Avedro

STATISTICAL ANALYSIS PLAN

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

ACP-KXL-308

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Table of Contents

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1.0	[redacted]	New Document
2.0	[redacted]	Additional clarification added [redacted] Additional minor updates. [redacted]

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSCVA	Best Spectacle Corrected Visual Acuity
CRF	Case Report/Record Form
CSR	Clinical Study Report
CXL	Corneal Collagen Cross-Linking
D	Diopter
ECC	Endothelial Cell Count
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
ITT	Intent to Treat
K_{max}	Maximum Keratometry
LOCF	Last Observation Carried Forward
MAR	Missing at Random
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	Manifest Refraction Spherical Equivalent
NEI-VFQ 25	National Eye Institute Visual Functioning Questionnaire
OCT	Optical Coherence Tomography
[redacted]	[redacted]
PP	Per Protocol

PT	Preferred Term
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
UCVA	Uncorrected Visual Acuity

1 INTRODUCTION

This study is a multicenter, randomized, sham-controlled evaluation of the safety and efficacy of epithelium-on corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus. The objectives of this study are to evaluate the safety and efficacy of epithelial-on corneal collagen cross-linking in impeding the progression of, and/or reducing maximum corneal curvature (K_{max}) in eyes with progressive keratoconus.

This Statistical Analysis Plan (SAP) describes data-handling and statistical procedures to be used for the analysis and reporting of efficacy and safety data collected under Avedro Protocol ACP-KXL-308 (version 11 Oct 2018) and presented in the clinical study report (CSR). They are based on those presented in Section 10, Statistical Hypotheses and Methods of Analyses, of the study protocol. Any post-hoc or exploratory analyses not specified in this SAP will be identified as such when they are presented in the CSR. This SAP will have been developed and finalized prior to locking the clinical database.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline, entitled "Guidance for Industry: Structure and Content of Clinical Study Reports."

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

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

2.2 STUDY DESIGN

This study is a multicenter, randomized, sham-controlled evaluation of the safety and efficacy of epithelium-on corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus. Each subject will have at least one eye randomized to either the CXL Treatment group or the Sham Treatment/Control group. If both eyes meet the eligibility criteria, both eyes may be enrolled in the study, however one eye will be treated first and the second eye treated [redacted] after the first eye.

Two treatment regimens will be tested using the following combinations of riboflavin ophthalmic solution(s) and UVA:

Treatment 1 (CXL Treatment)

- [redacted] riboflavin ophthalmic solution [redacted] + [redacted] riboflavin ophthalmic solution [redacted]
- UVA irradiation [redacted]
- Supplemental oxygen

Treatment 2 (Sham Treatment)

- 0.0% riboflavin ophthalmic solution ([redacted] Placebo)
- UVA [redacted]

2.2.1 Number of Study Eyes

Up to 275 study eyes with progressive keratoconus (183 in CXL Treatment group and 92 in the Sham Treatment group) will be randomized to provide at least 160 and 80 evaluable eyes in the CXL Treatment group and Sham Treatment group, respectively, at the 6 and 12 month follow-up examinations.

2.2.2 Randomization and Masking Procedures

[redacted] Randomization between the CXL Treatment group and Sham Treatment/Control group will be in a 2:1 ratio within each stratum.

[redacted]

The following assessments will be conducted by a masked examiner who will not be aware of which treatment has been performed:

- Best Spectacle Corrected Visual Acuity (BSCVA) at Months 1, 3, 6, and 12
- Uncorrected Visual Acuity (UCVA) at Months 1, 3, 6, and 12
- Manifest Refraction at Months 1, 3, 6, and 12.

The masked examiner will not have access to the subject's medical and/or study records which would unmask him/her to the study treatment. The masked examiner will not conduct any study examinations on that subject beyond the visual measurements indicated with the endpoint assessment.

