A Phase 3, Multi-center, Randomized, Double-masked, Placebo/Sham-controlled Study to Evaluate the Safety and Efficacy of Oxygen Enriched, Non-invasive Epithelium-on Corneal Collagen Cross-linking in Eyes with Keratoconus

PROTOCOL NUMBER:	GLK-202-02
NCT Number	NCT05759559
IND NUMBER:	077882
VERSION NUMBER:	1.0
VERSION DATE:	18 NOVEMBER 2022
STUDY PHASE:	3
SPONSOR:	Glaukos Corporation One Glaukos Way Aliso Viejo, CA 92656
MEDICAL MONITOR/ CONTACT INFORMATION:	[redacted]

A Phase 3, Multi-center, Randomized, Double-masked, Placebo/Sham-controlled Study to Evaluate the Safety and Efficacy of Oxygen Enriched, Non-invasive Epithelium-on Corneal Collagen Cross-linking in Eyes with Keratoconus

SPONSOR SIGNATORIES

[redacted]

[redacted]

Date

[redacted]

Date

[redacted]

Date

[redacted]

Date

1. SYNOPSIS

Study Phase:	Phase 3
Protocol Title:	A Phase 3, Randomized, Double-masked Multicenter Study to Evaluate the Safety and Efficacy of Oxygen Enriched, Non-invasive Epithelium-on Corneal Collagen Cross-linking in Eyes with Keratoconus
Objective:	The objectives of this study are to evaluate the safety and efficacy of epithelial-on corneal collagen cross-linking (CXL) in impeding the progression of, and/or reducing maximum corneal curvature in eyes with keratoconus.
Study Population:	This study is a multicenter study that will be conducted at up to 40 investigational sites in the United States in approximately 290 eyes with [redacted] keratoconus.
Study Duration:	The expected study duration for each subject is approximately [redacted], with a 45-day screening window and approximately [redacted] post treatment follow-up as a combination of 12-month post-treatment primary efficacy evaluation period followed by a [redacted]) and a [redacted]
Inclusion Criteria:	**Subjects <u>must</u> meet all of the following criteria in order to be enrolled into the trial. Study eyes must meet all of the ocular criteria to be included in the trial:** 1. Be between 12 and 55 years of age, male or female, of any race; 2. Provide written informed consent and sign a HIPAA form prior to performing any Screening visit activities. Subjects who are under the age of 18 (or have not yet reached the age of majority per local regulations) will need to sign an assent form as well as having a parent or legal guardian sign an informed consent 3. Willingness and ability to follow all instructions and comply with schedule for follow-up visits; 4. For females capable of becoming pregnant, agree to have urine pregnancy testing performed prior to randomization of each study eye [redacted]; must not be lactating, and must agree to use a medically acceptable form of birth control for at least one week prior to the randomization [redacted] continue to use the method for one month following [redacted] treatment. Acceptable forms for birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (e.g. hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);

	5. Having topographic and clinical evidence of keratoconus defined as the following: [redacted]
Exclusion Criteria:	**Subjects <u>must not</u> meet any of the following criteria in order to be enrolled into the trial:** 1. Contraindications, sensitivity or known allergy to the use of the test article(s) or their components, or to the Investigator's standard-of-care pre-treatment medications or to the protocol-specified post-treatment medications; 2. If female, be pregnant, nursing or planning a pregnancy or have a positive urine pregnancy test prior to the randomization or treatment of either eye or during the course of the study; [redacted] 7. Previous ocular condition (other than refractive error) in the eye to be treated that may predispose the eye for future complications. For example:

	[redacted] 8. A history of delayed epithelial healing in the eye to be treated or a current condition that may interfere with or prolong epithelial healing; [redacted] 10. A history of previous corneal cross-linking treatment in the eye to be treated; 11. Have used an investigational drug or device within 30 days of screening or be concurrently enrolled in another investigational drug or device trial within 30 days of the study; [redacted]
Study Design and Primary Efficacy Evaluation Criteria:	This is a multicenter, randomized, sham-controlled study of the safety and efficacy of oxygen enriched, epithelium-on corneal collagen cross-linking (CXL). Up to 290 study eyes with progressive keratoconus will be enrolled to provide at least 261 evaluable eyes for the primary efficacy endpoint. Study eyes will be randomized in a 2:1 ratio to receive CXL treatment or sham/control treatment. The primary efficacy endpoint is the mean change in K_{max} from baseline to Month 12. [redacted]
Study Treatment(s):	[redacted] Randomization between the CXL treatment group and sham control group will be in a 2:1 ratio within each stratum. [redacted] • <u>CXL Treatment Group:</u> The corneal epithelium will not be removed. The study eye will receive [redacted] Riboflavin Ophthalmic Solution [redacted] Riboflavin Ophthalmic Solution [redacted] The eye will be irradiated [redacted] • <u>Sham Treatment/Control Group:</u> The corneal epithelium will not be removed. The study eye will receive [redacted] Placebo [redacted]

	[redacted] Placebo The eye will be irradiated Further details regarding the CXL treatment and Sham treatment are provided in Section 10.2.2.2. If both eyes of a subject are eligible for the study, both eyes may be enrolled in the study and each eye will be randomized separately. However, one eye will undergo the study procedure first. The second eye can be randomized and undergo the study procedure between the Week 1 and Month 3 visits for the first eye. Each eye will follow the examination schedule through crossover Month 6 (Visit 16) relative to the day the study procedure was performed in that eye.
Examination Schedule:	Following the screening period (Day -45 to Day -1), study eyes will be randomized (Day 1) to either the CXL Treatment group or the Sham Treatment/Control group. Study eyes will receive the study treatment on Day 1 per the randomization assignment. CXL Treatment Group: Post-procedure, study eyes in the CXL Treatment group will be assessed at Day 2, Day 4, Week 1, Months 1, 3, 6, and 12. Additional clinical visits may be scheduled at the discretion of the Investigator. Sham Treatment/Control Group: Post-procedure, study eyes in the Sham Treatment/Control group will be assessed at Day 2, Day 4, Week 1, Months 1, 3, 6, and 12. Additional clinical visits may be scheduled at the discretion of the Investigator. [redacted]
Safety Evaluations:	• Pentacam Pachymetry • Intraocular pressure (IOP) • Adverse events (AEs) • Best Spectacle Corrected Visual Acuity (BSCVA) assessed using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts • Slit lamp biomicroscopy • Manifest refraction • Dilated fundus exam • Endothelial Cell Count (ECC)

	• Macular Optical Coherence Tomography (OCT) [redacted]
Efficacy Evaluations:	[redacted]
Sample Size/Power:	The sample size for this study is based on unequal group sizes with the number of eyes in the crosslinked group being 2 times greater than in the control group (2:1 randomization). Two hundred sixty-one (261) eyes (174 in the cross-linking treatment group and 87 in the control group) provides greater than 99% power [redacted] between the cross-linking treatment group and the control group at Month 12. [redacted] Additionally, this sample size yields [redacted] in the mean change in K_{max} from baseline at Month 12. The sample size for this study is determined to be 290 eyes [redacted]

1.1. STUDY SCHEDULE

Visit Name	Screen	Treatment	POST-TREATMENT VISITS[13]						
			1 Day Day 2	3 Day Day 4	1 Wk Wk 1	1 MO Mo 1	3 MO Mo 3	6 MO Mo 6	12 MO Mo 12
Study Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit Window	Day -45 to -1	Day 1	Day 2 to 3	Day 4 to 5	Day 6 to 15	Day 22 to 43	Day 85 to 99	Day 180 to 210	Day 360 to 390
Procedure									
Informed Consent/ Assent	X								
Medical & Medication History[1]	X	X	X	X	X	X	X	X	X
Demographics	X								
BSCVA[2]	X					M[11]	M[11]	M[11]	M[11]
UCVA[2]	X		X	X	X	M[11]	M[11]	M[11]	M[11]
Manifest Refraction	X					M[11]	M[11]	M[11]	M[11]
Intraocular Pressure Measurement[3]	X					X	X	X	X
Slit Lamp Exam	X	X[9]	X	X	X	X	X	X	X
Dilated Fundus Examination[4]	X						X	X	X
Pentacam Tomography and Pachymetry[5]	X					X	X	X	X
Ultrasound Pachymetry		X[10]							
Endothelial Cell Count[6]	X						X	X	X
Macular and anterior segment OCT[7]	X					X[12]	X	X	X
Adverse Event Query		X	X	X	X	X	X	X	X
Study Treatment		X							
Pregnancy Test[8]		X							

[1] Ocular status and/or history including history of contact lens wear. Non-specific questioning should be used at each visit to determine other vision-related complaints, complications, or adverse events.

[2] Distance BSCVA and UCVA will be performed using a calibrated ETDRS eye chart and recording the total number of letters that are read correctly.

[3] Intraocular pressure measurement by Goldmann applanation tonometry at the slit lamp. A Tonopen or Pneumotonometer may be used only if applanation tonometry is medically contraindicated or deemed to be unreliable. Contraindication must be documented in the subject's chart.

[4] The status of the lens, optic disc (including cup/disc ratio), macula, retinal vessels and peripheral retina should be examined.

[5] Pentacam measurements are performed using the Pentacam [redacted]

[6] Endothelial cell counts will be obtained via specular microscopy. [redacted]

[7] Anterior segment and macular optical coherence tomographies (OCTs) [redacted]

[8] Females capable of becoming pregnant must have urine pregnancy testing performed prior to randomization of the study eye [redacted] must not be lactating, and must agree to use a medically acceptable form of birth control for at least one week prior to the randomization [redacted] and continue to use the method for one month following [redacted] treatment.

[9] Slit lamp exam on treatment day should be performed prior to randomization and immediately following treatment.

[10] Ultrasound pachymetry should be performed on Treatment day after completion of the riboflavin or placebo ophthalmic solutions, prior to initiating UV treatment.

[11] Measurements indicated by an "M" will be conducted by a masked examiner who will not be aware of which treatment has been performed. The masked examiner should not conduct any study examinations on that subject beyond the assessments indicated with the "M".

[12] Only anterior segment OCT is required at Visit 6 (Month 1).

[13] Subject needs to complete all follow-up visits with the Investigator and/or study team on site.

Ocular Assessments will be performed only on the study eye.

