverse events (SAEs)

3.4 STUDY POPULATION

Up to 3,000 subjects with asymmetric corneas will be enrolled. After providing informed consent and documenting it in writing, subjects with keratoconus, forme fruste keratoconus, post-LASIK ectasia, pellucid marginal degeneration, forme fruste pellucid marginal degeneration, diurnal fluctuation after RK, or Terrien's marginal degeneration will be screened for participation in the study. Screening evaluations may be performed at any time within 3 months preceding or on Day 0, and subjects must fulfill the following criteria:

Inclusion Criteria:

1. Diagnosis of keratoconus, forme fruste keratoconus, post-LASIK ectasia, pellucid marginal degeneration, forme fruste pellucid marginal degeneration, history of radial keratotomy with fluctuating vision, or Terrien's marginal degeneration.
2. Must have provided informed consent, documented it in writing, and have been given a copy of the signed informed consent form.
3. Must be willing and able to return for scheduled treatment and follow-up examinations for the duration of the study.
4. Must be at least 8 years of age.

Exclusion Criteria:

1. Corneal thickness < 375 microns measured by ultrasound or Pentacam.
2. Contraindications or sensitivities to any study medications or their components.
3. Pregnancy or breastfeeding.
4. Any history of herpes simplex corneal disease in an eye to be treated.
5. Nystagmus or any other condition that would, in the judgement of the investigator, prevent a steady gaze during the treatment.
6. Inability to cooperate with diagnostic tests.
7. Enrollment in another ophthalmic clinical trial.

Randomization:

Randomization will be stratified by indication and by investigational site, with study subjects randomly assigned to one of three treatment groups. The three treatment groups consist of CXLO Corneal Strengthening Solution combined with one of 3 different UVA exposure parameters. The UVA treatment parameters will consist of:

- Group 1: 4 mW/cm^2 cycled On/Off automatically at 15 second intervals for 20 minutes (total UVA corneal surface dose of 2.4 J/cm^2),
- Group 2: 6 mW/cm^2 cycled On/Off automatically at 15 second intervals for 20 minutes (total UVA corneal surface dose of 3.6 J/cm^2), and
- Group 3: 4 mW/cm^2 cycled On/Off automatically at 15 second intervals for 30 minutes (total UVA corneal surface dose of 3.6 J/cm^2).

4.0 STUDY TREATMENTS

4.1 INVESTIGATIONAL TREATMENT

One or both eligible eyes may be enrolled and procedure performed on the same day or on different days. Subjects eligible for enrollment will be instructed to instill Polytrim (or Floraquinolone or other appropriate broad spectrum antibiotic if the subject is hypersensitive) 4 times daily into the eligible eye(s) one day prior to treatment

A. Instill anesthetic eye drops.

B. Place a lid speculum in each eye undergoing treatment.

C. Use a sterile ophthalmic sponge hydrated with saline or anesthetic drops to gently swab the surface of the cornea to remove mucus and any other debris and to enhance riboflavin penetration into the cornea. The epithelium is not to be removed, as treatment with an intact epithelium has the potential to halt progression of the disease while reducing post-procedure pain, complications related to epithelial debridement, and promoting faster vision recovery to baseline CDVA.

D. Apply a sterile corneal sponge protector to the surface of the cornea to serve as a reservoir for CXLO Corneal Strengthening Solution.

E. Saturate the sponge protector with several drops of CXLO Corneal Strengthening Solution. Thereafter, to assure for continuous application of CXLO solution to the surface of the cornea, keep the sponge moistened by applying 1-2 drops of CXLO solution every 1-3 minutes for 10-90 minutes (this range is required as different corneas load at different rates and the surgeon will visually confirm sufficient stromal loading later in the procedure).

F. After 10-20 minutes of saturation, remove the lid speculum. Examine the eye using a slit lamp or slit light to confirm adequate saturation of the cornea, referencing the “flip-chart” of slit-lamp images, a copy of which is provided in Appendix 1. If the cornea is not adequately saturated, repeat the CXLO Corneal Strengthening Solution application instructions above,

and re-assess corneal saturation via slit-lamp or slit light examination every 5-10 minutes until adequate corneal stromal saturation is confirmed.

G. After confirming adequate stromal saturation, irrigate the corneal epithelium with artificial tears for approximately 30 seconds prior to UVA illumination to avoid the "sunscreen" effect of riboflavin in the epithelium.

H. Place the lid speculum(s) prior to UVA light application.

I. Perform UVA illuminator calibration, centering of the beam, and application instructions in accordance with Appendix 3, which will result in a 12 mm diameter UVA spot size on the cornea.

J. Perform UVA illumination in accordance with the UVA irradiance, dose, and 15 second on/off interval to which the subject has been randomized. Magnetic treatment cards are provided, each of which are labeled with the respective randomization UVA treatment parameters specified in Section 3.4 above. The 15-second UVA on/off interval is controlled automatically by the UVA illumination device. To initiate the randomized UVA treatment cycle, swipe the respective magnetic treatment card through the magnetic card reader on the UVA illumination device. Record the irradiance and duration of UVA exposure.

K. Riboflavin solution is <u>not</u> to be instilled during UVA light application, due to the sunscreen effect of the riboflavin which would diminish UVA irradiance required for stromal cross-linking. Apply artificial tears/gels and/or other moistening solutions every 30-60 seconds during the UVA light application to avoid corneal drying. These artificial tear solutions may be stored overnight at room pressure under different atmospheric oxygen levels to test the effects of dissolved oxygen variations due to storage and altitude on cross-linking.

L. After completion of the procedure:

1. The lid speculum is removed.

2. Polytrim™ (or Floraquinolone or other appropriate broad spectrum antibiotic if subject is hypersensitive), and anti-inflammatory drops are instilled. These may include Ciprofloxacin or Vigamox (or similar) and a nonsteroidal such as Voltaren, Acular or Xibrom. A topical steroid may also be instilled.

3. Post-procedure the surgeon may prescribe:

   i. Brand or generic Polytrim™ or other antibiotic qid (i.e. Ciprofloxicin or Vigamox). These drops may be continued for up to a week if surgical judgment suggests this might benefit the patient.

   ii. Topical nonsteroidal anti-inflammatory (i.e. Acular, Acuvail, Voltaren Xibrom) up to qid for up to 6 days postop.

   iii. Topical Steroid (FML, Pred Forte, Flarex, etc.) qid 4 days postoperatively,, although steroids can be used longer if corneal haze develops.

iv. Topical anesthetic (e.g. Proparacaine 0.5% every 6 hours as needed for up to 24 hours post-procedure).

v. Over the counter oral analgesics such as ibuprofen, acetaminophen, or even narcotics may be taken for discomfort. Prescription pain meds such as acetaminophen with an opiate and/or a gabapentin modulator such as Lyrica may also be prescribed short term for patient comfort. Application of cold or ice packs may be recommended for improved comfort.

M. Punctal plugs can be placed at the surgeon's discretion if needed to improve the tear film.

Treating both eyes on the same day:

2 options:

1. Sequential epithelium preparation, sequential UVA light administration: Prepare epithelium in one eye, load the cornea with CXLO Corneal Strengthening Solution, then prepare the epithelium in the second eye prior to initiating the UV light source. While one eye is receiving UVA light therapy, the other eye is receiving the loading dose of topical CXLO solution.
2. Bilateral epithelium preparation, simultaneous UV light treatment: Prepare epithelium in both eyes, and initiate CXLO solution drops in both eyes. After 10-90 minutes of loading both eyes with riboflavin, the eyes will be checked with a slit lamp or slit beam check. UV light treatment in both eyes will then be performed.

Post-Procedure Treatment Regimen Details:

Topical corticosteroids and antibiotics as per standard surgeon regimen following other UV procedures such as PRK may be used. Topical nonsteroidal medications and dilute anesthetic drops may be used as needed for early postop discomfort, but should be discontinued by post-procedure day 6.

5.0 STUDY PROCEDURES

5.1 INFORMED CONSENT

Prior to recruitment of any subjects into the study, written approval of the protocol, and informed consent and assent forms, must be obtained from the Institutional Review Board (IRB) for each participating clinical site.

Informed consent and assent forms, the assent form being applicable to subjects less than 18 years old, must be obtained and documented in writing prior to the initiation of any study procedures. The subject (or the subject's legally authorized representative) and the minor (when applicable) must be allowed sufficient time to thoroughly read (or have explained) the respective consent/assent form, which will be written at a level that can be understood by someone with minimal education.

The Investigator or his/her designee should answer any questions that the subject/representative might have. If the adult subject/parent/guardian and the minor, when applicable, agree to participate in the study, i.e., provides informed consent and assent, the subject/representative must sign both copies of the informed consent/assent forms. The witness and the Investigator must also sign both copies of these forms. One copy of these forms will be given to the subject/representative. If applicable, it will be provided in a certified translation of the local language.

Subjects who provide informed consent (and assent, if applicable) and document this in writing will be screened for eligibility. Screened subjects will be recorded on site-specific screening logs and once they are determined as being eligible, they will be enrolled into the study.

5.2 ASSIGNMENT OF SUBJECT IDENTIFICATION

A subject identification number (ID) will be assigned at screening. This ID should be used on all study-related documents. To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form.

5.3 CONCOMITANT AND EXCLUDED THERAPIES

Concomitant medications are any prescription drugs used by a subject during the study, until conclusion of study participation (Month 6-9) or early termination. The CRF will record administration of these medications.

No other experimental or investigational treatments are allowed during this study, including ocular experimental and investigational treatments in either eye.

5.4 TIMING OF STUDY ASSESSMENTS

All procedures will be performed according to the following schedule unless otherwise specified. When assessments are scheduled, subjects will be instructed to remove contact lenses prior to screening – 2 weeks prior for rigid/gas permeable contact lenses and 3 days prior for soft or scleral lenses – unless subject has no suitable vision correction option.

Pre-Procedure:

Assessments:

- UCVA
- Manifest refraction
- CDVA
- Pentacam corneal tomography
- Pachymetry by ultrasound or other scanning device such as Pentacam
- Slit lamp examination
- Intraocular pressure (IOP)

- Dilated fundus exam (or documented dilated fundus exam by another provider within 1 year)
- Medial history
- Contact lens history
- History of previous eye surgeries

***Optional* Assessments:**

- Quality of life and/or comfort survey questions such as VFQ-25.
- Optional assessments including corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.
- Previous ophthalmic history such as:
    - Previous old eyeglass prescriptions & topographic maps may be requested and documented.
    - UCVA within the past 3 months (if evaluation was performed at the same clinic as that involved in this study);
    - CDVA within the past 3 months (if evaluation was performed at the same clinic as that involved in this study);
    - Manifest refraction within the past 3 months (if evaluation was performed at the same clinic as that involved in this study).

Day 1 Post-Procedure:

Assessments:

- UCVA
- Slit lamp examination

***Optional* Assessments:**

- CDVA
- Manifest Refraction
- IOP
- Pachymetry
- Optional assessments including Pentacam corneal tomography, corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.

***Optional* Visit Days 2-10 (If Post-Procedure Day 1 shows incomplete epithelium healing):**

Assessments:

- UCVA
- Slit lamp exam
- IOP

***Optional* Assessments:**

- Manifest refraction and CDVA
- Pachymetry
- Optional assessments including Pentacam corneal tomography, corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.

Interim visits may also be suggested in which similar safe non-invasive measurements may be obtained. Manifest refraction and non-contact corneal biomechanical and/or non-invasive biometry measurements may be obtained. These non-invasive measurements can be performed as frequently as the surgeon believes would be useful, especially in circumstances where the patient's vision and refraction can be expected to be changing rapidly.

***Optional* 1-2 month visit:**

Some patients may experience significant changes in their refractive error, and may benefit from an optional visit at 1-2 months to get a new prescription for glasses or contact lenses.