[redacted]

[redacted]

2.2.4 Efficacy Assessments

2.2.4.1 Maximal corneal curvature

The maximum corneal curvature (K_{max}) is the maximum keratometry at the apex of the cone, measured on the Pentacam corneal topography image. It is assessed at the following visits:

- Visits 1 (Day -45 to -1)
- Visit 6 (1 month)
- Visit 7 (3 months)
- Visit 8 (6 months)
- Visit 9 (12 months).

2.2.4.2 Manifest Refraction Spherical Equivalent

The Manifest Refraction Spherical Equivalent (MRSE) will be evaluated at baseline and each follow-up exam beginning at 1 month. MRSE is calculated as: MRSE = sphere + 1/2 cylinder.

2.2.4.3 Visual Acuity (BSCVA and UCVA)

The number of letters read from the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart from the BSCVA and UCVA will be evaluated at screening, baseline, and each follow-up exam beginning at 1 month.

2.2.5 Safety Assessments

A primary safety assessment is the BSCVA assessed at the following visits:

- Visits 1 (Day -45 to -1)
- Visit 6 (1 month)
- Visit 7 (3 months)
- Visit 8 (6 months)
- Visit 9 (12 months).

The incidence of serious ophthalmic adverse events (AEs) is also a primary safety assessment.

The following are additional safety assessments:

- Adverse events
- Slit lamp biomicroscopy
- Pentacam Pachymetry
- Intraocular pressure using Goldmann applanation tonometry
- Manifest refraction
- Dilated fundus exam
- Endothelial cell counts
- Macular optical coherence tomography.

2.2.6 Other Assessment(s)

2.2.6.1 Anterior Segment OCT

Anterior segment optical coherence tomography will be performed at Screening, 1, 3, 6, and 12 month examinations.

2.2.7 Questionnaires

2.2.7.1 National Eye Institute Visual Functioning Questionnaire

The self-administered version of the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ 25) will be administered at screening to establish the subject's baseline and at the 1, 3, 6 and 12 month examinations.

2.2.8 Schedule of Events

The Schedule of Events is presented in Table 1.

Table 1. Schedule of Events

Procedure	Screen	Treatment		POST-TREATMENT VISITS[13]					
			1 DAY	3 Day	1 WK	1 MO	3 MO	6 MO	12 MO
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -45 to -1	Day 0	Day 1 to 2	Day 3 to 4	Day 5 to 14	Day 21 to 42	Day 84 to 98	Day 180 to 210	Day 360 to 390
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
NEI-VFQ 25	X					X	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 HR [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 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.

3 STATISTICAL METHODS

3.1 GENERAL METHODS

3.1.1 Computing Environment

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

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in patient data listings. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated by treatment group for continuous variables. Descriptive statistics for categorical variables will include number and percentage of subjects or eyes, as appropriate. Confidence intervals will be provided where appropriate.

Means, medians, and confidence intervals will be reported to one decimal place. Standard deviations will be reported to two decimal places. Minimum and maximum will be reported to the same number of decimal places displayed on the Case Report/Record Form (CRF) or by the laboratory/vendor. P-values will be reported to 4 decimal places.

All testing and confidence intervals will use a two-sided significance level of 5% unless otherwise specified.

3.1.3 Baseline Value and Change from Baseline

Baseline value is defined as the most recent non-missing value obtained immediately prior to administration of the test article [redacted] Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each study eye (i.e., post-dose – baseline).

[redacted]

[redacted]

3.2 HANDLING OF MISSING/INCOMPLETE VALUES

Missing data can reduce the statistical power of a study and produce biased estimates leading to invalid conclusions. Therefore, every effort will be made to ensure complete, accurate, and timely data collection, to avoid missing data. Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified for investigation and possible resolution by Data Management prior to the study database lock.

[redacted]

Based on a similar study conducted by Avedro, study UVX-002 (*NDA 203-324, UVX*-002 *Table 14.2.1.1.1*), the percentage of missing data for the Month 6 K_{max} change from baseline endpoint in the CXL group was 8%. It is anticipated the rate of missing data for this study will be similar to the 8% rate for both the CXL and sham treatment groups.