[redacted]

Visit Name	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Visit #	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
[redacted] t Procedure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed Consent/ Assent							
Medical & Medication History[1]	X	X	X	X	X	X	X
Demographics							
BSCVA[2]					M[11]	M[11]	M[11]
UCVA[2]		X	X	X	M[11]	M[11]	M[11]
Manifest Refraction					M[11]	M[11]	M[11]
Intraocular Pressure Measurement[3]					X	X	X
Slit Lamp Exam	X[9]	X	X	X	X	X	X
Dilated Fundus Examination[4]						X	X
Pentacam Tomography and Pachymetry[5]					X	X	X
Ultrasound Pachymetry	X[10]						
Endothelial Cell Count[6]						X	X
Macular and anterior segment OCT[7]					X[12]	X	X
Adverse Event Query	X	X	X	X	X	X	X
Study Treatment	X						
Pregnancy Test[8]	X						

[1] Ocular status and/or history including history of contact lens wear. Non-specific questioning should be used at each visit to determine other vision-related complaints, complications, or adverse events.

[2] Distance BSCVA and UCVA will be performed using a calibrated ETDRS eye chart and recording the total number of letters that are read correctly.

[3] Intraocular pressure measurement by Goldmann applanation tonometry at the slit lamp. A Tonopen or Pneumotonometer may be used only if applanation tonometry is medically contraindicated or deemed to be unreliable. Contraindication must be documented in the subject's chart.

[4] The status of the lens, optic disc (including cup/disc ratio), macula, retinal vessels and peripheral retina should be examined.

[5] Pentacam measurements are performed using the Pentacam [redacted]

[6] Endothelial cell counts will be obtained via specular microscopy. [redacted]

[7] Anterior segment and macular optical coherence tomographies (OCTs) will be performed [redacted]

[8] Females capable of becoming pregnant must have urine pregnancy testing performed prior to randomization of the study eye [redacted] must not be lactating, and must agree to use a medically acceptable form of birth control for at least one week prior to the randomization visit, [redacted] and continue to use the method for one month following [redacted] treatment.

[9] Slit lamp exam on treatment day should be performed prior to randomization and immediately following treatment.

[10] Ultrasound pachymetry should be performed on Treatment day after completion of the riboflavin or placebo ophthalmic solutions, prior to initiating UV treatment.

[11] Measurements indicated by an "M" will be conducted by a masked examiner who will not be aware of which treatment has been performed. The masked examiner should not conduct any study examinations on that subject beyond the assessments indicated with the "M".

[12] Only anterior segment OCT is required at Visit 14 [redacted]

[13] Subject needs to complete all follow-up visits with the Investigator and/or study team on site.

Ocular Assessments will be performed only on the study eye.

TABLE OF CONTENTS

SPONSOR SIGNATORIES 2
1. SYNOPSIS 3
1.1. STUDY SCHEDULE 8
1.2. CROSSOVER SCHEDULE 10
TABLE OF CONTENTS 12
2. LIST OF ABBREVIATIONS 16
3. BACKGROUND AND RATIONALE 18
3.1. NONCLINICAL EXPERIENCE 19
3.2. PREVIOUS HUMAN EXPERIENCE 20
4. STUDY OBJECTIVES 25
5. OVERALL STUDY DESIGN 25
6. STUDY POPULATION 26
6.1. NUMBER OF SUBJECTS 26
6.2. STUDY POPULATION CHARACTERISTICS 26
6.3. INCLUSION CRITERIA 26
6.4. EXCLUSION CRITERIA 27
6.5. WITHDRAWAL CRITERIA 28
7. STUDY PARAMETERS 28
7.1. EFFICACY EVALUATIONS 28
7.1.1. PRIMARY EFFICACY ENDPOINT 29
7.1.2. SECONDARY EFFICACY ENDPOINT 29
7.2. SAFETY EVALUATIONS 29
8. INVESTIGATIONAL PRODUCT(S) 29
8.1. [redacted] RIBOFLAVIN OPHTHALMIC SOLUTIONS [redacted] 29
8.2. PLACEBO SOLUTION 30
8.3. UV-A IRRADIATION SYSTEM (KXL HIGH POWER) 30
8.4. OXYGEN DELIVERY SYSTEM 30
8.5. SUPPLY/LABELING/PACKAGING 31
8.6. STORAGE REQUIREMENTS 31
8.6.1. RIBOFLAVIN OPHTHALMIC SOLUTIONS 31
8.6.2. UV-A IRRADIATION SYSTEM 31

8.6.3. STUDY MATERIALS 31
8.7. ACCOUNTABILITY, RETURN, OR DISPOSAL OF TEST ARTICLE(S) 31
9. RANDOMIZATION 32
9.1. KERATOCONUS SEVERITY 32
9.2. ALLOCATION OF STUDY TREATMENT 32
9.2.1. CXL TREATMENT GROUP 33
9.2.2. SHAM TREATMENT/CONTROL GROUP 33
10. STUDY PROCEDURES 33
10.1. INFORMED CONSENT/HIPAA 33
10.1.1. ENROLLMENT 33
10.2. STUDY PROCEDURES 34
10.2.1. VISIT 1 [redacted] SCREENING VISIT 34
10.2.2. VISIT 2 (DAY 1): TREATMENT 34
10.2.3. VISITS 3 (DAY 2 TO 3): DAY 2 AND VISIT 11 [redacted] 40
10.2.4. VISIT 4 (DAY 4 TO 5): DAY 4 AND VISIT 12 [redacted] 40
10.2.5. VISIT 5 (DAY 6 TO 15): WEEK 1 AND VISIT 13 [redacted]
10.2.6. VISIT 6 (DAY 22 TO 43): MONTH 1 AND VISIT 14 [redacted]
10.2.7. VISIT 7 (DAY 85 TO 99): MONTH 3 AND VISIT 15 [redacted]
10.2.8. VISIT 8 (DAY 180 TO 210): MONTH 6 AND VISIT 16 [redacted]
10.2.9. VISIT 9 (DAY 360 TO [redacted] 43
10.2.10. VISIT 10 [redacted] 44
10.3. ADDITIONAL/UNSCHEDULED VISITS 44
10.3.1. MISSED VISIT 44
10.3.2. EXIT VISIT 44
10.4. STUDY TERMINATION 44
10.5. SUBJECT STUDY DURATION 44
10.5.1. COMPLETED SUBJECTS 44
10.5.2. DISCONTINUED SUBJECTS 44
10.6. MONITORING AND QUALITY ASSURANCE 45
10.6.1. MONITORING 45

10.6.2. INSTITUTIONAL REVIEW BOARD 45
11. ADVERSE EVENTS 45
11.1. RELATIONSHIP OF TEST ARTICLE TO EACH ADVERSE EVENT 46
11.2. SEVERITY OF ADVERSE EVENT(S) 46
11.3. OUTCOME OF ADVERSE EVENT(S) 46
11.4. SERIOUS ADVERSE EVENTS AND SERIOUS UNEXPECTED SUSPECTED ADVERSE REACTIONS 47
11.4.1. DEFINITIONS 47
11.5. SERIOUS AND UNANTICIPATED ADVERSE DEVICE EFFECTS 48
11.6. NON-SERIOUS DRUG OR DEVICE OR ANTICIPATED DEVICE ADVERSE EVENTS 48
11.7. PROCEDURES FOR REPORTING ADVERSE EVENTS 48
11.8. PROCEDURES FOR REPORTING A SERIOUS ADVERSE EVENT 48
12. STATISTICAL HYPOTHESES AND METHODS OF ANALYSES 49
12.1. GENERAL METHODS 49
12.2. STUDY POPULATIONS 50
12.2.1. INTENT-TO-TREAT POPULATION 50
12.2.2. SAFETY POPULATION 50
12.2.3. PER PROTOCOL POPULATION 50
12.3. EFFICACY VARIABLES 50
12.4. SAMPLE SIZE 50
12.5. PRIMARY EFFICACY ANALYSES 50
12.5.1. PRIMARY EFFICACY ENDPOINT 50
12.6. SECONDARY EFFICACY ANALYSES 51
12.6.1. SECONDARY EFFICACY ENDPOINT 51
12.7. HANDLING OF MISSING DATA AND DATA AFTER INTERCURRENT EVENTS 51
[redacted]
12.9. INTERIM ANALYSIS 52
12.10. PREVENTION OF BIAS 52
12.11. MULTIPLICITY ADJUSTMENT 52
12.12. SAFETY ANALYSIS 52
12.12.1. OVERALL INCIDENCE OF ADVERSE EVENTS 53
12.13. ADDITIONAL ANALYSIS 53

[redacted]

13. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES 54
13.1. PROTECTION OF HUMAN SUBJECTS 54
13.1.1. COMPLIANCE WITH INFORMED CONSENT REGULATIONS 54
13.1.2. COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD REGULATIONS 55
13.1.3. COMPLIANCE WITH THE DECLARATION OF HELSINKI 55
13.1.4. SUBJECT CONFIDENTIALITY 55
13.1.5. DOCUMENTATION 55
13.1.6. RETENTION OF DOCUMENTATION 55
13.2. RECORDING OF DATA ON SOURCE DOCUMENT AND ELECTRONIC CASE REPORT FORMS (ECRFS) 56
13.3. CHANGES IN THE CONDUCT OF THE STUDY 56
14. APPENDIX A: ASSESSMENT INSTRUCTIONS 57
14.1. VISUAL ACUITY TESTING 57
14.2. SLIT LAMP EXAMS 57
14.3. PENTACAM TOPOGRAPHY 58
14.4. SPECULAR MICROSCOPY 59
15. INVESTIGATOR SIGNATURE PAGE 60
16. REFERENCES 61

2. LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AS	Anterior Segment
BSCVA	Best Spectacle Corrected Visual Acuity
[redacted]	[redacted]
CXL	Corneal Cross-linking
D	Diopter
DHHS	Department of Health and Human Services
ECC	Endothelial Cell Count
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IOP	Intraocular Pressure
ITT	Intent-to-Treat
K_{max}	Maximum corneal curvature
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	Manifest Refraction Spherical Equivalent
[redacted]	[redacted]
OCT	Optical Coherence Tomography
PP	Per Protocol
[redacted]	[redacted]
[redacted]	[redacted]

SAE	Serious Adverse Event
UCVA	Uncorrected Visual Acuity
UV-A	Ultraviolet-A light
VA	Visual Acuity

3. BACKGROUND AND RATIONALE

Keratoconus is a naturally occurring ocular condition characterized by progressive thinning and steepening of the central cornea. As a result of this weakening, the cornea protrudes under the force of intraocular pressure and bows outward. This creates progressive steepening and thinning of the cornea, irregular astigmatism, and loss of uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA). Rigid contact lenses can be used to improve visual acuity in patients, but keratoconus can progress to the point that corneal transplantation is required to restore useful vision.