Assessments:

- UCVA
- Slit lamp exam
- Pachymetry (ultrasound and/or Pentacam)
- Pentacam corneal tomography
- IOP

***Optional* Assessments:**

- Optional assessments including corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.
- Manifest refraction
- CDVA
- Medical and contact lens history will be recorded

Month 3 (60-120 days):

Assessments:

- UCVA
- Manifest refraction with CDVA
- Slit lamp exam (including rating of corneal haze if present from 0 (none) to 4)
- Pachymetry (ultrasound and/or Pentacam)
- Pentacam corneal tomography
- Medical and contact lens history will be recorded.
- IOP will be measured.

***Optional* Assessments:**

- Quality of life and/or comfort survey questions.
- Optional assessments including corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.

Month 6 (150-210 days):

Assessments:

- UCVA
- Manifest refraction with CDVA
- Slit lamp exam (including rating of corneal haze if present from 0 (none) to 4)
- Pachymetry (ultrasound and/or Pentacam)
- Pentacam corneal tomography
- Medical and contact lens history will be recorded.
- IOP will be measured.

***Optional* Assessments:**

- Quality of life and/or comfort survey questions.
- Optional assessments including corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.

Optional 1, 2, and 3 Year Post-Procedure Visits:

Patients may elect to return for 1, 2, and 3 year post-procedure visits as well as interim visits as per surgeon judgment.

Assessments:

- UCVA
- Manifest refraction with CDVA
- Slit lamp examination (including rating of corneal haze if present from 0 (none) to 4)
- Pachymetry (ultrasound and/or Pentacam)
- Pentacam corneal tomography
- Medical and contact lens history will be recorded.
- IOP will be measured.

Optional* Assessments*:

- Patient may be asked to answer quality of life and/or comfort survey questions.
- Optional assessments including corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.

Option for additional simultaneous or sequential treatments:

- Patients may undergo a repeat CXL procedure following their 6-month visit. Patients will exit the study on that visit, and then will be re-enrolled as a new patient, and must meet all of the inclusion and exclusion criteria, and investigators must follow the same protocol as outlined above.

Unscheduled Visits

Interim visits may also be suggested in which similar, safe, non-invasive measurements may be obtained. Manifest refraction and non-contact corneal biomechanical and/or non-invasive biometry measurements may be obtained. These non-invasive, measurements can be performed as frequently as the surgeon feels would be useful, especially in circumstances where the patient's vision and refraction can be expected to be changing rapidly. Only unscheduled visits related to adverse event follow up will be recorded in the CRFs.

The timing of each scheduled assessment is summarized in Appendix 2.

5.5 WITHDRAWAL CRITERIA

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care.

5.6 FOLLOW UP OF WITHDRAWN OR TERMINATED SUBJECTS

Subjects who withdraw from the study will be followed for safety where possible and encouraged to return for follow-up visits for any unresolved safety events.

Subjects who withdraw from the study will be asked to complete procedures outlined in the 6-9 month visit (if withdrawn prior to that visit). Subjects who are terminated due to adverse events will be followed, if possible, at least until resolution or stabilization of the adverse event.

6.0 SAFETY PARAMETERS

Safety assessments include adverse events/serious adverse events, visual acuity loss, slit lamp findings, and intraocular pressure. The reporting time period is from the day cross-linking is performed through the last through the last study visit.

6.1 DEFINITIONS OF ADVERSE EVENTS

An adverse event is any untoward and unintended sign, symptom or disease temporally associated with the use of an investigational drug or device, or other protocol-imposed intervention, regardless of the suspected cause. Conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF. Changes in a chronic condition of disease that are consistent with natural disease progression are NOT adverse events and also should not be recorded on the AE pages of the CRF.

6.1.1 Serious Adverse Events (SAE)

An AE should be classified as an SAE and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE places the subject at immediate risk of death)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions.
- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study.
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

6.1.2 Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a drug or device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence. Anticipated adverse events are identified in Section 6.3. UADEs also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.2 ADVERSE EVENT ASSESSMENT AND DOCUMENTATION

All subjects who have been exposed to the study treatment will be evaluated for adverse events. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents and CRF using standard medical terminology.

All adverse events will be evaluated beginning with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the subject's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form.

All AEs will be characterized by the following criteria:

- Date of onset
- Event diagnosis
- Intensity or severity
- Expectedness
- Relatedness to study treatment
- Treatment or action taken.
- Outcome

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If more than one distinct adverse event occurs, each event should be recorded separately. However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the CRF rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs.

Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension $\Rightarrow$fainting and fall to floor $\Rightarrow$head trauma $\Rightarrow$neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

6.2.1 Classification of Adverse Events by Intensity/Severity

All adverse events should be graded on a three-point scale (mild, moderate, severe) for intensity/severity, defined as a qualitative assessment of the level of discomfort of an adverse event as is determined by the Investigator or reported to him/her by the subject. The assessment

of intensity is made irrespective of study procedure relationship or seriousness of the event and should be evaluated according to the following scale:

Mild:	Awareness of sign or symptom, but easily tolerated.
Moderate:	Discomfort enough to cause interference with usual activity.
Severe:	Incapacitating with inability to work or do usual activity.

There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events listed in Section 7.1.1.

6.2.2 Expectedness

All AEs will be evaluated as to whether they are expected or unexpected.

Expected (anticipated):	An adverse event is expected when the nature, severity, or degree of incidence was previously described. Expected adverse events are listed in 7.3.
Unexpected (unanticipated):	An adverse event is unexpected when the nature, severity, or degree of incidence was not previously described.

6.2.3 Relatedness

The study investigator will evaluate if the AE is related to the corneal cross-linking procedure. Relationship is defined in the following manner:

Not related: The event is **clearly related to other factors** such as subject's clinical state, therapeutic interventions, concomitant disease or therapy administered to the subject, and does not follow a known response pattern to the procedure.

Related: The event **follows a reasonable, temporal sequence from the time of procedure and/or follows a known response pattern to the study procedure and cannot be reasonably explained by other factors** such as subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject.

6.2.4 Treatment or Action Taken

Action taken in response to an adverse event will be recorded as:

- None
- OTC or Rx drug added
- Non-drug treatment/procedure
- Hospitalization or ER visit

Action taken with study procedure will be recorded as:

- None
- Study procedure interrupted
- Study procedure discontinued

6.2.5 Outcome

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death
- Unknown.

6.3 ANTICIPATED ADVERSE EVENTS

Epithelial Defect – A breach in the corneal epithelium that does not heal within 24 hours.

Persistent Epithelial Defect - A breach in the corneal epithelium that does not heal within 2 weeks.

Significant Decrease in Visual Acuity – loss of ≥2 lines CDVA

Sterile Infiltrates – Gray-white lesions caused by acute immune response to corneal damage.

Central Stromal Scars – New, significant corneal opacity in the central stromal region.

Corneal Haze – Cloudy or opaque appearance of the cornea. Grade Scale: 0 = clear cornea; 1 = focal areas of minimal stromal clouding or reticulation; 2 = diffuse mild stromal clouding or reticulation; 3 = Diffuse stromal clouding or reticulation somewhat obscuring the iris details; 4 = focal or diffuse areas of dense stromal haze obscuring iris detail.

Infectious Keratitis – Microbial infection of the epithelium or stroma**.**

Corneal Melt – A progressive, rapidly expanding, erosive, non-infectious, corneal ulcer.

Non-Infectious Keratitis – Inflammation of the cornea not associated with an infection.

Eye Pain – Eye pain lasting for >5 days.

Conjectiva Hyperemia – Eye redness.

Foreign Body Sensation – Patient reports a feeling of a foreign body (e.g. gravel or sand) in the eye lasting >24 hours.

Corneal Hydrops – Acute corneal edema caused by a break in Descement membrane.

Herpes Simplex Virus (HSV) Reactivation – Epithelial keratitis, stromal keratitis, or disciform edema proven or clinically diagnoses as being caused by HSV.

Disease progression – Increase of ≥4D K_{max} as assessed by topography or tomography or loss of > 2 lines of CDVA.

Photophobia – Sensitivity to light lasting >24 hours.

Elevated Intraocular Pressure (IOP) – IOP ≥30 mmHg or an increase in IOP of ≥10 mm from baseline recorded on two separate occasions or an increase in IOP that requires intervention.

Dry Eye Syndrome (DES) – Irritation of corneal surface due to inadequate production of tears that is consistently worse than the patient's pre-procedure state longer than 3 months after the cross-linking procedure.

Endophthalmitis – Diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause.

Iritis – Presence of inflammatory cells in the anterior chamber. The presence of aqueous flare alone is not considered to constitute iritis.

Iridocyclitis – Presence of inflammatory cells in both the aqueous and vitreous.

6.4 SERIOUS ADVERSE EVENT AND UNANTICIPATED ADVERSE DEVICE EFFECT REPORTING

Serious Adverse Events (SAE) and unanticipated adverse device effects (UADE) must be reported to the study sponsor (CXLUSA, LLC) and study Principal Investigator (PI) as soon as possible and no later than **24 hours** after the investigator first learns of the event.

For initial reports, investigators should record all case details that can be gathered within the reporting timeframe. The contact information for CXLUSA and the PI is below:

Study Sponsor:

CXLUSA, LLC

CONTACT PERSON: ROY RUBINFELD, M.D.
11200 ROCKVILLE PIKE, SUITE 150
ROCKVILLE, MD 20824
PHONE: (301) 908-8091

Study Principal Investigator:

GREGG J. BERDY, M.D., F.A.C.S.
ASSISTANT PROFESSOR OF CLINICAL OPHTHALMOLOGY
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
ST. LOUIS, MO 63110
C/O OPHTHALMOLOGY ASSOCIATES
12990 MANCHESTER ROAD, SUITE 200
ST. LOUIS, MO 63131
PHONE: (314) 966-5000
FAX: (314) 909-6666

Relevant follow-up information should be submitted to the sponsor as soon as it becomes available and/or upon request. For some events, the sponsor or his designee may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the study sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.0 STUDY DISCONTINUATION

The study sponsor has the right to terminate participation of an investigator, or this study, at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete.
- Study has reached maximal enrollment.

8.0 STATISTICAL PLAN

Change from baseline will be calculated as follow-up visit – baseline. The baseline visit will be defined as Visit 1 (Pre-procedure visit). The required analyses and target endpoints include, but are not limited to those listed below. In general, continuous variables will be analyzed with two-sample t-tests for changes from baseline in normally distributed variables. For non-parametric data sets, Wilcoxon Signed Rank tests will be utilized. Patient demographics will be summarized using descriptive statistics (means, medians, standard deviations, etc.).

Subject demographic characteristics and background variables will be summarized. Treatment differences with respect to baseline characteristics will be discussed in the final study report and assessed.

All subjects enrolled in the study will be included as part of the safety analysis. All eyes treated (single or both eyes of an individual subject) will be included in the analysis of safety and efficacy.

To determine efficacy, standard statistical methods such as p value analyses of continuous variables will be used along with newer artificial intelligence algorithms such as *Logitboost* or *Random Forest* to detect groupings and correlations of various outcome variables.[1] Large data sets will be analyzed and in these analyses stratification by age, diagnosis, severity of disease, gender, tomography, topography metrics and other such criteria will be used to answer key questions related to the science and effects of treatments.

Reference: [1]***Statistical Learning for Biomedical Data*** JD Malley, KG Malley, S Pajevic Cambridge University Press, 2011).

8.1 EFFICACY ENDPOINTS

The primary efficacy endpoint of this trial is change in corrected distance visual acuity (CDVA) at the last required study visit (6 months post-op), compared to baseline. CDVA will be evaluated by an observer who is masked to the treatment protocol to which study subjects have been assigned. All eyes treated (single or both eyes of an individual subject) will be included in the analysis of efficacy.

The Secondary Endpoints will be:
1. Change in UCVA at 6 months, compared to baseline.
2. Change in K_{max}, compared to baseline.