To assess the pattern of missing data, any missing observations for the primary efficacy endpoint will be described in detail and evaluated for assessment of possible bias. For each of the two treatment groups, 95% confidence intervals for the difference in means or proportions stratifying on missing/not-missing the primary endpoint will be performed for the following baseline demographics and characteristics:

- Age
- Sex (female / male)
- Race (white / non-white)
- Ethnicity (Hispanic / non-Hispanic)
- Baseline keratoconus disease severity [redacted]

3.2.1 Multiple Imputation

Multiple imputation will be the method for handling missing data in the primary efficacy endpoint analysis (i.e., the primary endpoint is the Month 6 change from baseline in K_{max}). [redacted]

The MAR assumption implies that the covariates in the model can account for differences in the distribution of missing variables for observed and missing cases. [redacted] However, to assess the robustness of this MAR assumption, multiple sensitivity analyses will be performed, including an analysis which assumes the primary endpoint missing data pattern is Missing Not at Random (MNAR).

[redacted] The initial imputation to produce a monotonic missing data pattern for the MNAR

imputation will be performed by using the same method as described for the MAR imputation.

3.2.2 Observed Case

Observed Case will be used for supplemental analysis of the primary efficacy endpoint analysis. Observed Case analyses will be based on the study eyes with non-missing values.

3.2.3 Last Observation Carried Forward

Last Observation Carried Forward (LOCF) will be used for supplemental analysis of the primary efficacy endpoint analysis. For the LOCF analyses, if a study eye is missing the analysis value, the post-baseline value most recent to the missing observation will be imputed for the analysis.

3.3 ANALYSIS POPULATIONS

3.3.1 Intent-to-Treat Population

The intent-to-treat (ITT) population includes all randomized study eyes that had at least one post-treatment follow-up efficacy assessment. The ITT population is designated as the primary population for all efficacy analyses.

3.3.2 Safety Population

The safety population is comprised of all study eyes that received the study treatments [redacted].

The safety population will be used for the analysis of the safety endpoints.

For the safety analyses where patient is the unit of analysis, a patient will be in the CXL treatment group if either study eye is in the CXL treatment group. If a patient has both eyes in the control group, or only one eye in the study and that eye is in the control group then that patient will be in the Control group.

The following additional Safety Populations will also be used.

3.3.2.1 Safety Population – All CXL Treated Eyes

This population consists of study eyes which received the CXL procedure [redacted]. In the safety analyses which use this population "baseline" will be when the eye received the CXL procedure.

3.3.2.2 Safety Population – All CXL Treated Patients

This population consists of patients who received the CXL procedure (in either or both eyes). In the safety analyses which use this population a patient's "baseline" will be the last observation prior to when the patient first receives the CXL procedure in either eye.

3.3.3 Per-Protocol Population

The per protocol (PP) population is a subset of the ITT population and is comprised of study eyes that complete the study without any major protocol deviations and that have non-missing data available for the primary endpoint. The PP population will be used to provide supportive efficacy analyses.

Major protocol deviations include deviations to the inclusion and exclusion criteria, and deviations affecting data integrity as determined by the medical monitor. Subjects with major protocol deviations will be excluded from the PP population and these subjects and their data will be provided in a listing. Patients in the ITT population

who were excluded from the PP population due to major protocol deviations related to COVID-19 will also be indicated.

In the analysis of the PP population study eyes will be analyzed in the treatment group according to the treatment received.

The PP population analyses are supportive analyses.

3.4 ANALYSIS ENDPOINTS

3.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the Month 6 change from baseline in K_{max}.

3.4.2 Secondary Efficacy Endpoint

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

[redacted]

3.4.4 Safety Variables

The primary safety endpoints for this study are:

- Incidence of treatment emergent ocular adverse events
- Loss in BSCVA

[redacted]

The incidence of treatment emergent adverse events 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]

3.4.5 Questionnaires

3.4.5.1 National Eye Institute Visual Functioning Questionnaire

Change from baseline to Month 12 in the composite, and each of the vision-targeted subscales on the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ 25) will be summarized by treatment group.