Keratoconus is the most frequent, known indication for corneal transplantation, accounting for about 15% of the corneal transplants performed in the United States.[1] Corneal transplantation has inherent risks that could result in permanent loss of vision and significantly impact the patient's quality of life during the surgical recovery phase, with lost work time and often permanent changes in lifestyle. Any modality, such as corneal collagen cross-linking, that can delay or prevent corneal transplantation in patients with these conditions is of great benefit.

Riboflavin 5'-phosphate sodium (Vitamin B2) is the precursor of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze oxidation/reduction reactions involved in a number of metabolic pathways. When used in conjunction with ultraviolet A light (UVA), riboflavin 5'-phosphate acts as a photoenhancer and generates singlet oxygen which is responsible for cross-linking of collagen.

The corneal collagen cross-linking procedure is intended to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma. Corneal collagen cross-linking is performed by pretreating the cornea with riboflavin ophthalmic solution before UV-A (365 nm) exposure. Exposure of the cornea to the UV-A after topical administration of riboflavin has been shown to induce cross-linking of the corneal collagen fibrils with a resultant increase in tensile strength and diameter of the collagen fibrils. Clinically, cross-linking has been shown to stabilize the corneal curvature in eyes with keratoconus.

Corneal collagen cross-linking using riboflavin and UV-A was first used clinically in 1998 in Dresden, Germany.[2] Since then, corneal cross-linking has been studied and clinically used worldwide for the treatment of ectatic disorders, including keratoconus. [3-10]

The corneal cross-linking procedure using the riboflavin ophthalmic solutions PHOTREXA® VISCOUS and PHOTREXA® and the KXL® System was approved by the U.S Food and Drug Administration (FDA) in 2016 for the treatment of [redacted] keratoconus and corneal ectasia following refractive surgery.

The approved cross-linking procedure entails debridement of the epithelium (epithelium-off) to allow for penetration of the riboflavin into the stroma. The epithelial removal/debridement commonly produces pain, redness, light sensitivity, a temporary decrease in vision (caused by an irregularity in the corneal surface as the epithelium re-surfaces the cornea), and an increase in susceptibility to infection.

This current study is being conducted to assess the safety and efficacy of oxygen enriched, corneal collagen cross-linking without epithelial debridement (epithelium-on) in eyes with [redacted] keratoconus. The epithelium-on procedure consists of a riboflavin formulation containing a permeability enhancer that allows riboflavin diffusion to the corneal stroma without the need to remove the epithelium. This is followed by UV-A irradiation with supplemental oxygen. It is expected that the oxygen enriched,

epithelium-on corneal cross-linking procedure will be efficacious in reducing or halting the progression of keratoconus without the risks associated with epithelial removal.

3.1. Nonclinical Experience

Nonclinical studies have been conducted to evaluate the safety of transepithelial riboflavin formulations containing benzalkonium chloride (BAC) as a permeability enhancer, as well to establish the safety of transepithelial corneal cross-linking in the presence of supplemental oxygen.

GLP Rabbit Ocular Irritation Study

An ocular irritation and safety study was performed under good laboratory practices, evaluating the ocular safety of riboflavin formulated with different concentrations [redacted] after acute topical ocular dosing in New Zealand White rabbits. [redacted] No abnormal findings or gross lesions were observed upon necropsy and no adverse clinical observations were reported throughout the life of the study.

Non-GLP Rabbit Study

The objective of this non-GLP study was to evaluate the safety of corneal cross-linking procedure related to stromal haze and corneal swelling in normoxic and hyperoxic environments in the rabbit. This study consisted of 3 groups of 2 or 4 female New Zealand White rabbits. Animals underwent a single procedure on Day 1 in which the right eye was treated with VibeX Rapid™ [redacted] after epithelial debridement or ParaCel™ [redacted] and VibeX Xtra™ with or without oxygen therapy. All Groups received UV light administered [redacted] pulsed 1 second on, 1 second off, for a total of 8 minutes. A balanced salt solution (BSS) was applied during UV light administration every minute to keep the eye moist until the UV-A illumination was complete.

[redacted]

[redacted]

There was no evidence of endothelial loss in treated corneas in all animals in all 3 groups.

3.2. Previous Human Experience

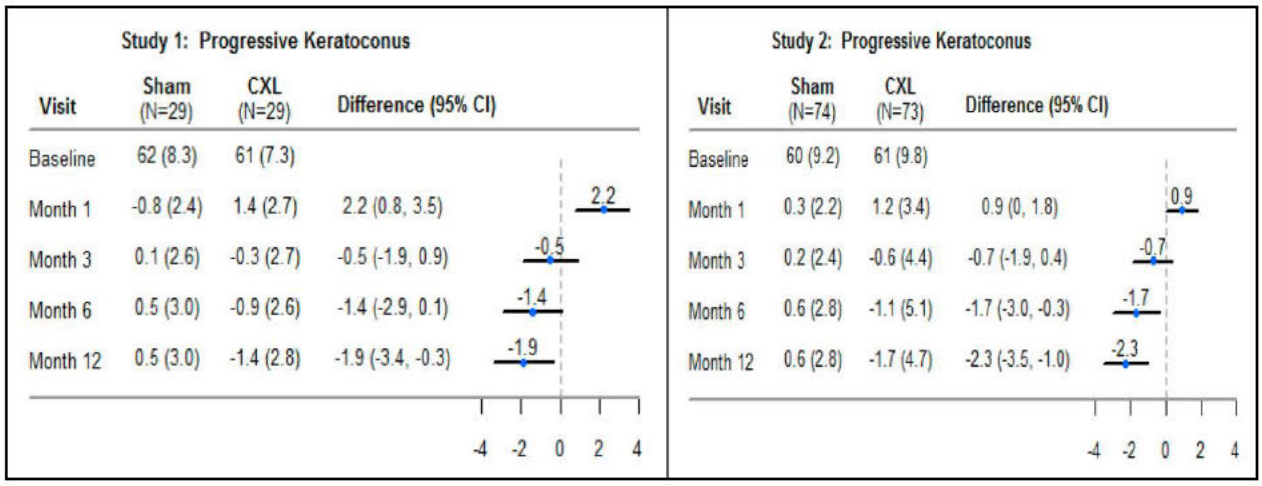
FDA approved Avedro's corneal collagen cross-linking products Photrexa Viscous, Photrexa and the KXL System for use in corneal collagen cross-linking in the treatment of progressive keratoconus and corneal ectasia following refractive surgery in 2016. The approved cross-linking procedure entails debridement of the epithelium (epithelium-off) to allow for penetration of the riboflavin into the stroma.

Approved Epithelium-off Corneal Cross-linking (5.4 J/cm^2)

The safety and effectiveness of riboflavin ophthalmic solution and UV-A irradiation (365 nm; 3 mW/cm^2) for performing corneal collagen cross-linking (with epithelial debridement) in eyes with progressive keratoconus were evaluated in two prospective, open-label, randomized, sham-controlled trials in the U.S. (Studies UVX-001 and UVX-002). One eye of each subject was deemed the study eye and randomized to receive either the corneal cross-linking (CXL) procedure or the sham procedure. Patients were followed for safety and efficacy for 12 months after the CXL procedure. Patients who received the sham procedure were able to receive the CXL procedure in their study eyes 3 months after the sham procedure. Study UVX-001 enrolled 58 progressive keratoconus patients and 49 post refractive surgery corneal ectasia patients. Study UVX-002 enrolled only progressive keratoconus patients (147 patients).

In Studies UVX-001 and UVX-002, the average age of keratoconus subjects was 33 years and the average baseline maximum corneal curvature (K_{max}) was 61 diopters (D). At Month 12 in study UVX-001, the CXL treated keratoconus eyes had an average K_{max} reduction of 1.4 D compared to an average increase in K_{max} of 0.5 D in the sham treated eyes for a difference of 1.9 D between the treatment groups. In study UVX-002 at Month 12, the CXL treated eyes had an average K_{max} reduction of 1.7 D compared with an average increase in K_{max} of 0.6 D in the sham treated eyes for a difference of 2.3 D between the treatment groups (see **Figure 1**).

Figure 1: Mean Change from Baseline Kmax in Patients with Progressive Keratoconus (UVX-001, UVX-002)



Post-baseline missing data were imputed using last available K_{max} value. For the sham study eyes that received the cross-linking treatment after baseline, the last K_{max} measurement recorded prior to receiving cross-linking treatment was used in the analysis at later time points.

In progressive keratoconus subjects, the most common ocular adverse reactions in any CXL-treated eye were corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision. These events are expected sequelae following epithelial corneal debridement and occurred at a higher incidence than observed in control (sham group) subjects, who did not undergo debridement or UV exposure. The majority of adverse events reported resolved during the first month, while events such as corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye, and eye pain, and decreased visual acuity took up to 6 months to resolve. Corneal opacity or haze took up to 12 months to resolve. In 1-2% of subjects, corneal epithelium defect, corneal edema, corneal opacity and corneal scar continued to be observed at 12 months.

<u>US Clinical Studies of Epithelium-off Corneal Cross-linking</u> [redacted]

Studies KXL-001 and KXL-002 were Phase 3, multi-center, randomized, placebo-controlled studies of the safety and efficacy of high power/accelerated corneal collagen cross-linking performed with UV-A irradiation [redacted] and [redacted] riboflavin ophthalmic solution [redacted] in eyes with keratoconus. In these studies, the cross-linking was performed after removal of the epithelium (i.e., epithelium off) and the cornea irradiated [redacted] continuously for 4 minutes [redacted] These studies are completed and data analysis is in progress.