Additional analyses will be performed in subgroups of patients using standard statistical stratification methods, including patients over the age of 35, patients under the age of 18, disease severity, and patients with and without pre-procedure corneal scars. Results in male vs. female patients and post LASIK ectasia vs. primary keratoconus will also be evaluated.

8.2 SAMPLE SIZE JUSTIFICATION

Three thousand subjects will be enrolled in this open-label, prospective multicenter trial. One or both eyes of each patient may be enrolled and evaluated, based on whether treatment is unilateral or bilateral, based on clinical indications. All eyes treated (single or both eyes of an individual subject) will be included in the analysis of safety and efficacy.

A substantial number of eyes will need to be treated and evaluated in this study in order to obtain sufficient data to facilitate the analysis of potential differences between and among patient groups for each study indication. For example, it is expected that presenting disease severity, prior treatment (e.g. Intacs), subject age, and corneal thickness will impact the magnitude of effect of procedure efficacy for the treatment of keratoconus, forme fruste keratoconus, post-LASIK ectasia, pellucid marginal degeneration, and forme fruste pellucid marginal degeneration. Accordingly, in order to perform analyses with adequate study power, a large sample size is required.

A large sample size for a study involving fewer but similar indications is not unprecedented, as FDA clearance was previously granted for the conduct of a clinical study involving only keratoconus and post-LASIK ectasia (ref: http://clinicaltrials.gov/ct2/show/NCT01459679). Although that study was a Phase 3 clinical trial, it is expected that the study power needed to support analyses and conclusions of this proposed CXXLUSA study will be similar and further justifies the proposed sample size.

8.3 SAFETY

AEs, SAEs, and other findings will be summarized by presenting the percentages of subjects with each event. Continuous endpoints will be summarized using summary statistics such as means, medians, standard deviations, minima, maxima, and relevant percentiles.

9.0 RECORD RETENTION

The investigator shall maintain all subject records for a period of two years after the investigation is discontinued and FDA is notified.

The investigator must maintain accurate records of the receipt of all investigational material shipped by the sponsor, including the date and lot numbers received. In addition, accurate records must be kept on the amount and date that the investigational material, by lot number, was used and for each subject.

The investigator must assure that study supplies are used only in conjunction with subjects enrolled in the study and under the direct supervision of the investigator or co-investigators.

10.0 STUDY MONITORING REQUIREMENTS

CXLUSA, LLC, or designee, will monitor this study. Study monitoring involves the following elements:

CXLUSA personnel, or designee, may meet in person or via teleconference with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator and support staff with the study protocol.

CXLUSA personnel, or designee, may meet in person or via teleconference with the investigators at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the investigator, and that study data are being correctly recorded.

CXLUSA personnel, or designee, may visit in person or communicate via teleconference with the clinical site at any time during the course of the study to review and/or collect completed case report forms. Additionally, telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

11.0 PROTOCOL DEVIATIONS/AMENDMENTS

An investigator may deviate from the protocol to protect the life or physical well-being of a subject in an emergency, and must notify the sponsor and the reviewing IRB within 5 working days after the emergency occurred. Except in such an emergency, an investigator may not deviate from the protocol unless he/she obtains the prior approval of CXLUSA. FDA and IRB/EC approval is also required in accordance with 812.35(a).

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Revision History:

Revision	Effective Date	Description of Changes
00	3 September, 2014	Initial Release
01	2 October, 2014	Study design modified to randomized controlled to 3 UVA treatment parameters.
02	13 April 2015	Increased minimal corneal thickness to 375 microns ; added that CXLUSA will convene a DSMB to review safety information after 250 subjects are treated; modified performance of certain diagnostic procedures from "may be" to "will be" performed; clarified that "epi-off" is not one of the procedures to be performed.
03	9 November, 2015	Pentacam tomography mandatory instead of optional pre-op and in mandatory follow up visits; added 3-year optional follow up; changed post riboflavin instillation wash with artificial tears from 3-5 minutes to approx. 30 seconds; added requirement to record "Date of Onset" of any adverse events; upgraded instructions for UVA light calibration, centering, and application (Appendix 3), other minor clarifications of existing requirements.
04	14 October, 2016	Additional exclusion criteria added (nystagmus or any condition investigator believes would prevent steady gaze during treatment, inability to cooperate with diagnostic tests, enrollment in another ophthalmic trial); changed last required study visit from 8 months to 6 months post-op; changed mandatory assessment from 4 months to 3 months post-op; secondary endpoints changed from UCVA, K_{max}, and manifest refraction spherical equivalent (MRSE) to UCVA and K_{max}; deleted DSMB assessment after 250 subjects treated; CDVA to be assessed by masked evaluator; clarified that all eyes treated (single or both eyes of individual subject) will be included in analysis of safety and efficacy; clarified Sect. 4.1 that epithelium is not to be removed; other minor changes.
04.1	27 October, 2016	Deleted "Official Correspondent: Geoffrey Hervey, JD" from cover page to avoid confusion as to parties to contact; clarified study population age in 1.0 Protocol Summary from > 8 years old to >= 8 years old; Sect. 4.1, corrected information related to same-day treatment options from "3 options" to "2 options".
04.2	14 November, 2016	In response to IRB comments, changed exclusion criteria of "Active herpes simplex corneal disease" to "Any history of herpes simplex corneal disease in an eye to be treated" and changed post-op topical anesthetic from "Tetracaine 0.5% to 0.05% PRN eye pain for up to 3 days" to "Proparacaine 0.5% every 6 hours as needed for up to 24 hours post-procedure".

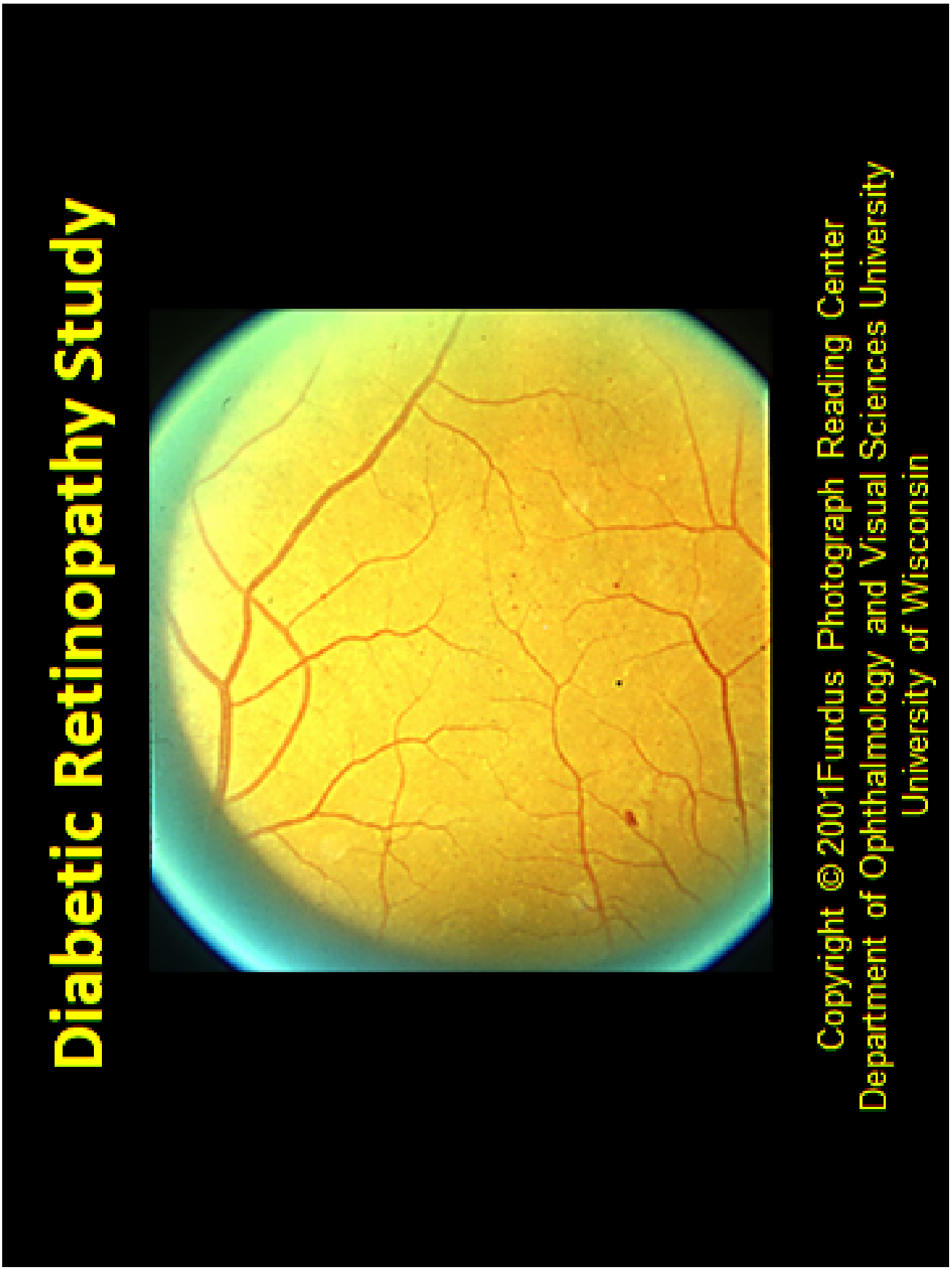
APPENDIX 1: FLIP CHART OF RIBOFLAVIN CORNEAL LOADING

Riboflavin Corneal Loading
CXL-05 Study Flip Chart
11.10.15 Draft
CXL USA

All Study Investigators Must
Review this Entire Presentation
Prior to Participating
in the Study

Introduction:
Flip Chart Precedents
Botany, Medicine, Ophthalmology


Leaf Color Chart
Irrigated Rice Research Consortium (IRRC)
in collaboration with the University of California Cooperative Extension


Diabetic Retinopathy Study
Copyright © 2001Fundus Photograph Reading Center
Department of Ophthalmology and Visual Sciences University
University of Wisconsin

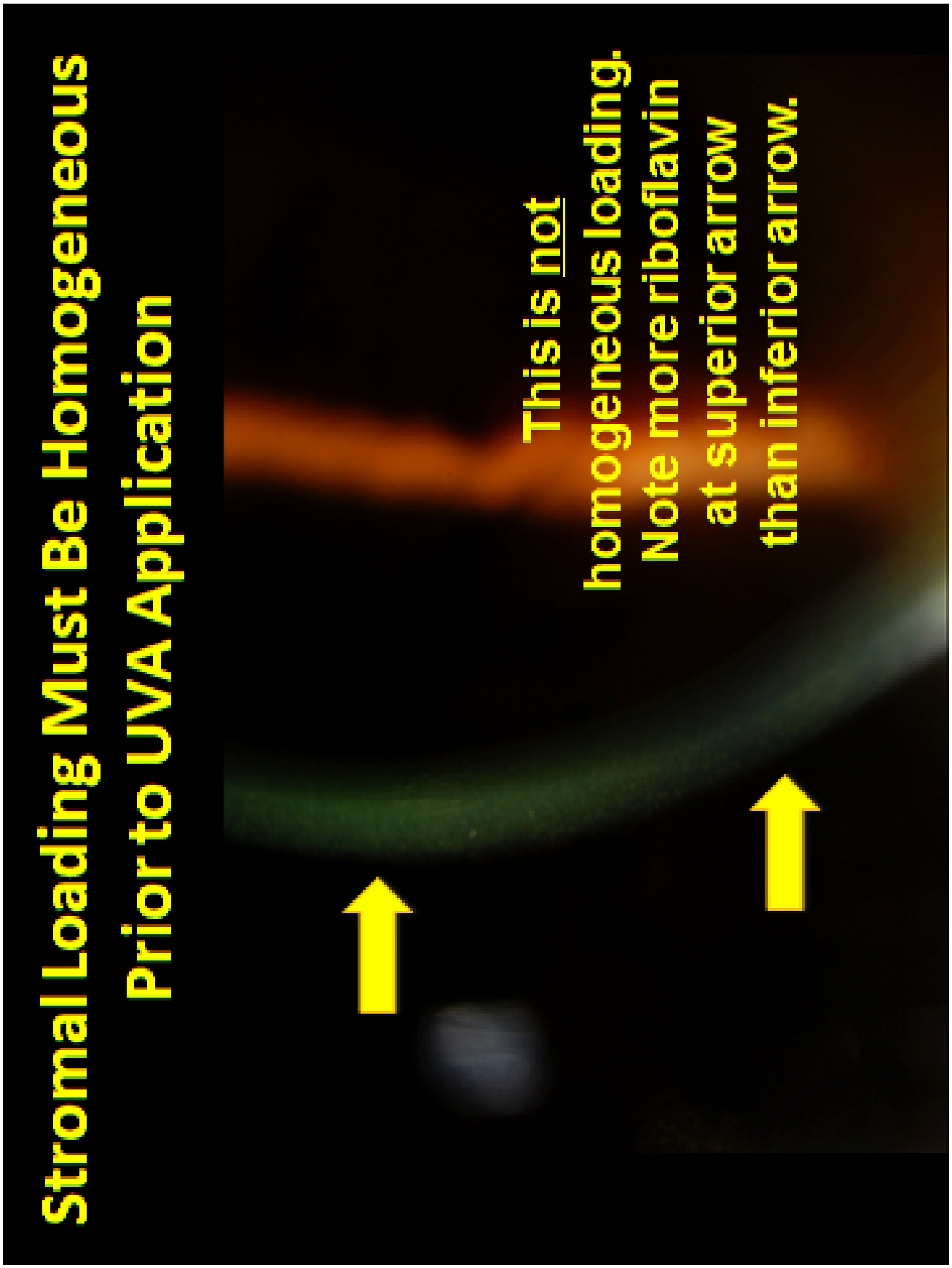
Three Key Aspects to Corneal Riboflavin Loading