3.5 PATIENT DISPOSITION AND EVALUABILITY

3.5.1 Patient Disposition

Patient disposition (enrollment, randomization, study completion) will be presented for each study eye by treatment group and overall. The number and percentage of study eyes in the ITT, Safety and PP population will be presented. The numbers of study eyes completing and not completing the study, as well as reasons for discontinuations will also be summarized. Patients discontinued for reasons related to COVID-19 will also be indicated.

Additionally, the number of patients/study-eyes assessed at each of the scheduled visits will be summarized by treatment group and overall.

A listing of all patients affected by the COVID-19 related study disruption will be provided by patient ID and by investigational site. The patient listing will include the patient disposition and a description of how the patient's participation was affected.

3.5.2 CXL Treatment by Study Visit

The number of study eyes receiving the CXL procedure will be presented as randomized for the ITT Population by treatment group overall and by site.

The number of study eyes at each scheduled visit will be [redacted]

3.5.3 Protocol Deviations

Protocol deviations will be presented in a patient listing by treatment group. Protocol deviations related to COVID-19 will be indicated.

3.6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

3.6.1 Demographics

Patient demographics and baseline characteristics will be summarized by treatment group and overall for the ITT, Safety Populations, and Per Protocol populations.

Descriptive statistics will be provided for age. Frequencies and percentages will be tabulated for sex, race, and ethnicity. Contact lens use and baseline Keratoconus Severity [redacted] will also be summarized:

3.6.2 Medical History

Patient medical history will be presented in patient listings by treatment group.

3.6.3 Ocular History

Patient ocular history will be presented in patient listings.

3.7 EFFICACY ANALYSIS

3.7.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the Month 6 change from baseline in K_{max}. The primary efficacy null hypothesis is that there is no difference between the CXL Treatment group and the Sham Treatment/Control group in the mean Month 6 change from baseline in K_{max}. 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: $\mu_T - \mu_C = 0$

H_a: $\mu_T - \mu_C \neq 0$.

Where:

- μ_T is the mean K_{max} change from baseline to 6 months for the CXL Treatment group
- μ_C is the mean K_{max} change from baseline to 6 months for the Sham Treatment/Control group.

[redacted]

The primary efficacy analysis will be performed on the ITT population using multiple imputation the main analysis method for handling missing data.

The primary efficacy endpoint criterion is [redacted] Month 6 change from baseline in K_{max} between the CXL Treatment group and the Sham Treatment/Control group.

[redacted]

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

Note: Missing data handling methods are described in Section 3.2.

The primary efficacy analysis will also be performed for patients in the ITT population who were NOT affected by COVID-19 (e.g., Month 6 visit within the visit window). If these results differ from the primary analysis of all patients in the ITT population, the data will be examined to gain an understanding for the difference and additional analyses may be presented.

[redacted]

3.7.2 Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoint is the Month 12 change from baseline in K_{max}. The secondary efficacy null hypothesis is that there is no difference in the mean Month 12 change from baseline in K_{max} between the cross-linking treated eyes from this study and the historical control group. The alternative hypothesis is that there is a difference.

[redacted]

The secondary efficacy endpoint criterion is [redacted] Month 12 K_{max} change from baseline between the CXL Treatment group and the Sham Treatment/control group.

This analysis will be performed on the ITT population as the main analysis using the Month 12 LOCF Method (defined in Section 3.2).

[redacted]

Note: Missing data handling methods are described in Section 3.2.

3.7.3 Control of Type I Error Rate

Both the primary and secondary efficacy endpoint (K_{max} change from baseline at Months 6 and 12, respectively) are tested at the two-sided 0.05 Type I error rate. The secondary efficacy endpoint analysis will only be considered statistically significant if the primary efficacy endpoint analysis is statistically significant.

[redacted]

[redacted]

[redacted]

3.8 SAFETY ANALYSIS

All safety analyses will be performed on the Safety Population.