<u>ACP-PiXL-101: Dose Escalation, Safety Study of Epithelium-on Corneal Cross-linking</u> [redacted]

Glaukos study ACP-PiXL-101 was performed at the Singapore National Eye Centre in Singapore and was designed to evaluate the safety of trans-epithelial corneal cross-linking. This Phase 1 study was conducted in blind eyes with normal corneas. Cross-linking was performed with the epithelium intact, a two-part transepithelial riboflavin formulation [redacted] a high-power UV-A Irradiation System [redacted] Five (5) patients with functionally blind eyes were enrolled and treated in the Phase 1 study. Two sequential UV dose groups [redacted] were

evaluated. Three (3) patients were assigned to Dose Group 1 and 2 patients were assigned to Dose Group 2 Patients were evaluated at screening, Day 0 (treatment day) and Day 1, week 1, and 1 and 3 months after treatment. Study evaluations included slit lamp evaluations, corneal tomography, anterior segment optical coherence tomography (OCT), specular microscopy and adverse event (AE) query. There were no treatment-related serious adverse events (SAE) reported in this study. In conclusion, cross-linking performed using transepithelial riboflavin, , and high-power UV-A at doses of was well tolerated in this study.

ACP-KXL-308: A Phase 3, Multi-center Study to Evaluate the Safety and Efficacy of Epithelium-on Corneal Collagen Cross-linking in Eyes with Progressive Keratoconus

This was a multicenter, randomized, sham-controlled study of the safety and efficacy of epithelium-on corneal collagen cross-linking (CXL). Study eyes were randomized in a 2:1 treatment allocation to receive CXL treatment or Sham/Control treatment, and was stratified on baseline keratoconus severity (mild, moderate, severe) in the study eye within each clinical trial site.

A total of 280 eyes of 201 subjects were randomized of which 189 eyes of 156 subjects received CXL treatment and 90 eyes of 83 subjects received Sham/Control treatment for a total of 279 treated eyes. This resulted in a total of being treated with CXL , and subjects

After the Month 6 Visit, at which time eyes in the Sham/Control group 88 eyes of 81 subjects who received CXL treatment during the study

The study met both its primary and secondary efficacy criteria in that the mean difference in change from baseline in LS mean K_{max} between the CXL group and the Sham/Contro

At the Month 6 Visit in the change from baseline in K_{max} between the CXL treatment group and Sham/Control treatment group. In the CXL treated eyes, respectively, while in the group of Sham/Control eyes, At the Month 12 Visit, from baseline in CXL treated eyes and in Sham/Control eyes, respectively.

Although the primary efficacy analysis was performed on the ITT population [redacted] the robustness of the result was supported by sensitivity analyses on the ITT and PP populations [redacted]

The secondary efficacy analysis was performed on the ITT population [redacted]
The robustness of the result was supported by sensitivity analyses on the ITT population [redacted]

At the Month 6 Visit, the mean change from baseline in K_{max} for all 277 CXL treated eyes [redacted]

At the Month 6 Visit, the mean (SD) change from baseline in K_{max} for Sham/Control CXL crossover eyes was [redacted]

[redacted]

The safety of CXL treatment was based on an analysis of ocular and non-ocular treatment-emergent adverse events, as well as an analysis of MRSE, BSCVA, UCVA, dilated fundus examination parameters, central corneal thickness, IOP, endothelial cell count, macular central subfield thickness, [redacted]

From baseline through the Month 6 Visit, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Epithelium-on collagen corneal cross-linking using riboflavin ophthalmic solutions [redacted] in conjunction with UV-A irradiation and [redacted] is safe and effective for the treatment of [redacted] keratoconus in adolescents and adults.

Together, these clinical and nonclinical data support the investigation of epithelium-on corneal cross-linking as described in this clinical protocol for the treatment of [redacted] keratoconus.

4. STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and efficacy of epithelial-on corneal collagen cross-linking in reducing, or impeding the progression of, the maximum corneal curvature (K_{max}) in patients with [redacted] keratoconus.

5. OVERALL STUDY DESIGN

This is a multicenter, randomized, double-masked, sham-controlled study of the safety and efficacy of oxygen enriched, epithelium-on corneal collagen cross-linking for the treatment of [redacted] keratoconus.

The primary efficacy endpoint is the mean change in K_{max} from baseline to Month 12.

Subjects with a diagnosis of [redacted] keratoconus will be screened for participation in this clinical study. Subjects that may be candidates for cross-linking will be asked to participate in this study and will undergo the required screening procedures to determine study eligibility. Prior to any study data being collected for screening purposes, informed consent will be obtained. After completing screening procedures, compliance with inclusion and exclusion criteria will be evaluated. Once it has been determined that the subject meets all inclusion and exclusion criteria, the Investigator will identify the eye to be treated as the study eye. If both eyes meet the eligibility criteria, both eyes may be enrolled in the study and each eye will be randomized separately. However, one eye will be treated first and the second eye randomized and treated [redacted] after the first eye.

Following the screening period (Day -45 to Day -1), study eyes will be randomized on Treatment Day (Day 1) prior to receiving study treatment. [redacted] Randomization between the CXL treatment group and sham treatment/control group will be in a 2:1 ratio within each stratum within each clinical site. Study eyes will receive one of the following treatments based on the randomization allocation:

- CXL Treatment Group: The corneal epithelium will not be removed. The study eye will receive [redacted] Riboflavin Ophthalmic Solution [redacted] Riboflavin Ophthalmic Solution [redacted] The eye will be irradiated [redacted]
- Sham Treatment/Control Group: The corneal epithelium will not be removed. The study eye will receive [redacted] Placebo [redacted] Placebo [redacted] The eye will be irradiated [redacted]

Further details regarding the CXL treatment and Sham treatment are provided in Section 10.2.2.2.

Post-procedure, eyes will be assessed at Day 2, Day 4, Week 1, Months 1, 3, 6, and 12 and at Day 2, Day 4, Week 1, Months 1, 3, and 6 [redacted]. Additional clinical visits may be scheduled at the discretion of the Investigator. Pentacam measurements, manifest refraction, Uncorrected Visual Acuity (UCVA), Best

Spectacle Corrected Visual Acuity (BSCVA), specular microscopy, dilated fundus examination, Optical Coherence Tomography (OCT) [redacted] and intraocular pressure (IOP) will be obtained at baseline and at the specified times after the treatment. Safety monitoring throughout the study will include observations at appropriate times for AEs, new findings on ophthalmic examination, dilated fundus examination, and slit lamp examination.

Post-procedure follow-up visits and assessments will be contingent on the type of study treatment:

CXL Treatment Group: Post-procedure, study eyes in the CXL Treatment group will be assessed at Day 2, Day 4, Week 1, Months 1, 3, 6, and 12. Additional clinical visits may be scheduled at the discretion of the Investigator.

Sham Treatment/Control Group: Post-procedure, study eyes in the Sham Treatment/Control group will be assessed at Day 2, Day 4, Week 1, Months 1, 3, 6, and 12. Additional clinical visits may be scheduled at the discretion of the Investigator.

[redacted]

6. STUDY POPULATION

6.1. Number of Subjects

Up to 290 study eyes with [redacted] keratoconus will be randomized to provide at least 261 (174 in the CXL treatment group and 87 in the control group) evaluable eyes for the primary efficacy endpoint. [redacted]

6.2. Study Population Characteristics

This study is a multicenter study that will be conducted at approximately 40 investigational sites in the United States in approximately 290 eyes with [redacted] keratoconus.

6.3. Inclusion Criteria

Subjects must meet all of the following criteria in order to be enrolled into the trial. Inclusion criteria specific to ocular conditions should be evaluated separately for each eye being screened into the study:

1. Be between 12 and 55 years of age, male or female, of any race;
2. Provide written informed consent and sign a HIPAA form. Subjects who are under the age of 18 (or have not yet reached the age of majority per local regulations) will need to sign an assent form as well as having a parent or legal guardian sign an informed consent;
3. Willingness and ability to follow all instructions and comply with schedule for follow-up visits;
4. For females capable of becoming pregnant, agree to have urine pregnancy testing performed prior to randomization of each study eye [redacted] must not be lactating, and must agree to use a medically acceptable form of birth control for at least one week prior to the randomization visit, [redacted] and

continue to use the method for one month following [redacted]. Acceptable forms for birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (e.g., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);

5. Having topographic and clinical evidence of keratoconus defined as the following:



6.4. Exclusion Criteria

Subjects <u>must not</u> meet any of the following criteria in order to be enrolled into the trial. Exclusion criteria specific to ocular conditions should be evaluated separately for each eye being screened into the study:

1. Contraindications, sensitivity or known allergy to the use of the test article(s) or their components, or to the Investigator's standard-of-care pre-treatment medications or to the protocol-specified post-treatment medications;
2. If female, be pregnant, nursing or planning a pregnancy or have a positive urine pregnancy test prior to the randomization or treatment of either eye or during the course of the study;

[redacted]

7. Previous ocular condition (other than refractive error) in the eye to be treated that may predispose the eye for future complications. For example:
   [redacted]
8. A history of delayed epithelial healing in the eye to be treated or a current condition that may interfere with or prolong epithelial healing;
   [redacted]
10. A history of previous corneal cross-linking treatment in the eye to be treated;
11. Have used an investigational drug or device within 30 days of screening or be concurrently enrolled in another investigational drug or device trial within 30 days of the study;
    [redacted]

6.5. Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time. Subjects experiencing adverse safety events will be followed until the event resolves or stabilizes, or until the subject completes the study, whichever is first. The Investigator may discontinue a subject if a Serious Adverse Event (SAE) occurs, and it is in the subject's best interest not to continue in the study. When a subject withdraws early from the study, a final examination will be performed at the time of withdrawal, if possible. Subjects withdrawn from the study will not be replaced.

7. STUDY PARAMETERS

7.1. Efficacy Evaluations

The following parameters will be assessed as measures of efficacy of the cross-linking treatment:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline in maximum corneal curvature (K_{max}) between the CXL treatment group and the Sham treatment/control group at Month 12.

7.1.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is the mean change from baseline in maximum corneal curvature (K_{max}) between the CXL treatment group and the Sham treatment/control group at Month 6.

7.2. Safety Evaluations

The following safety parameters will be assessed:

[redacted]

8. INVESTIGATIONAL PRODUCT(S)

8.1. [redacted] Riboflavin Ophthalmic Solutions [redacted]

The trans-epithelial riboflavin kit consists of 2 riboflavin ophthalmic solutions [redacted] Each riboflavin ophthalmic solution is sterile filtered and filled under aseptic conditions in 2.25 mL glass syringes with luer lock adapter and sealed for topical ophthalmic use. Each pre-filled syringe is placed in a labeled, light-blocking package.