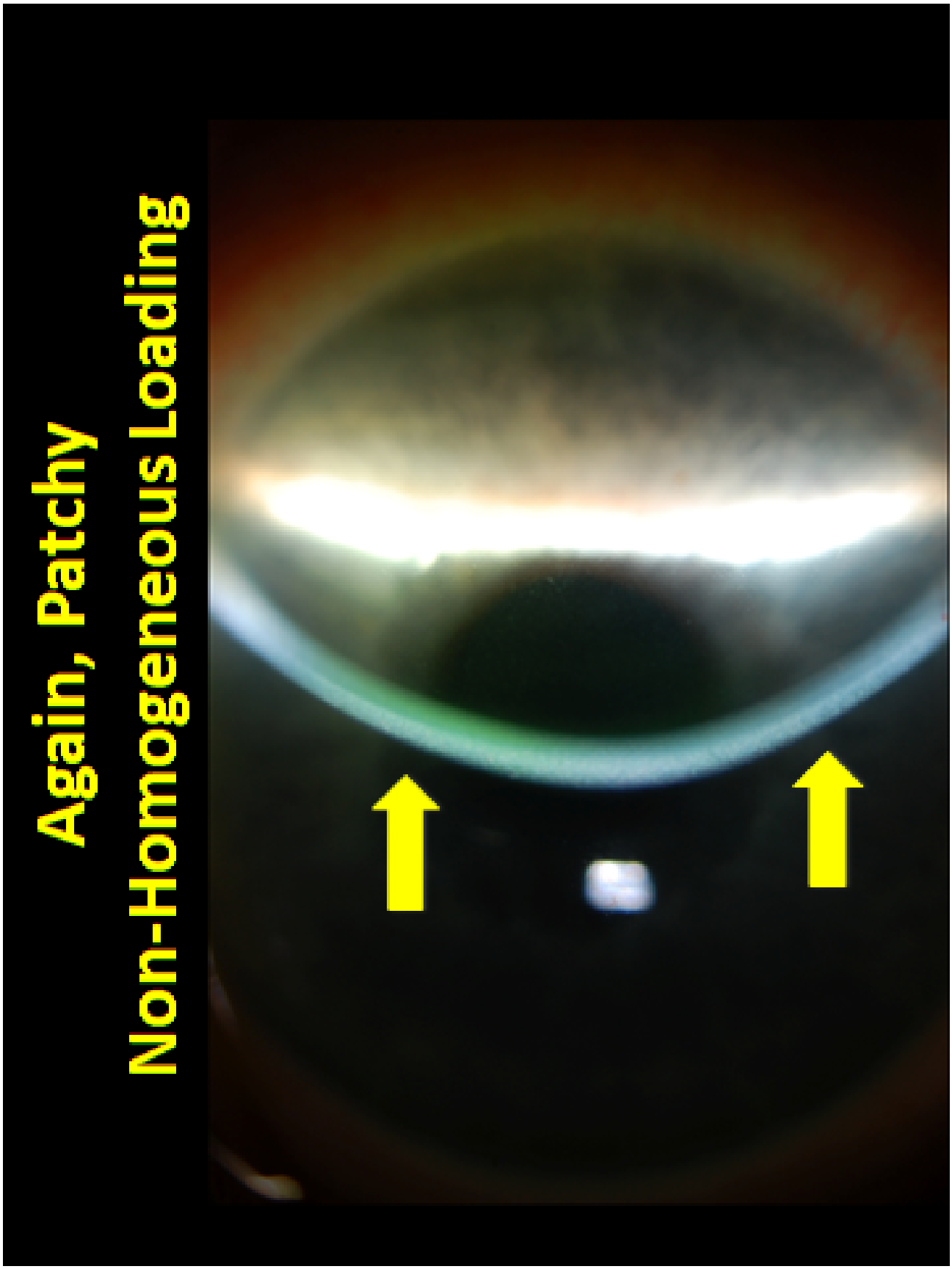
1. **Homogeneity**
   (Is the loading even or uneven/patchy?)
2. **Concentration**
   (How much riboflavin green color is present?)
3. **Location**
   (Where in the cornea is the riboflavin?)

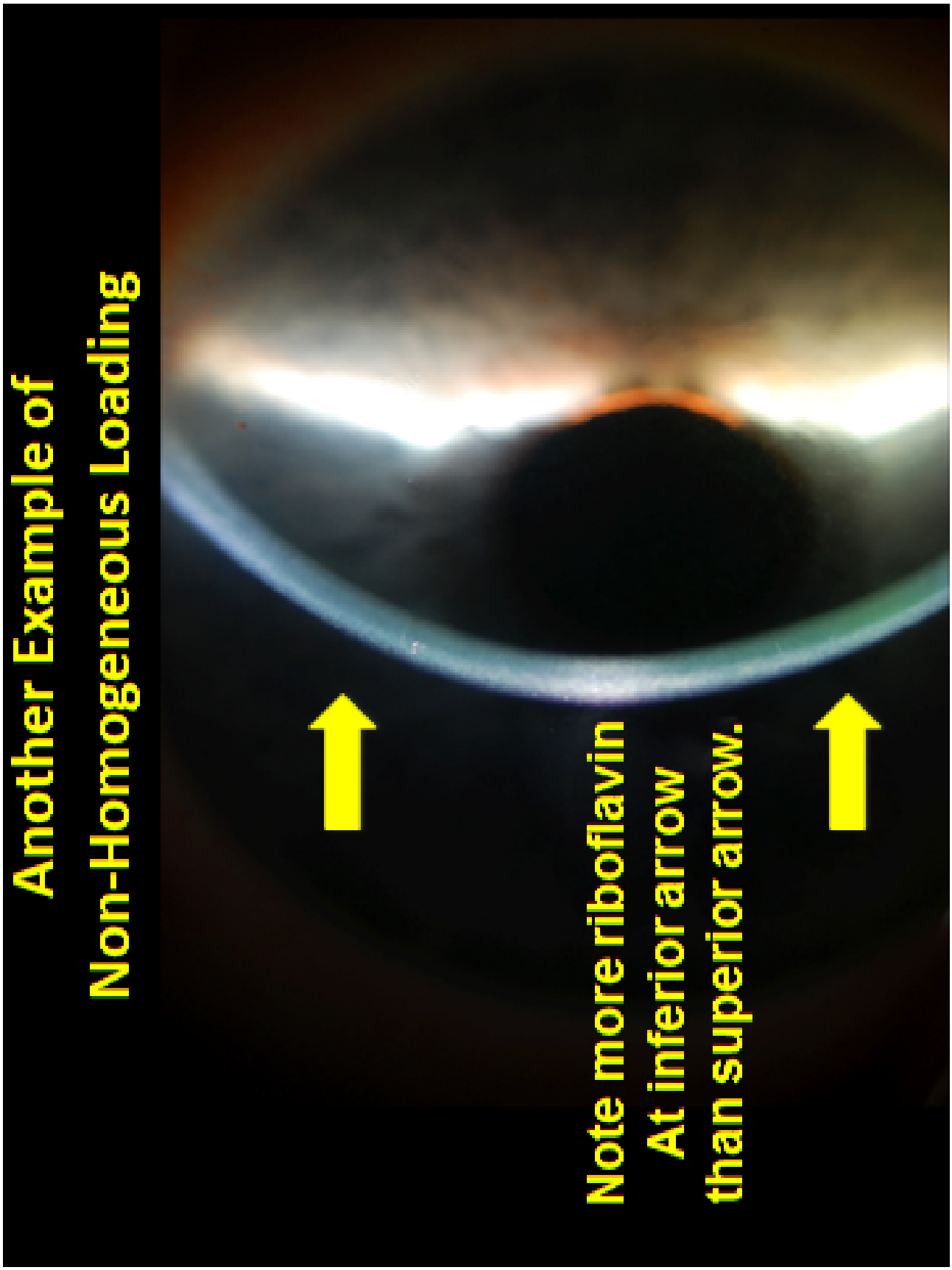
Slit Lamp Examination Must be Performed after Riboflavin Loading of the Cornea and Prior to UVA Application to Confirm Adequate Corneal Riboflavin Loading. Riboflavin Has a Distinct Green Appearance on SL Examination.

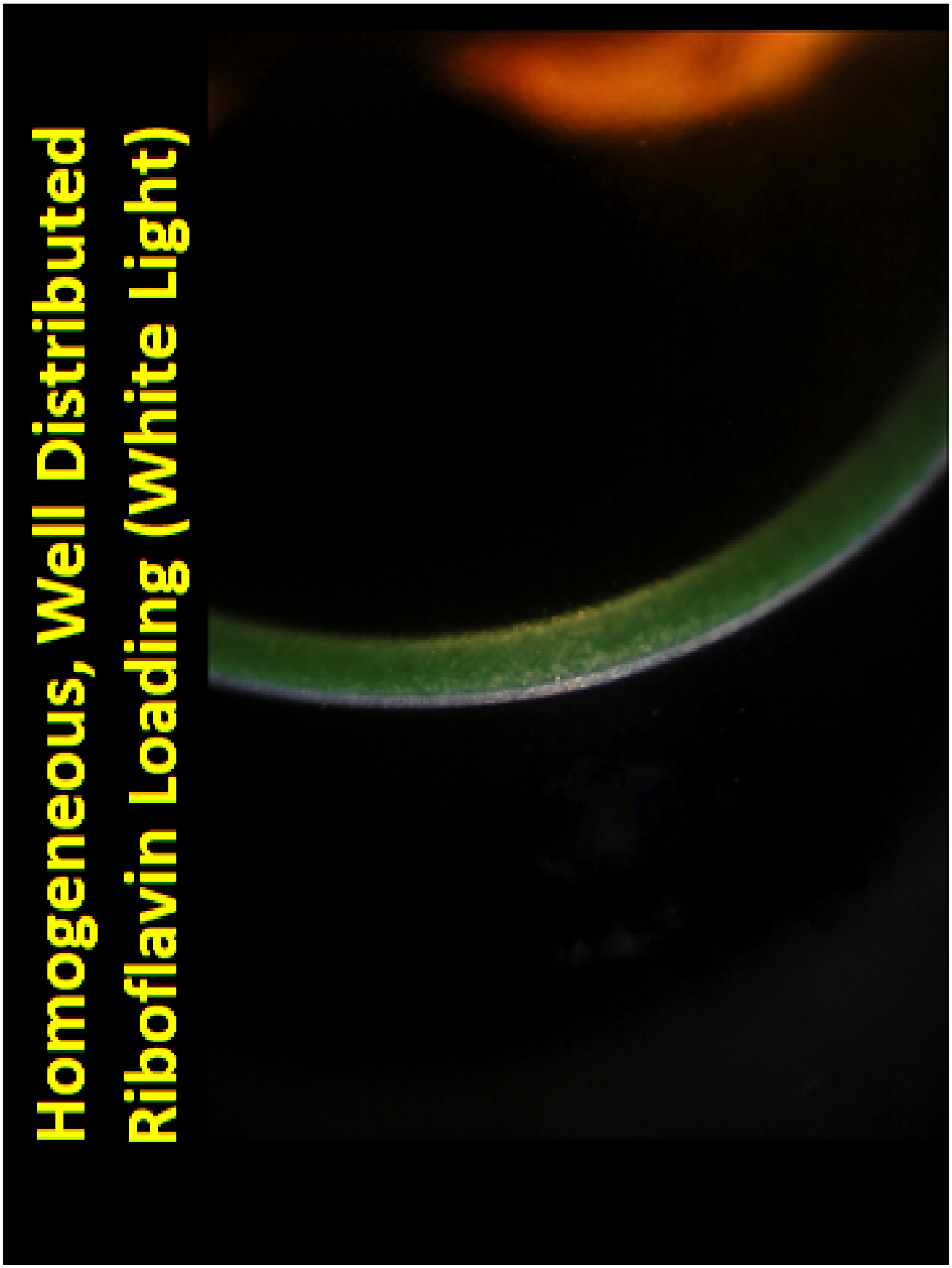
White and Cobalt Blue Light
are Both Helpful in Slit Lamp
Assessment of Corneal Loading
Cobalt Blue
Slit Lamp Beam
White Slit
Lamp Beam

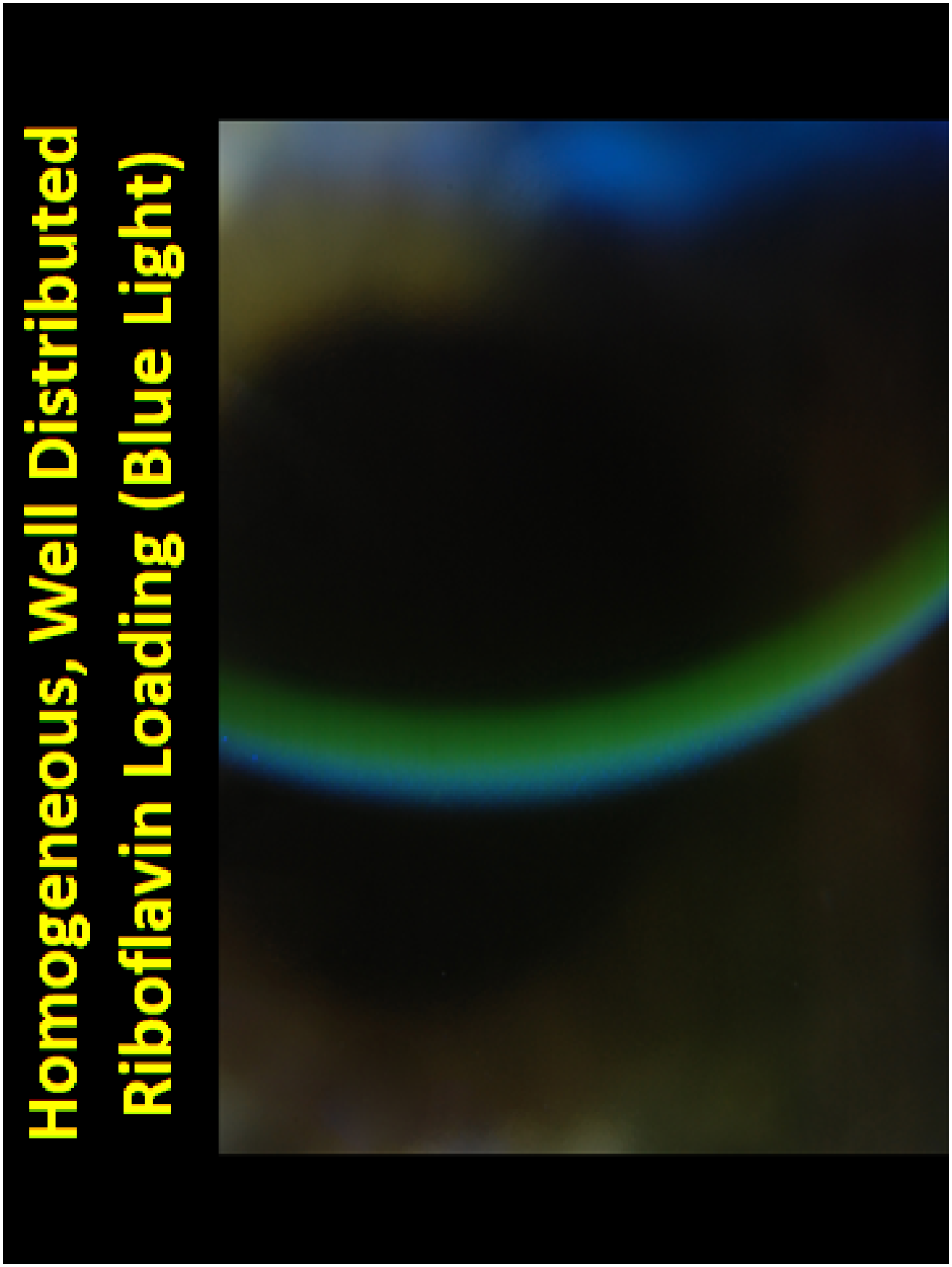
1. Homogeneity
Objective: Homogeneous
(Not Patchy) Loading


Stromal Loading Must Be Homogeneous
Prior to UVA Application
This is not
homogeneous loading.
Note more riboflavin
at superior arrow
than inferior arrow.


Again, Patchy
Non-Homogeneous Loading


Another Example of
Non-Homogeneous Loading
Note more riboflavin
At inferior arrow
than superior arrow.

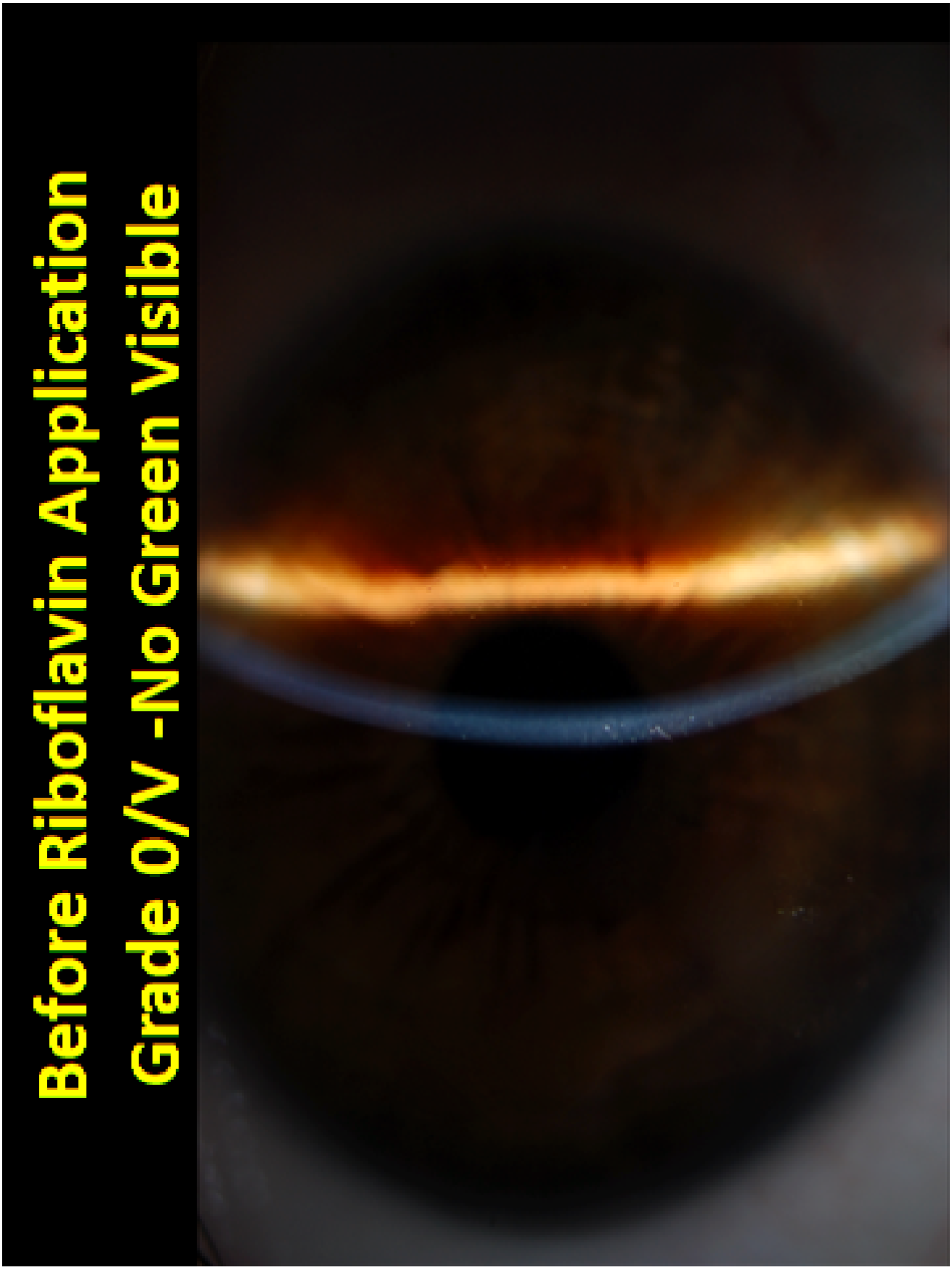

Homogeneous, Well Distributed
Riboflavin Loading (White Light)