Ingredient	Purpose
[redacted]	

Ingredient	Purpose
[redacted]	

8.2. Placebo Solution

The Placebo [redacted]

Ingredient	Purpose
[redacted]	

8.3. UV-A Irradiation System (KXL High Power)

The UV-A irradiation system is an electronic medical device which delivers ultraviolet light [redacted] in a circular pattern onto the cornea. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. [redacted]

8.4. Oxygen Delivery System

The oxygen delivery system ([redacted] provides supplemental oxygen to the cornea during UV illumination, for enhancing the cross-linking reaction. [redacted]

[redacted]

8.5. Supply/Labeling/Packaging

The riboflavin ophthalmic solutions and placebo are provided in 2.25 mL glass syringes with plunger rod in light-blocking packaging.

8.6. Storage Requirements

8.6.1. Riboflavin Ophthalmic Solutions

The riboflavin ophthalmic solutions and placebo should be stored at [redacted] and care should be taken to minimize exposure of the syringe to light once removed from its protective packaging.

[redacted]

8.6.2. UV-A Irradiation System

The UV-A irradiation system should be operated at ambient temperature of [redacted] and relative humidity of [redacted] non-condensing. Additional information regarding the maintenance and storage of the UV-A Irradiation System is included in the UV-A Irradiation System Operator's Manual.

8.6.3. Study Materials

All test article(s) and unused [redacted] must be stored in a locked area with access limited to the Investigator and designated personnel. All investigational materials will be returned to the secure area with access limited to the Investigator and designated personnel. Used [redacted] will be stored in the subject's source binder.

8.7. Accountability, Return, or Disposal of Test Article(s)

The Investigator must keep accurate accounts of the receipt, usage, return/disposal of all investigational products. Additionally, the Investigator must document details of the treatment procedure and the

amounts of riboflavin or placebo ophthalmic solutions used during the procedure, including lot numbers, for each study eye.

9. RANDOMIZATION

[redacted]

9.2. Allocation of Study Treatment

Subjects will be considered enrolled in the study once they have signed the informed consent form and been randomized. Study eyes of subjects that meet all the inclusion criteria and none of the exclusion criteria will be randomized to either the CXL Treatment group or the Sham Treatment/Control Group in a 2:1 allocation ratio. [redacted] Randomization will occur on Day 1 (Visit 2) immediately prior to cross-linking or sham treatment per Section 10.2.2. [redacted]

Subjects with bilateral keratoconus in which both eyes qualify for the study may have both eyes designated as study eyes by the Investigator; each eligible eye will be randomized independently. One eye will undergo the study procedure first. The second eye can be randomized to undergo the study procedure between [redacted] for the first eye.

Subjects may be re-screened if they are not randomized within 45 days of screening examinations, or if they have a history of [redacted] keratoconus [redacted] at the time of initial screening. Subjects who fail to meet any of the other eligibility criteria (do not meet any other inclusion criteria or meet any exclusion criteria) cannot be re-screened and will be documented as screen failures.

A [redacted] randomization scheme [redacted] will not be revealed to the participating Investigators or study site personnel.

9.2.1. CXL Treatment Group

Study eyes randomized to the CXL treatment group will undergo cross-linking treatment as described in Section 10.2.2.2.1, within 45 days of the completion of the screening measurements. Cross-linking must be performed on the same day as randomization, which will be considered Day 1.

9.2.2. Sham Treatment/Control Group

Eyes randomized to the control group will undergo a sham treatment, as described in Section 10.2.2.2.2, within 45 days of the completion of the screening measurements. Sham treatment must be performed on the same day as randomization, which will be considered Day 1.

10. STUDY PROCEDURES

10.1. Informed Consent/HIPAA

In accordance with the provision of 21 CFR Part 50, prior to a subject's participation in the study, the study will be discussed with each subject and subjects wishing to participate will sign a HIPAA authorization form and give written informed consent using an informed consent form. In addition, subjects who are under the age of 18 (or have not yet reached the age of majority per local regulations) will need to sign an assent form as well as have a parent or legal guardian sign an informed consent form. The informed consent and assent forms must be the most recent versions that have received approval by an Institutional Review Board (IRB).

The study will be explained to the prospective subject by the Investigator or designee. The subject will be informed that he/she is free to terminate participation in the study for any reason. The original signed consent form will be retained in the study chart. Once the informed consent has been signed, a subject number will be assigned which will consist of a 3-digit site number (e.g., 101) and a sequential 3-digit number (e.g., 001).

10.1.1. Enrollment

Subjects will be considered enrolled in the study if they have signed the informed consent and been randomized. Screening procedures may occur from 1 to 45 days prior to Treatment.

If the subject is a woman of childbearing potential, she must not be pregnant or lactating, and must have a negative urine pregnancy test at the time of enrollment. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (e.g., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).

10.2. Study Procedures

10.2.1. Visit 1 (Day -45 to -1): Screening Visit

All screening examination procedures will be performed by the Investigator or by delegated staff. Subjects will sign a consent form before any clinical protocol procedures or tests specific to the study protocol are performed, including for females of childbearing potential, the requirement to use a medically acceptable method of birth control one week prior to treatment and continue to use the method for one month following [redacted] treatment. Contact lens wearers only: after signing the informed consent form, must remove contact lenses for a 1-week period prior to the screening refraction and subject must agree to remain out of their contact lenses from the time of treatment until the 1-month visit is completed. A contact lens wearer is defined as someone who has worn contact lenses in the eye to be treated in the last 30 days.

Potential cross-linking candidates will undergo a complete eye examination to determine their eligibility for study participation. A complete ocular history, medical history and medication history will be obtained. The complete eye examination and ocular history will include:

- Confirmation that the study informed consent form has been signed
- History of contact lens wear
- UCVA (ETDRS)
- BSCVA (ETDRS)
- Manifest refraction
- Pentacam measurements, including
    - Pachymetry
    - Keratometry
    - Topography
- IOP (by Goldmann applanation tonometry)
- Slit lamp biomicroscopy
- Dilated fundus examination
- Specular microscopy for ECC
- Anterior segment and macular OCT [redacted]

Manifest refractions will be recorded on the source documents in the Investigator's usual notation (plus or minus cylinder format). All manifest refractions will be recorded on the electronic case report forms (eCRFs) for the study using negative cylinder format. Additional instructions for these test procedures are provided in Section 14 (Appendix A).

10.2.2. Visit 2 (Day 1): Treatment

All baseline measurements are to be completed and all eligibility requirements confirmed prior to randomization (Visit 2/Day 1).

The following will be performed at Visit 2 prior to Treatment:

- Updates to subject's medical and ocular history, medication, and ocular status

- Negative urine pregnancy test in females of childbearing potential
- Slit lamp biomicroscopy

Once it has been confirmed that the subject and study eye are eligible for the study, the study eye will be randomized. Sites will use the EDC system to randomize the subject's eye to either the CXL or Sham Treatment. [redacted]. The EDC system will record the subject and site number, [redacted] and the randomized assignment (either CXL Treatment or Sham Treatment). The Investigator or designee should print a copy of this information from the EDC system and maintain it in the subject's source document.

The following will be performed at Visit 2 during and/or after Treatment:

- Ultrasound pachymetry
    - Performed following the completion of Riboflavin or Placebo drop instillation [redacted]
- Slit lamp biomicroscopy
    - [redacted]
- AE collection (post-randomization)

10.2.2.1. Pre-Treatment Medications

Pre-treatment medications should be prescribed using the Investigator's standard of care. All pre-treatment medications will be recorded in the subject's chart.

10.2.2.2. Study Treatment

10.2.2.2.1. CXL Treatment

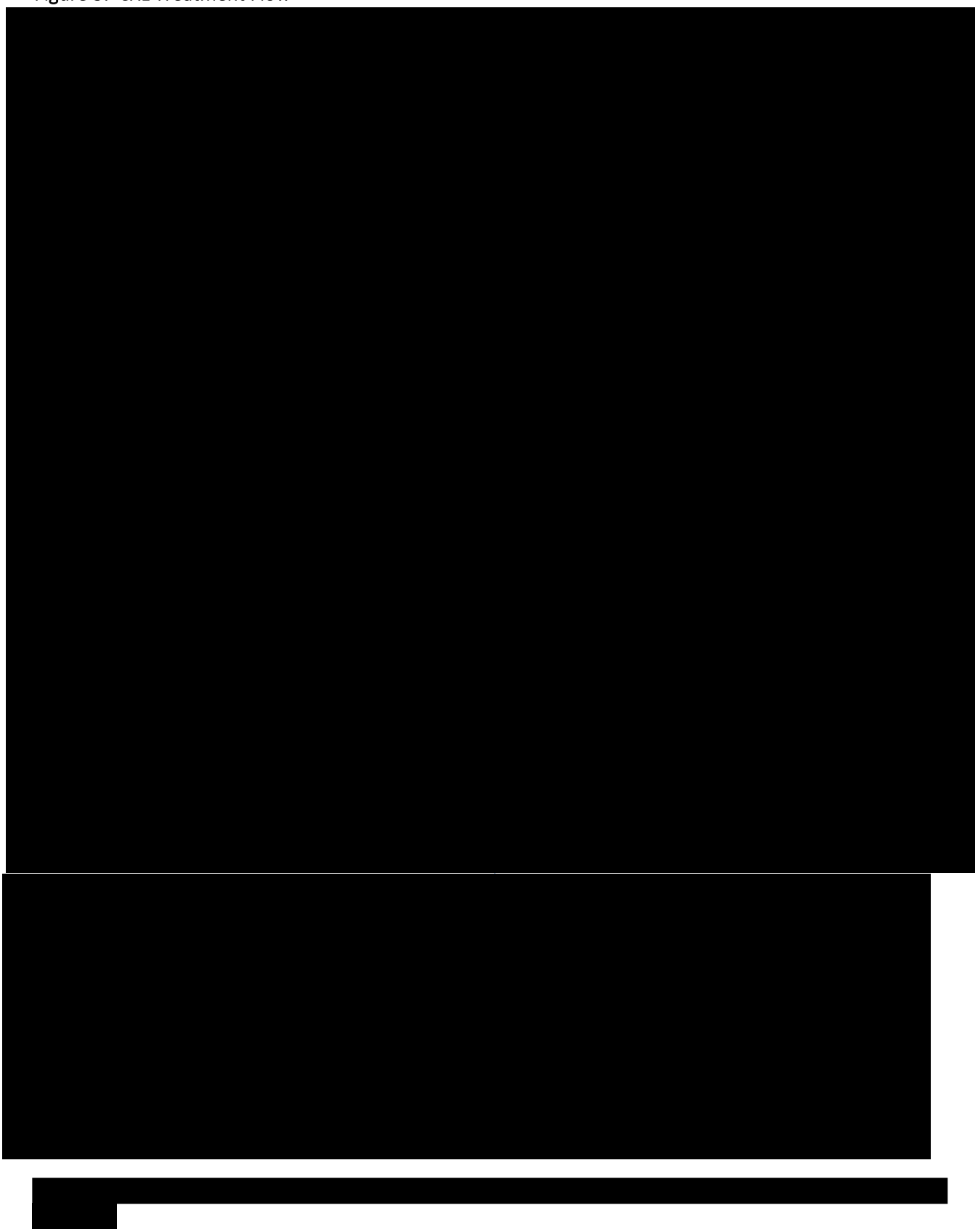
The corneal epithelium will not be removed. [redacted]