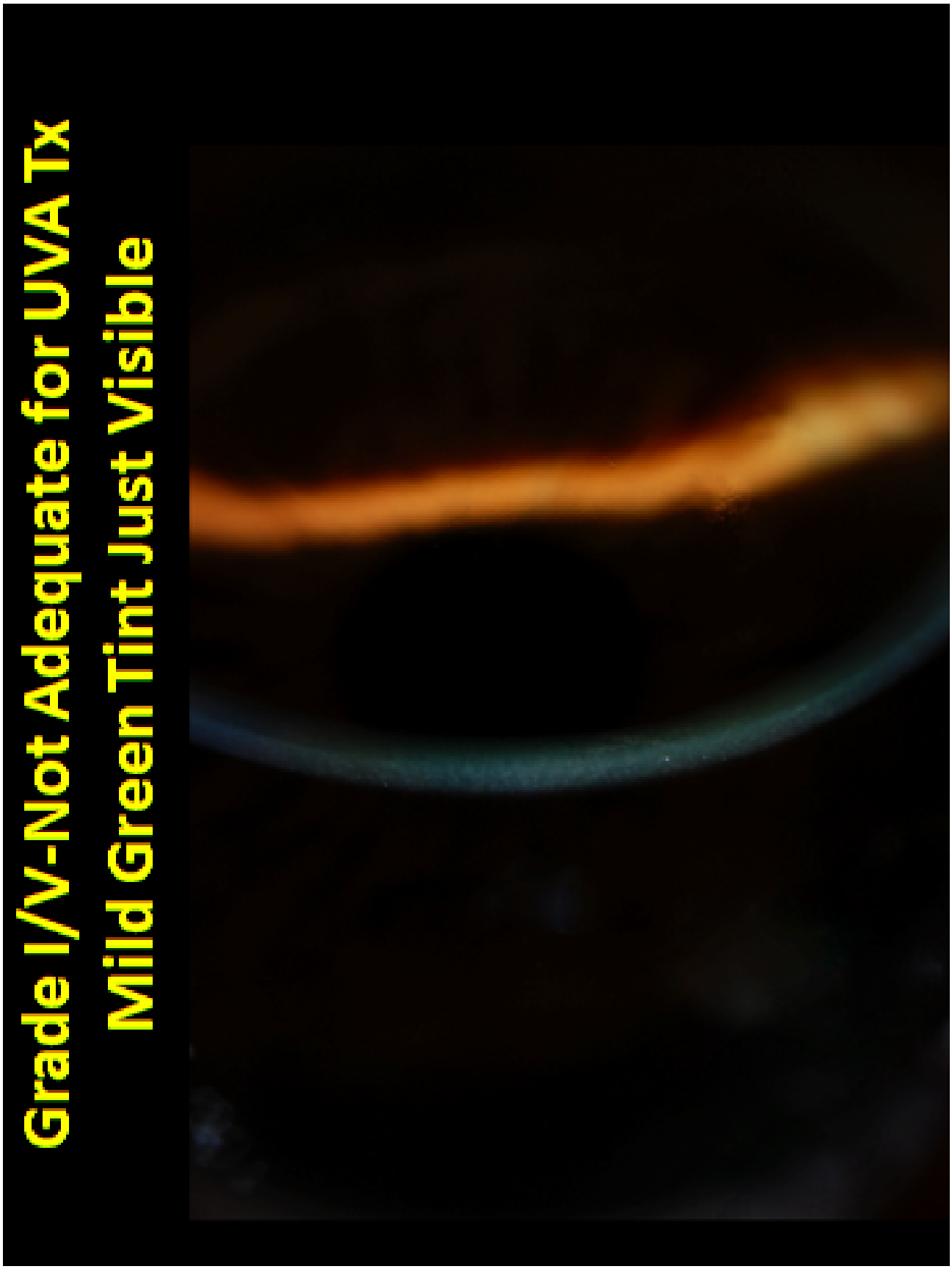

Homogeneous, Well Distributed
Riboflavin Loading (Blue Light)

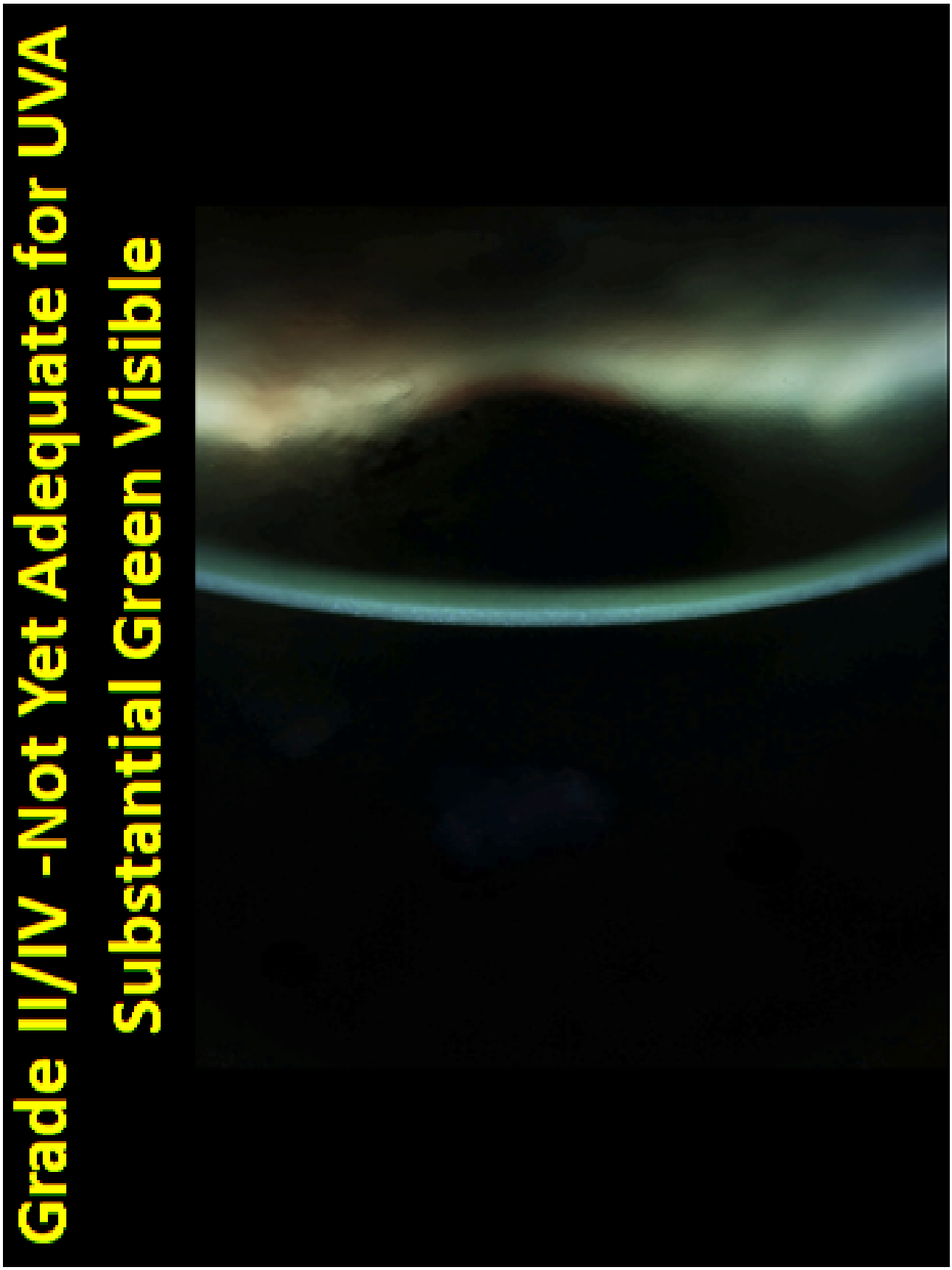
2. Concentration

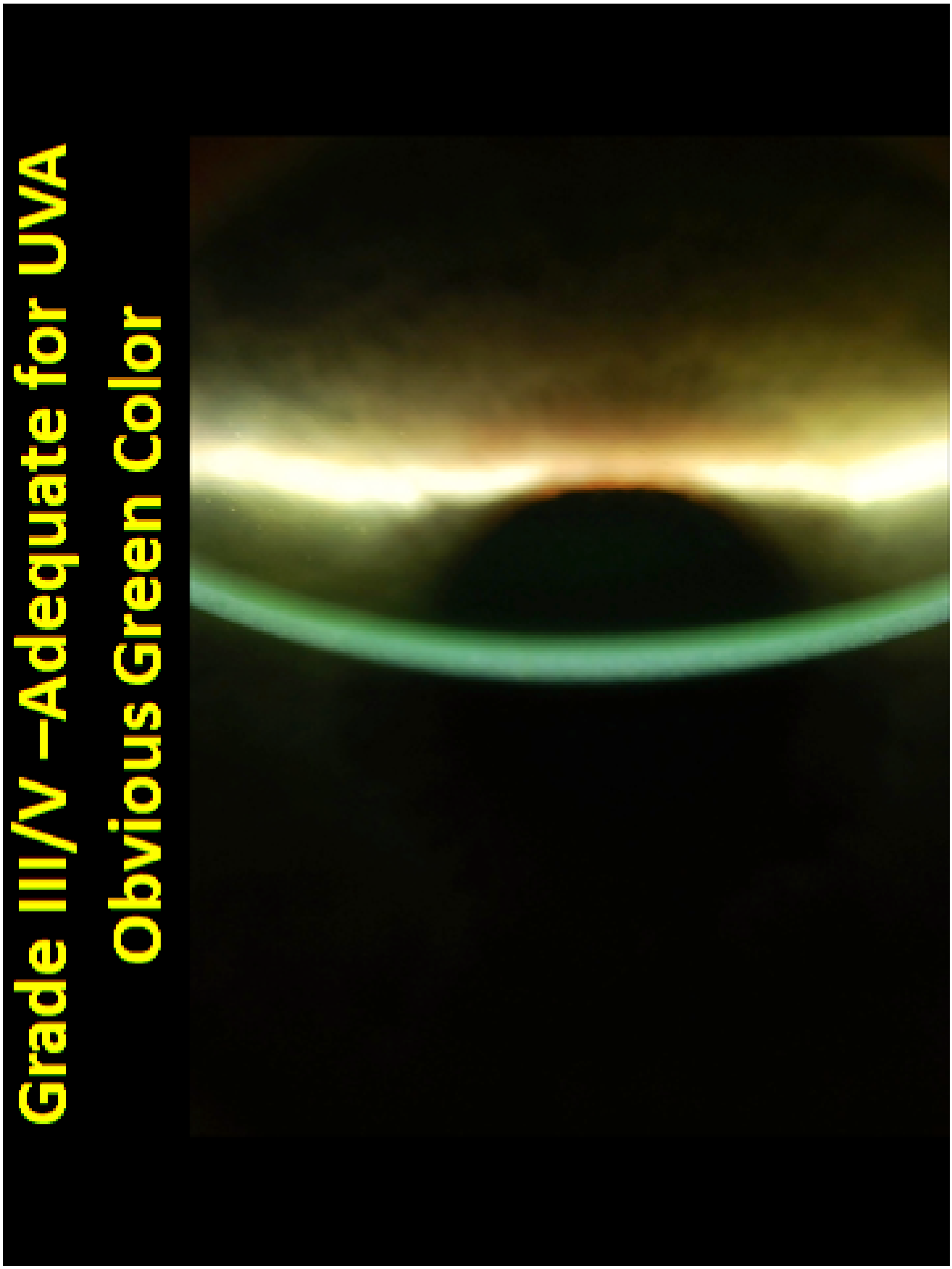
Objective: Grades III-V/V Prior to UVA Application.

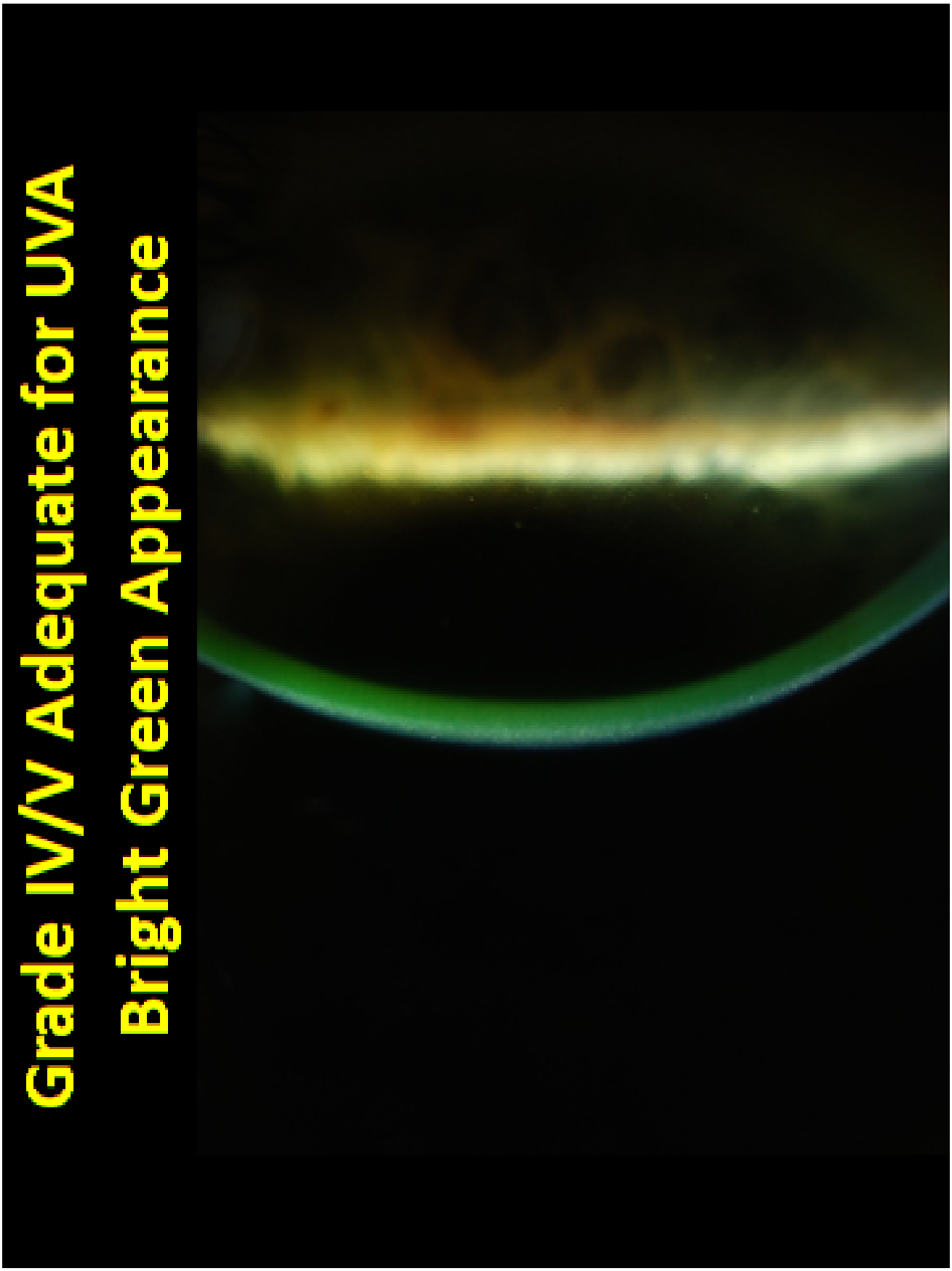
Riboflavin acts as a catalyst so Grade V/V is not more effective than Grade III.