[redacted] the UV-A irradiation system should be turned on [redacted] UVA [redacted]

[redacted]

[redacted] eference flow chart below for the CXL Treatment flow (**Figure 3**).

Figure 3: CXL Treatment Flow



10.2.2.2.2. Sham Treatment

The corneal epithelium will not be removed. [redacted] the UV-A irradiation system should be turned on to deliver UV-A [redacted]

[redacted] Reference flow chart below for the Sham Treatment flow (**Figure 4**).

Figure 4: Sham Treatment Flow



10.2.2.3. Post-Treatment Medications

Prescriptions for post-treatment medications and post-treatment instructions will be given to all treated subjects and reviewed prior to discharge. [redacted]

- [redacted]

[redacted]

[redacted]

10.2.3. Visits 3 (Day 2 to 3): Day 2 and Visit 11 [redacted]

The following will be performed at Visit 3 and Visit 11:

- Documentation of interim medical, [redacted]
- Removal of bandage contact lens
- UCVA (ETDRS)
- Slit lamp biomicroscopy
- Documentation of any AEs

10.2.4. Visit 4 (Day 4 to 5): Day 4 and Visit 12 [redacted]

The following will be performed at Visit 4 and Visit 12:

- Documentation of interim medical, medication, and ocular status
- [redacted]
- UCVA (ETDRS)
- Slit lamp biomicroscopy
- Documentation of any AEs

10.2.5. Visit 5 (Day 6 to 15): Week 1 and Visit 13 [redacted]

The following will be performed at Visit 5 and Visit 13:

- Documentation of interim medical, medication, and ocular status
- [redacted]
- UCVA (ETDRS)
- Slit lamp biomicroscopy
- Documentation of any AEs

For subjects that have both eyes that are eligible to participate in the study, the second eye may be randomized and receive study treatment at this visit after completion of the protocol required examinations for the first study eye. The treatment must be performed as required in Section 10.2.2.2. [redacted] The subject will be required to return for examination during the visit windows for the Day 2, Day 4, Week 1, Months 1, 3, 6, and 12 post-procedure visits and for the [redacted]

[redacted] NOTE: If the subject is a female of childbearing potential, a urine pregnancy test is required to be performed prior to the second eye treatment.

10.2.6. Visit 6 (Day 22 to 43): Month 1 and Visit 14 [redacted]

An examiner who is masked to treatment assignment will be used to measure the UCVA, BSCVA, and manifest refraction at the 1-month examination. The masked examiner is a qualified study team member whom the Investigator has designated the responsibility of conducting this protocol requirement. The masked examiner will not be aware of the subject's treatment assignment. The masked examiner should not have access to the subject's medical and/or study records, which would unmask them to the subject's treatment assignment, and should not discuss the treatment with the subject. The masked examiner should not conduct any study examinations on that subject beyond the visual measurements indicated on the Schedule of Visits.

The following will be performed at Visit 6 and Visit 14:

- Documentation of interim medical, medication, and ocular status
- UCVA (ETDRS) (conducted by a masked examiner)
- BSCVA (ETDRS) (conducted by a masked examiner)
- Manifest refraction (conducted by a masked examiner)
- Pentacam measurements, including
    - Pachymetry
    - Keratometry
    - Topography
- IOP (by Goldmann applanation tonometry)
- Slit lamp biomicroscopy
- Only Anterior segment OCT [redacted]
- Documentation of any AEs

For subjects that have both eyes that are eligible to participate in the study, the second eye may be randomized and receive study treatment at this visit after completion of the protocol required examinations for the first study eye. The treatment must be performed as required in Section 10.2.2.2. [redacted] The subject will be required to return for examination during the visit windows for the Day 2, Day 4, Week 1, Month 1, 3, 6, and 12 post-procedure visits and for the [redacted] [redacted] NOTE: If the subject is a female of childbearing potential, a urine pregnancy test is required to be performed prior to the second eye treatment.

10.2.7. Visit 7 (Day 85 to 99): Month 3 and Visit 15 (Day 85 to 99): Month 3 Post Crossover [redacted]

An examiner who is masked to treatment assignment will be used to measure the UCVA, BSCVA, and manifest refraction at the 3-month examination.

The following will be performed at Visit 7 and Visit 15:

- Documentation of interim medical, medication, and ocular status
- UCVA (ETDRS) (conducted by a masked examiner)
- BSCVA (ETDRS) (conducted by a masked examiner)
- Manifest refraction (conducted by a masked examiner)
- Pentacam measurements, including
    - Pachymetry
    - Keratometry
    - Topography
- IOP (by Goldmann applanation tonometry)
- Slit lamp biomicroscopy
- Specular microscopy for ECC
- Anterior segment and macular OCT [redacted]
- Dilated fundus examination
- Documentation of any AEs

For subjects that have both eyes that are eligible to participate in the study, the second eye may be randomized and receive study treatment at this visit after completion of the protocol required examinations for the first study eye. The treatment must be performed as required in Section 10.2.2.2. [redacted] he subject will be required to return for examination during the visit windows for the Day 2, Day 4, Week 1, Month 1, 3, 6, and 12 post-procedure visits and for the [redacted] NOTE: If the subject is a female of childbearing potential, a urine pregnancy test is required to be performed prior to the second eye treatment.

10.2.8. Visit 8 (Day 180 to 210): Month 6 and Visit 16 [redacted]

An examiner who is masked to treatment type will be used to measure the UCVA, BSCVA, and manifest refraction at the 6-month examination.

The following will be performed at Visit 8 and Visit 16:

- Documentation of interim medical, medication, and ocular status
- UCVA (ETDRS) (conducted by a masked examiner)
- BSCVA (ETDRS) (conducted by a masked examiner)
- Manifest refraction (conducted by a masked examiner)
- Pentacam measurements, including
    - Pachymetry
    - Keratometry

  - Topography
- IOP (by Goldmann applanation tonometry)
- Slit lamp biomicroscopy
- Specular microscopy for ECC
- Anterior segment and macular OCT [redacted]
- Dilated fundus examination
- Documentation of any AEs

10.2.9. Visit 9 (Day 360 to 390): [redacted]

An examiner who is masked to treatment type will be used to measure the UCVA, BSCVA, and manifest refraction at the 12-month examination.

The following will be performed at Visit 9:

- Documentation of interim medical, medication, and ocular status
- UCVA (ETDRS) (conducted by a masked examiner)
- BSCVA (ETDRS) (conducted by a masked examiner)
- Manifest refraction (conducted by a masked examiner)
- Pentacam measurements, including
  - Pachymetry
  - Keratometry
  - Topography
- IOP (by Goldmann applanation tonometry)
- Slit lamp biomicroscopy
- Specular microscopy for ECC
- Anterior segment and macular OCT [redacted]
- Dilated fundus examination
- Documentation of any AEs

[redacted]

10.3. Additional/Unscheduled Visits

The Investigator may schedule subjects for additional clinic visit(s) at his/her discretion to ensure subject safety, such as subjects who have any AEs, including, but not limited to, ocular events.

10.3.1. Missed Visit

If a subject does not attend their scheduled visit, every attempt will be made to reschedule the visit within the visit window.

10.3.2. Exit Visit

An Exit visit will be scheduled for any subject that is discontinued from the study. Procedures conducted at an Exit visit are the same as those listed for the Month 12 visit in the Schedule of Visits for subjects who discontinue prior to Month 12 (Visit 9) [redacted] for subjects who [redacted] If early removal from the study is necessary, every effort will be made to perform an Exit examination before the subject is discontinued from the study.

10.4. Study Termination

The study may be stopped at any time by the Sponsor with appropriate notification.

10.5. Subject Study Duration

The expected study duration for each subject following treatment is [redacted] when only one eye receives the study treatment. For subjects that receive study treatment in both eyes, the study duration may be [redacted]

10.5.1. Completed Subjects

A completed eye is one that has not been discontinued and has completed the [redacted] visit (Visit 16).

10.5.2. Discontinued Subjects

Subjects/eyes may be discontinued prior to their completion of the study due to:

- Adverse event
- Death
- Protocol deviation
- Subject withdrew consent

- Subject became lost to follow-up
- Sponsor termination of study
- Lack of Efficacy
- Other

Note: Any subject may be discontinued for any sound medical reason. Notification of a subject discontinuation and the reason for discontinuation will be made available to the Sponsor and will be clearly documented on the subject's chart and CRF.

10.6. Monitoring and Quality Assurance

10.6.1. Monitoring

A monitor will be designated by the Sponsor to oversee the progress of the investigation. The monitor will be an employee of the Sponsor or a consultant to the Sponsor.

Sponsor will monitor all clinical studies in a manner consistent with any applicable health authority regulations including Good Clinical Practices (GCPs). Study monitoring involves the following elements:

Sponsor personnel will assess Investigators prior to the initiation of the study in order to review the adequacy of the patient population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the study protocol.

Sponsor personnel may meet 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.

Sponsor personnel may visit the clinical site at any time during the course of the study to ensure that the treatment procedures described in the protocol are being followed. Sponsor personnel may also observe examination techniques used by study personnel to ensure that the procedures being utilized are the procedures described in Appendix A to this protocol. Sponsor personnel will visit the clinical site to review and verify the accuracy of the eCRFs.

Remote monitoring may also be utilized between site monitoring visits. Sponsor personnel may require copies of source documents to be made available for off-site (remote monitoring). Subject data should be de-identified prior to transmission to Sponsor's personnel not at the Site.

Additionally, sites will be contacted as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

10.6.2. Institutional Review Board

This protocol and the informed consent form will be approved initially and reviewed by an IRB per the IRB's requirements constituted according to FDA regulations. SAEs will be reported to the IRB and the FDA in accordance with FDA regulations and IRB requirements.

11. ADVERSE EVENTS

An Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can therefore

be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality.

AEs that are observed by the Investigator or reported by the subject will be recorded on the study source documents and eCRFs. For all AEs, a description of the event, severity of the event, relationship to the test article, location of the event, date first observed, any action taken, its resolution and outcome will be recorded.

When completing the appropriate CRFs for reporting AEs, the Investigator will be asked to assess the AE for relationship, severity, and outcome as described below.

11.1. Relationship of Test Article to Each Adverse Event

Not Related: Based upon available information regarding subject history, disease process, relationship of AE to dosing and drug pharmacology, there is no reasonable relationship between the test and AE.

Possibly related: Relationship exists when the AE follows a reasonable sequence from the time of the test article administration but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

Probably related: Relationship exists when the AE follows a reasonable sequence from the time of the test article administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the test article and the suspect test article is the most likely of all causes.

Definitely related: Relationship exists when the AE follows a reasonable sequence from the time of the test article administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the test article and no other reasonable cause exists.

11.2. Severity of Adverse Event(s)

Additionally, the severity of each AE will be assessed. Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article relationship or seriousness of the event and should be evaluated according to the following scale:

Mild: Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.

Moderate: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.

Severe: Event is intolerable, necessitates additional therapy, or alteration of therapy and interferes with the subject's daily activities.

11.3. Outcome of Adverse Event(s)

Not Recovered/Not Resolved: One of the possible results of an AE outcome that indicates that the event has not improved or recuperated.

Recovered/Resolved: One of the possible results of an AE outcome that indicates that the event has improved or recuperated.

Recovered/Resolved with Sequelae: One of the possible results of an AE outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

Recovering/Resolving: One of the possible results of an AE outcome that indicates that the event is improving.

Unknown: Not known, not observed, not recorded, or refused.

Fatal: The termination of life as a result of an AE

11.4. Serious Adverse Events and Serious Unexpected Suspected Adverse Reactions

11.4.1. Definitions

The Sponsor and Investigator must comply with the applicable sections of 21CFR 312.32 and 21CFR 312.64(b) for IND safety reports. In accordance with these regulations, the following definitions apply:

- ADVERSE REACTION: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.
- SUSPECTED ADVERSE REACTION: Any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.
- SERIOUS ADVERSE EVENT (SAE)/SERIOUS SUSPECTED ADVERSE REACTION: An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
    - Death;
    - Life-threatening (an AE or Suspected Adverse Reaction that if, in the view of either the Investigator or Sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death);
    - In-patient hospitalization or prolongation of existing hospitalization;
    - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - A congenital anomaly/birth defect; or
    - A sight-threatening event.
        - An AE or suspected adverse reaction is considered "sight-threatening" if, in the view of either the Investigator or Sponsor its occurrence places the subject or subject at immediate risk of loss of sight. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused loss of sight.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

- UNEXPECTED ADVERSE EVENT: An AE or Suspected Adverse Reaction is considered "unexpected" if it is not consistent with the risk information described in the Riboflavin Ophthalmic Solutions (ROS 0250 and ROS 0185) Investigators Brochure, the UV-A Irradiation System Operator's manual, or is not listed at the specificity or severity that has been observed.

11.5. Serious and Unanticipated Adverse Device Effects

An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients." Since CDER has primary jurisdiction for the regulation of this combination product, serious and unanticipated adverse device effects will be reported to FDA and the IRB in accordance with the reporting requirements described in Section 11.8.

11.6. Non-serious Drug or Device or Anticipated Device Adverse Events

Non-serious drug or device AEs or anticipated device AEs and complications should be documented on the eCRFs and tabulated for reporting in the periodic safety reports to FDA.

11.7. Procedures for Reporting Adverse Events

Any AE should be reported to Sponsor and the IRB as required by the IRB, federal, state or local regulations and governing health authorities and recorded on the appropriate CRF along with the outcome. For all AEs, the reporting period begins when the subject signs the informed consent form and continues until the subject completes study participation (e.g. early termination or final study visit).

All AEs where a causal relationship between test article and the AE is at least a reasonable possibility (Suspected Adverse Reaction) and that are not expected (i.e., not listed in the Investigators Brochure or the Operator's Manual) are to be reported to Sponsor and the IRB as required by the IRB, federal, state or local regulations and governing health authorities. Preliminary determination of classification of an AE or adverse drug reaction as unexpected is the responsibility of the Investigator subject to the Sponsor's final determination.

11.8. Procedures for Reporting a Serious Adverse Event

The Investigator must immediately report SAEs that occur or are observed during the course of the study to Sponsor. In the event of an SAE, the site must complete a [redacted] and [redacted] **within 24 hours** of notification, observation, or occurrence of the SAE, whether or not complete information is available within this period. In case of incomplete information, the Investigator **must** provide follow-up information as soon as possible, again [redacted]

SAEs must be reported to the IRB according to the IRB requirements.

Important: The Investigator must report any SAE occurring at his/her site to Sponsor regardless of causality.

The Investigator is obligated to pursue and obtain information (e.g., medical records, discharge summaries) requested by Sponsor in addition to that information reported on the eCRF. All subjects experiencing an SAE must be followed until the subject completes the study or until the SAE resolves, whichever is first. All suspected adverse reactions that are both serious and unexpected are subject to expedited reporting.

SAE reports will be evaluated by the Sponsor. The IRB(s) and Investigators at other study sites will be informed as required.

Any adverse reaction that is both serious and unexpected shall be reported by the Sponsor to FDA and to all participating Investigators as soon as possible and in no event later than 15 calendar days after the Sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format. Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research that has responsibility for review of the IND/NDA. If FDA determines that additional data is needed, the agency may require further data to be submitted.

The Sponsor shall also notify FDA by means of rapid communication (telephone, facsimile transmission, or by e-mail) of any unexpected fatal or life-threatening adverse reaction as soon as possible but in no event later than 7 calendar days after the Sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research that has responsibility for review of the IND.

In addition to notifying FDA, the Sponsor will also notify each Investigator in an IND safety report of potentially serious risks as soon as possible and no later than 15 calendar days of any serious and unexpected, fatal, or life-threatening adverse reactions. The Investigators will promptly report these experiences to the IRB. If the IRB has different or specific reporting deadlines, reports should be made to the IRB in accordance with the IRB's requirements.

12. STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

12.1. General Methods

A detailed statistical analysis plan (SAP) will be developed and finalized prior to locking the database for this study. Required analyses and target endpoints that will be included in this SAP are summarized below. The methods by which each of these analyses is performed will be described in detail in the SAP. The required analyses and target endpoints include but are not limited to those listed below.

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows.

Descriptive statistics for continuous variables will include the mean, standard deviation, median, minimum and maximum; 2-sided 95% confidence intervals (CI) and/or 2-sided p-values will also be presented for efficacy endpoints. Descriptive statistics for categorical variables will include number and percentage of subjects or eyes, as appropriate. All testing and confidence intervals for endpoints will use a two-sided significance level of 5% unless otherwise specified.

12.2. Study Populations

12.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population includes all randomized study eyes. The ITT population will be analyzed as randomized and is designated as the primary population for all efficacy analyses.

12.2.2. Safety Population

The safety population is comprised of all study eyes that received study treatment. The safety population will be analyzed as treated and used for the analysis of the safety endpoints.

12.2.3. Per Protocol Population

The per protocol (PP) population is a subset of the ITT population and is comprised of study eyes without any major protocol deviations likely to effect the primary efficacy endpoint. Protocol deviations will be classified prior to analysis. The PP population will be analyzed as treated and used to provide supportive efficacy analyses.

12.3. Efficacy Variables

The primary efficacy variable for this study is the change from pretreatment baseline in K_{max} at each post-treatment follow-up time point.

[redacted]

12.4. Sample Size

The sample size for this study is based on unequal group sizes with the number of eyes in the crosslinked group being 2 times greater than in the control group (2:1 randomization). Two hundred sixty-one (261) eyes (174 in the cross-linking treatment group and 87 in the control group) provides greater than 99% power [redacted] cross-linking treatment group and the control group at Month 12. Additionally, this sample size yields [redacted] The sample size for this study is determined to be 290 eyes [redacted]

12.5. Primary Efficacy Analyses

12.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in K_{max} at Month 12. The primary efficacy null hypothesis is that there is no difference in the mean change from baseline in K_{max} between the CXL Treatment group and the Sham Treatment/control group at Month 12. The alternative hypothesis is that there is a difference.

The null (H_0) and alternative (H_a) statistical hypotheses for the primary efficacy endpoint, to be tested are:

H_0: $\mu_{T12} - \mu_{C12} = 0$

H_a: $\mu_{T12} - \mu_{C12} \neq 0$.

Where:

- μ_{T12} is the mean K_{max} change from baseline to Month 12 for the CXL treatment group
- μ_{C12} is the mean K_{max} change from baseline to Month 12 for the Sham treatment/control group

[redacted]

The study will be considered a success if the following is demonstrated:

- [redacted]

12.6. Secondary Efficacy Analyses

12.6.1. Secondary Efficacy Endpoint

The secondary efficacy endpoint is the Month 6 change from baseline in K_{max}. The secondary efficacy null hypothesis is that there is no difference in the mean Month 6 change from baseline in K_{max} between the CXL Treatment group and the Sham Treatment/control group. The alternative hypothesis is that there is a difference.

[redacted]

12.7. Handling of Missing Data and Data after Intercurrent Events

Handling of missing data and data after intercurrent events will be fully specified in the formal statistical analysis plan (SAP).