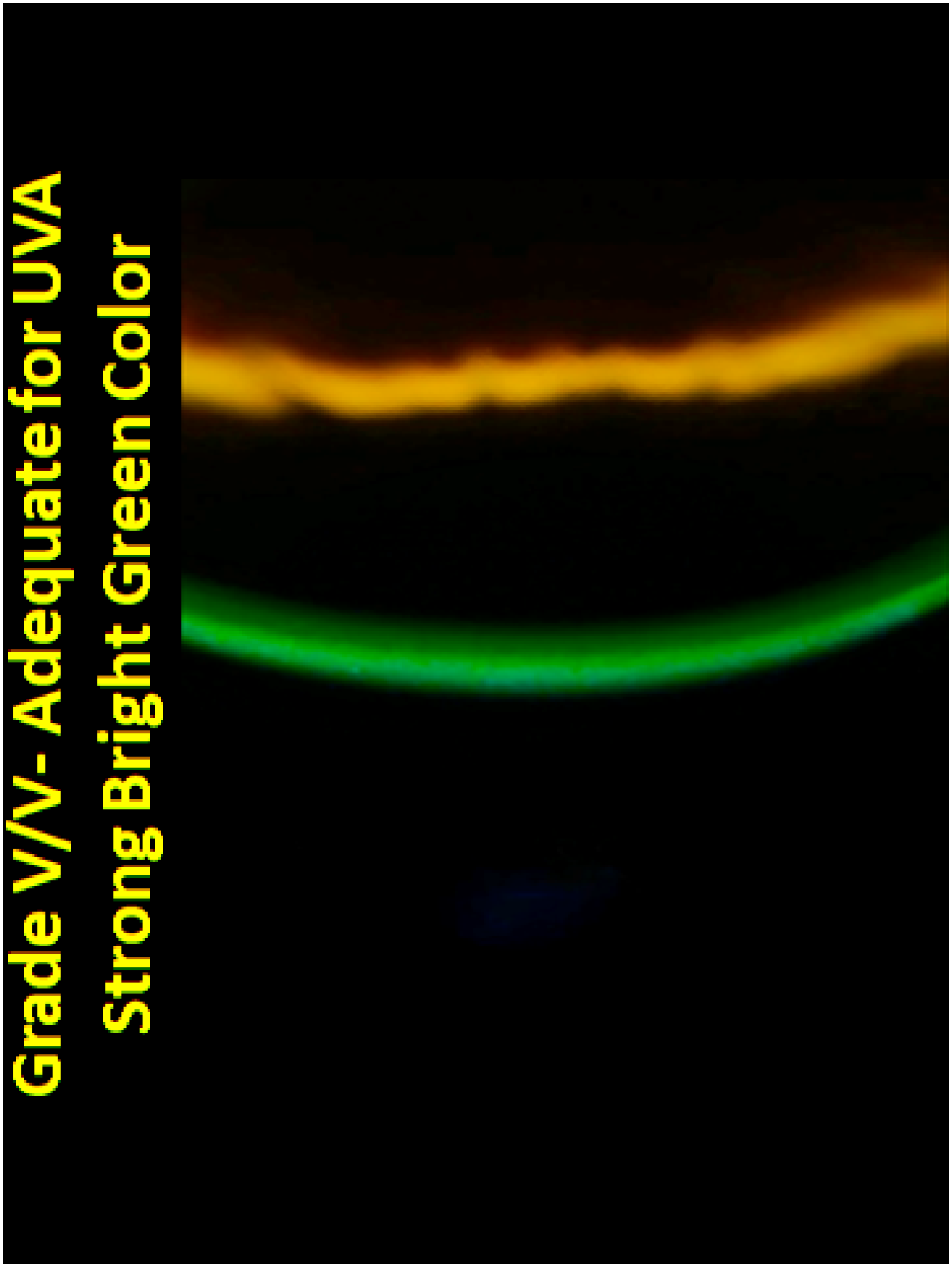

Before Riboflavin Application
Grade 0/V -No Green Visible


Grade I/V-Not Adequate for UVA Tx
Mild Green Tint Just Visible


Grade II/IV -Not Yet Adequate for UVA
Substantial Green Visible


Grade III/V –Adequate for UVA
Obvious Green Color

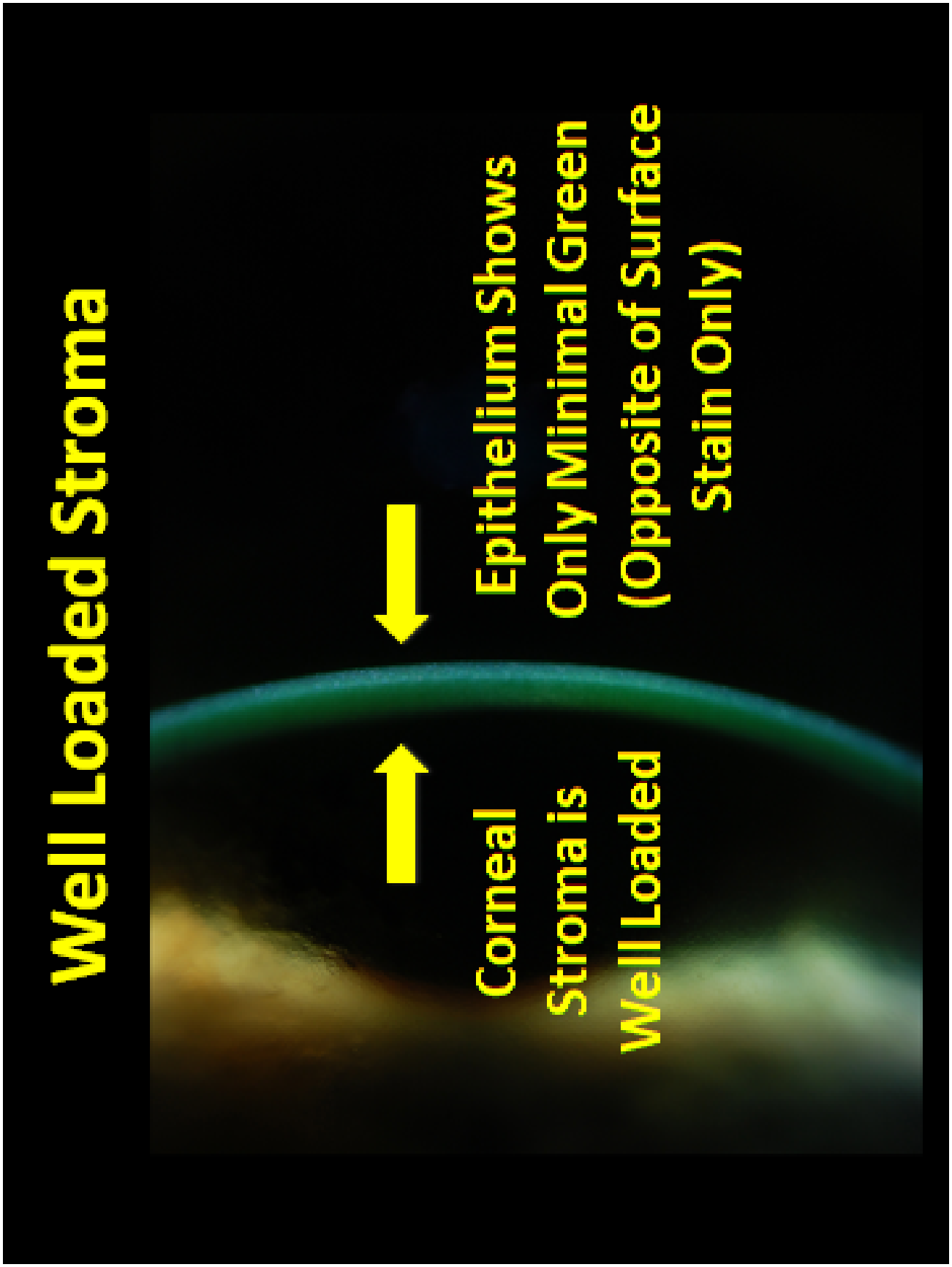

Grade IV/V Adequate for UVA
Bright Green Appearance


Grade V/V- Adequate for UVA
Strong Bright Green Color

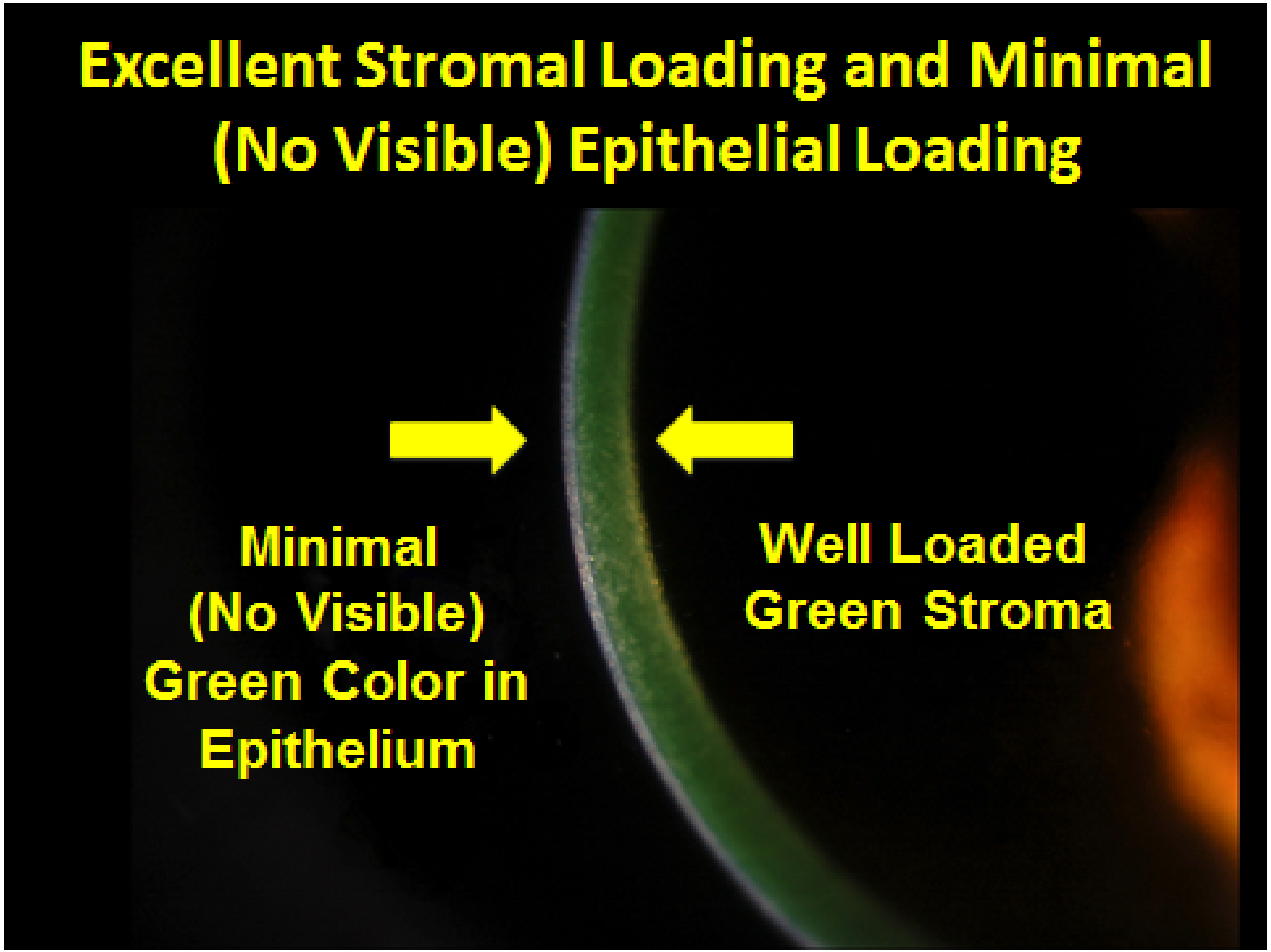
3. Location
Objective: Well Loaded Corneal Stroma and Minimal Loading of Epithelium to Optimize UVA Penetration into Corneal Stroma.

Anterior Chamber Flare is NOT Required
or Desirable Before UVA Application
Goal is to Cross-Link Cornea, not AC


Superficial Green Color
Only In Tear Film
Green in Surface
Tear Film Only
No Green in
Corneal Stroma


Well Loaded Stroma
Epithelium Shows Only Minimal Green (Opposite of Surface Stain Only)
Corneal Stroma is Well Loaded

Artificial Tears
After SL Confirmation of Adequate Stromal Riboflavin Loading, Applying Artificial Tears for ~30 Sec Allows the Epithelium to Clear Prior to UVA Application


Excellent Stromal Loading and Minimal (No Visible) Epithelial Loading
Minimal (No Visible) Green Color in Epithelium
Well Loaded Green Stroma


End of Presentation

APPENDIX 2: SCHEDULE OF ASSESSMENTS

	Pre-Procedure	Post-Op Day 1	*Optional Post-Op Days 2-10*	*Optional Post-Op Month 1-2*	Post-Op Month 3 (60-120 Days)	*Post-Op Month 6 (150-180 Days)*	Optional Post-Op 1 Year	Optional Post-Op 2 Year	Optional Post-Op 3 Year
Informed Consent	X								
Demographics	X								
Medical History/Concomitant Medications	X			X[3]	X	X	X	X	X
Contact Lens History	X			X[3]	X	X	X	X	X
History of Prior Eye Surgery	X								
Slit Lamp Exam	X	X	X	X	X	X	X	X	X
Fundus Exam	X[1]								
Intraocular Pressure (IOP)	X	X[3]	X	X	X	X	X	X	X
Uncorrected Visual Acuity (UCVA)	X	X	X	X	X	X	X	X	X
Corrected Distance Visual Acuity (CDVA)	X	X[3]	X[3]	X[3]	X	X	X	X	X
Manifest Refraction	X	X[3]	X[3]	X[3]	X	X	X	X	X
Pachymetry	X[2]	X[3]	X[3]	X	X[2]	X	X	X	X
Pentacam Corneal Topography/Tomography	X	X[3]	X[3]	X	X	X	X	X	X
Quality of Life Survey	X[3]				X[3]	X[3]	X[3]	X[3]	X[3]
Prior Eyeglass Prescriptions, UCVA, CDVA, and Topographic Maps	X[3]								
Other Optional Assessments	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]

[1] OR DOCUMENTED DILATED FUNDUS EXAM BY ANOTHER PROVIDER
[2] BY ULTRASOUND OR OTHER SCANNING DEVICE SUCH AS PENTACAM
[3] OPTIONAL ASSESSMENT PROCEDURES
[4] OTHER ASSESSMENTS INCLUDE **CORNEAL WAVEFRONT, OPTICAL COHERENCE TOMOGRAPHY (OCT), BRILLOUIN MICROSCOPY, ITRACE WAVEFRONT ABERROMETRY/TOPOGRAPHY, ORBSCAN CORNEAL TOPOGRAPHY, TOMOGRAPHY, CONTRAST SENSITIVITY TESTING, OR OTHER NON-INVASIVE DIAGNOSTIC TOOLS THAT MAY BE AVAILABLE TO AN INVESTIGATOR.**

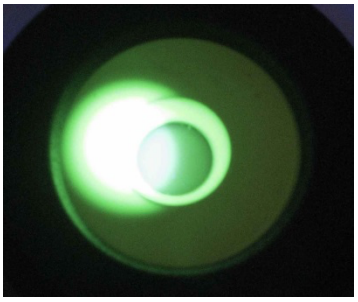
APPENDIX 3: UVA LIGHT CALIBRATION, CENTERING, AND APPLICATION INSTRUCTIONS

UVA Light Calibration, Centering, and Application Instructions to Ensure Safe UVA Treatment

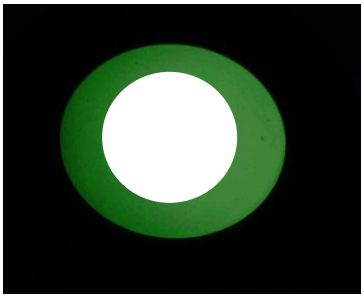
NOTE: Please read the CXLUSA UVA Illumination System User's Manual prior to initiating clinical use. No patient is to be treated with UVA unless adequate corneal stromal riboflavin loading has been confirmed by slit lamp examination using the grading system defined in the Study Flip Chart.

The UVA study device has a fixed, non-adjustable aperture. To achieve consistent 12 mm diameter circular UVA beam (for either 4 or 6 mW/cm^2 treatment) the following steps must be performed prior to every cross-linking procedure.

1. Put on a pair of safety glasses supplied with the UVA Illumination System.
2. Turn ON the UVA Illumination Source, and allow 10 minutes for warm-up prior to calibration.
3. Draw a 12 mm diameter circle on a white piece of paper.
4. Place the external radiometer on a solid surface (cart, counter-top, etc.).
5. Place the white piece of paper on top of the external radiometer.
6. Set the Shutter Select Switch on the front of the UVA illumination source to "Open".
7. Set the selector on the front of the Power Control Box mounted on the pole with caster base to "Single," to limit UVA output to the left emission aperture only.
8. Swipe a "Calibration" magnetic card through the card reader to activate UVA illumination and confirm that the UVA light is on by observing a bright white spot on the white piece of paper.
9. Adjust the distance from the left emission aperture optic to the paper until the beam spot size is the same as that of the 12 mm diameter circle, and record this distance.
10. Remove the paper from the top of the radiometer, and by moving the radiometer from side-to-side, verify that the 12 mm beam encompasses the **entire** area of the 9 mm diameter radiometer sensor. This assures that the radiometer will accurately measure UVA irradiance and that the UVA device will be properly calibrated.



Incorrect



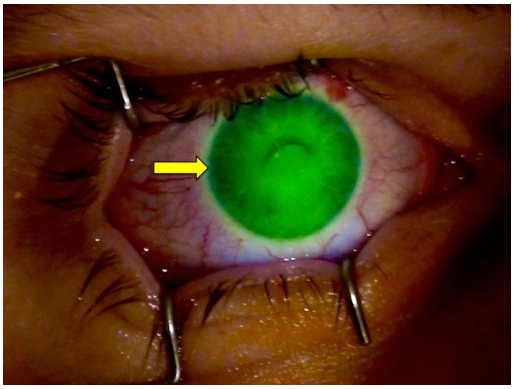
Correct

9 mm diameter radiometer sensor covered by 12 mm diameter UVA beam

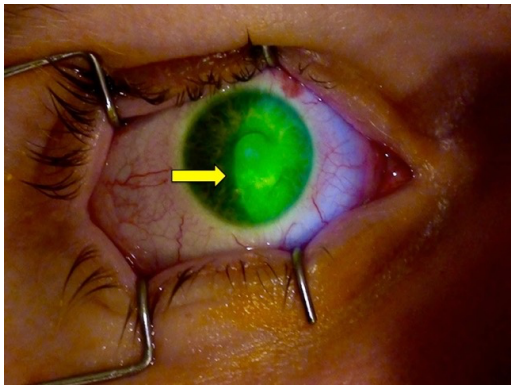
←

11. Turn the knob on the Intensity Adjustment box mounted on the pole with caster base clockwise/counterclockwise to adjust the UVA output to the desired irradiance (e.g. 4 or 6 mW/cm^2).
12. If simultaneous, bilateral corneal cross-linking will be performed, turn the selector switch on the front of the Power Control Box to "Dual". Note that the LED on top of the control box is illuminated.
13. Repeat calibration steps above to calibrate the right UVA emission aperture.
14. After completion of calibration procedures, re-swipe the Calibration card to close the illumination source shutter.
15. Ensure the patient is lying down in a comfortable position. Provide a pillow for their back or neck if needed to ensure comfort and reduce movement during the treatment. Instruct the patient to remain in this position without moving their head and, when necessary, repeat these instructions to avoid movement during the procedure.
16. For treatment, position the UVA optic at the distance from the cornea that was previously measured to create a 12 mm diameter circle. This consistently provides a 12 mm UVA beam spot size.
17. Swipe a Treatment card labeled with the Randomization Group to which the patient has been randomized.
18. Center the beam on the cornea. This is easily performed since the UVA beam spot size is easily delineated by bright fluorescence of the riboflavin-loaded cornea, assuring for easy and consistent beam centration. Use this fluorescence and easy visibility of the beam to confirm accurate positioning at the initiation UVA illumination, and throughout the Treatment procedure.

    If the patient moves, you will see the beam is off center. The image below shows a decentered beam that can be seen to not sufficiently cover the cornea (right yellow arrow) and to be decentered onto the eyelid (left yellow arrow). During the UV procedure, the centration is monitored in this fashion in each eye. In this image, no speculum has been placed. In the current study, speculae will be placed which will also assist in centration and placement of the UVA beam making these even more accurate and safer.



Beam Properly Centered



Beam Off Center

19. Monitor the patient's cooperation and eye position during the dark cycle of treatment i.e. when the UVA light has been turned off by the illumination source shutter. If the patient tends to look away from the optic, this is obvious and the patient should be instructed to look straight ahead again.

20. Be aware also of the cadence of UVA light turning on and off at consistent 15-second intervals. This is easily monitored by observation of the light turning on and off and by the audible sound of the illumination source shutter opening and closing.

21. To ensure optimum accuracy and precision in calibration, radiometers should be replaced 12 months after receipt.