[redacted]

[redacted]

12.9. Interim Analysis

This study will not have an interim analysis. [redacted]

12.10. Prevention of Bias

To prevent the interjection of bias and to maintain data integrity, the study will be fully double-masked at a subject and Sponsor level, [redacted] Additionally, the examiner for key procedures and diagnostic tests will be masked as well, as indicated in the procedure per study visit section of the study protocol.

12.11. Multiplicity Adjustment

A hierarchical testing strategy is used to maintain an overall 2-sided Type I Error of 0.05 when making inference on the primary and secondary efficacy endpoints, where inference on the secondary endpoint will only be made if the primary efficacy endpoint is successful [redacted]

12.12. Safety Analysis

The primary safety endpoints for this study are:

- Incidence of treatment emergent ocular AEs
- Loss in BSCVA

[redacted]

The incidence of treatment emergent AEs will be tabulated presented descriptively.

Additional safety analysis will be performed on the following data:

- Slit lamp biomicroscopy
- Pentacam Pachymetry
- IOP (applanation tonometry)
- Manifest refraction
- Dilated fundus examination

- Endothelial cell count
- Macular OCT

[redacted]

12.12.1. Overall Incidence of Adverse Events

The incidence of subjects reporting any treatment-emergent AE during the study will be presented. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. The number and percentage of subjects reporting ocular and non-ocular AEs will be tabulated by body system and preferred term. The number of subjects reporting AEs will also be summarized by relationship to the test article as well as severity of AEs. SAEs will be summarized in a similar fashion.

[redacted]

13. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with GCPs, including International Harmonization (ICH) Guidelines, and in general, consistent with the 1996 version of the Declaration of Helsinki. In addition, all applicable local, state and federal requirements relevant to the use of investigational agents in the countries involved will be adhered to. This study will be conducted in accordance with FDA's GCP regulations.

13.1. Protection of Human Subjects

13.1.1. Compliance with Informed Consent Regulations

Refer to 21 CFR Part 50 for requirements related to informed consent.

Written informed consent must be obtained from each subject (or subject's legal representative, if applicable) prior to participation in the study. In seeking informed consent, the following information shall be provided, at minimum, to each subject.

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the U.S. Food and Drug Administration may inspect records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- Notification that study results will be posted in the ClinicalTrials.gov website, when applicable: "A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time."

13.1.2. Compliance with Institutional Review Board Regulations

The Investigator will not deviate from the protocol without prior approval from the IRB and/or the Sponsor, unless such deviation is necessary to manage a medical emergency. The Investigator will notify the IRB and the Sponsor of any protocol deviation to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event, any later than 5 working days after the emergency occurred. All other revisions and/or amendments to the protocol that affect subject treatment, study outcome, or subject safety will be submitted in writing to the IRB and the Sponsor for approval prior to implementation if the changes or deviations to the protocol affect the scientific validity of the study or the rights, safety, or welfare of human subjects. In this case, the change will not be implemented until IRB approval is obtained. The Investigator will maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

Changes that affect the scientific validity of the study or the rights, safety, or welfare of human subjects may also require FDA and IRB approval prior to implementation. The Sponsor and Investigator will obtain such approvals, if required. Refer to 21 CFR Part 312.60 regarding other Investigator responsibilities.

13.1.3. Compliance with the Declaration of Helsinki

Refer to Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

13.1.4. Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors, and other authorized representative of Sponsor, the IRB approving this study, FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

13.1.5. Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files as well as the results of diagnostic tests. The Investigator's copy of the eCRFs serves as the Investigator's record of a subject's study-related data. All data related to the study will be recorded on eCRFs to be provided by Sponsor via an EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct. The Investigator must sign the completed eCRFs before its submission to Sponsor.

The EDC system will be designed and used per 21 CFR Part 11 and the "Computerized Systems Used in Clinical Trials Guidance for Industry."

13.1.6. Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of the test article and copies of eCRFs should be maintained on file for the duration specified in each site's Clinical Trial Agreement and per the requirements of 21 CFR Part 312, "E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry" part 5.5 and any local requirements.

13.2. Recording of Data on Source Document and Electronic Case Report Forms (eCRFs)

Adequate records will be maintained for the study including subject medical and surgical records, test reports, work sheets, nursing notes, signed informed consent forms, drug and device use records, adverse experience reports and information regarding subject discontinuation and reasons for discontinuation. All original source documentation will remain at the investigative site. Study data that are stored at the Investigator site in any electronic medical records system, that is not 21 CFR Part 11 compliant (e.g., Pentacam, OCT), should be printed and retained in the study files.

Sponsor personnel may require copies of source documents to be made available for off-site (remote) monitoring. Subject data should be de-identified prior to transmission to Sponsor's personnel not at the site.

All study data will be recorded onto eCRFs designed for the study.

13.3. Changes in the Conduct of the Study

Changes that affect the scientific soundness of the study or the rights, safety, or welfare of human subjects may also require FDA and IRB approval prior to implementation. The Sponsor and Investigator will obtain such approvals, if required.

14. APPENDIX A: ASSESSMENT INSTRUCTIONS

14.1. Visual Acuity Testing

Manifest Refraction and Best Spectacle Corrected Visual Acuity (ETDRS)

Manifest refraction (MR) and BSCVA testing should precede slit lamp examination, intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the eye. MR will be conducted using the site's standard refractive techniques. BSCVA will be assessed using the Early Treatment of Diabetic Retinopathy study (ETDRS) charts at 4 meters (13 feet and 1.5 inches, or 157.5 inches) by trained technicians. MR must be performed prior to BSCVA testing. BSCVA using ETDRS Chart 1 (right eye) or Chart 2 (left eye) at 4 meters will be performed.

The visual acuity chart may be either retro-illuminated ("back-lit"), or reflectance illuminated. If the latter, then the illumination must be checked at regular intervals to be consistent with ETDRS guidelines. The standard chart requires a distance from subject to chart of 4 meters. Ideally, the subject should be seated. Sites are directed to refer to the instructions on the commercial ETDRS charts.

Visual Acuity testing and recording methodology is described in the Visual Acuity Procedure Manual.

Uncorrected Visual Acuity (ETDRS)

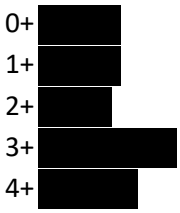
Uncorrected visual acuity (UCVA) testing should precede slit lamp examination, intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the eye.

UCVA will be assessed without the aid of refractive using the Early Treatment of Diabetic Retinopathy study (ETDRS) charts at 4 meters (13 feet and 1.5 inches, or 157.5 inches) by trained technicians.

NOTE: The study coordinator or any technician who has been delegated on the study Delegation of Authority Log to do so may perform refractions and visual acuity assessments.

14.2. Slit Lamp Exams

The slit lamp exam conducted by the Investigator should include a complete survey of the anterior segment including orbit/lids, lashes, pupil, conjunctiva, cornea, anterior chamber, iris, and lens. A grading of normal or abnormal will be noted at each visit. The following areas of the cornea should be examined – Epithelium, Descemet's membrane/endothelium, cornea-other. The grading of any abnormalities in any of the above-mentioned areas should be recorded using the following scale:



In addition, the corneal clarity should be examined in detail with specific recordings and grading of any abnormalities using the following scale:

0+ [redacted]
1+ [redacted]
2+ [redacted]
3+ [redacted]
4+ [redacted]

[redacted]

14.3. Pentacam Topography

[redacted] The median K_{max} value is to be reported in the eCRF. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.4. Specular Microscopy

The methods used for the collection and analysis of specular microscopy data are critically important to minimizing the variability associated with these measurements. Common sources of variability in specular microscopy are:

- difficulty in returning to same location on the cornea at each visit;
- poor image quality (less than 100 countable cells);
- technician error

[redacted]

An acceptable image has:

- distinct cells;
- at least 100 identifiable (countable) cells as a minimum, 150 cells preferred; and
- cells that can be grouped in a uniform area.

To capture a good image:

- make sure the subject is comfortable;
- instruct the subject to blink;
- instruct subject not to move and to open eyes wide;
- instruct subject to focus straight ahead or on the green light;
- be patient; and
- if necessary, use the manual setting. (Note that the use of the manual setting may require additional training).

15. INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Phase 3, Multi-center, Randomized, Double-masked, Placebo/Sham-controlled Study to Evaluate the Safety and Efficacy of Oxygen Enriched, Non-invasive Epithelium-on Corneal Collagen Cross-linking in Eyes with Keratoconus
Protocol Number:	GLK-202-02
Version Number:	1.0 (Original)
Version Date:	15 NOVEMBER 2022
Compound:	[redacted]
Study Phase:	3
Sponsor Name:	Glaukos Corporation

I have read this study protocol and I agree that it contains all the information required to conduct the study.

I agree to conduct the study as set out in this protocol and in accordance with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and applicable ISO/GCP guidelines.

_____

Name of Investigator (Print)

_____ _____

Signature of Investigator Date*

* Date of signature indicates date of approval

16. REFERENCES

1 Eye Bank Association of America Statistical Report, 2015.

2 Wollensak G, Spoerl E, Seiler T. Riboflavin/Ultraviolet-A-induced collagen cross-linking for the treatment of keratoconus. Am J Ophthalmol. 2003; 135:620-627.

3 Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. J Cataract Refract Surg. 2006; 32(5):837-45.

4 Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol. 2010 Apr;149(4):585-93.

5 Vinciguerra P, Albe E, Trazza S, Seiler T, Epstein D. Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus. Arch Ophthalmol. 209 Oct;127(10):1258-65.

6 Coskunseven E, Jankov MR 2nd, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. J Refract Surg. 2009 Apr;25(4):371-6.

7 Grewal DS, Brar GS, Jain R, Sood V, Singla M, Grewal SP. Corneal collagen crosslinking using riboflavin and ultraviolet-A light or keratoconus: one year analysis using Scheimpflug imaging. J Cataract Refract Surg. 2009 Mar;35(3):425-32.

8 Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus:long-term results. J Cataract Refract Surg. 2008 May;34(5):796-801.

9 Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg. 2008;34(5):796-801. doi: 10.1016/j.jcrs.2007.12.039.

10 Wittig-Silva C, Chan E, et al. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus. Ophthalmology 2014;121:812-821.

[redacted]