[redacted]

3.8.2 Adverse Events

Treatment Emergent adverse events (TEAEs) will be summarized by treatment group and categorized by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Drug Regulatory Affairs (MedDRA 15.1 or higher). TEAEs are adverse events (AEs) which occurred after study treatment administration or pre-existing AEs that worsened after study treatment administration.

The number and percentage of subjects reporting non-ocular AEs will be tabulated by body system and preferred term within each treatment and overall. The number and percentage of study eyes reporting ocular AEs will be tabulated by preferred term

within each treatment group and overall. The number of subjects/study eyes reporting AEs will also be summarized by relationship to the test article as well as severity of AEs. Serious adverse event (SAEs) will also be summarized by group and categorized by SOC and PT. An AE with a relationship to the test article of Possible, Probable, or Definite will be considered "Related".

AEs will be summarized over the following time periods based on the onset date of the TEAE:

- Baseline to Month 3: TEAEs with an onset date up to and including the Month 3 visit
- Baseline to Month 6: TEAEs with an onset date up to and including the Month 6 visit
- Study Period: All TEAEs.

For the presentation of AE incidences, the SOCs will be sorted alphabetically, and within SOC, the preferred term (PT) will be used and presented by decreasing total frequency.

The incidence of serious ophthalmic adverse events will be summarized by treatment group and presented in a listing.

Ocular and non-ocular AEs will be summarized separately. Each of these adverse event summaries will be provided for:

- Non-ocular AEs (Subject Level):
  - [redacted]
    - [redacted]
- Ocular adverse events (Study Eye Level):
  - [redacted]

[redacted]

3.8.2.1 Timing and Duration of Frequent Adverse Events

The timing of onset day, resolution day, and duration of TEAEs with an incidence >5% (i.e., > 5% in the CXL Treatment study eyes) will be summarized. This will include TEAE onset day, Resolution day, and Duration (in days).

[redacted]

3.8.3 BSCVA and UCVA

For the safety analysis, BSCVA and UCVA will be presented in terms of the number of ETDRS letters lost/gained or not changed from baseline by each treatment group.

[redacted]

3.8.4 Slit Lamp Biomicroscopy and Dilated Fundus Examination

Slit lamp biomicroscopy and dilated fundus examination data will be presented categorically (i.e., normal/abnormal) at baseline and each of the follow-up visits by treatment group. The following sites are assessed for slit lamp:

- Orbit/Lids
- Lashes

- Pupil
- Conjunctiva
- Cornea-Epithelium
- Cornea-Descemet's Membrane/Endothelium
- Corneal Clarity
- Cornea (Other)
- Anterior Chamber
- Iris
- Lens

The following are the assessments from the dilated fundus exam:

- Lens
- Macula
- Retinal Vessels
- Peripheral Retina
- Optic Disc
- Cup/Disc Ratio.

3.8.5 Pachymetry

The change in central pachymetry (as measured by Pentacam) from baseline will be evaluated at each follow-up exam beginning at 1 month. Differences in the mean changes from baseline between the CXL Treatment and Sham Treatment/Control groups will be reported.

[redacted]

3.8.6 Applanation Tonometry

Intraocular pressure (IOP) as assessed by Goldmann applanation tonometry will be presented at baseline and each follow-up visit by treatment group.

3.8.7 Manifest Refraction

For each scheduled assessment (Baseline, Months 1, 3, 6 and 12) the value and change from baseline will be summarized for each treatment group.

3.8.8 Pentacam Corneal Topography

The change from baseline in the assessments derived from the Pentacam corneal topography image will be evaluated at each follow-up exam beginning at 1 month. Differences in the mean changes from baseline between the CXL Treatment and Sham Treatment/Control groups will be reported.

[redacted]

3.8.9 Endothelial Cell Counts

Endothelial cell counts will be presented at baseline and each follow-up visit and the percent change from baseline will be calculated and presented by treatment group.

[redacted]

3.9 ADDITIONAL ENDPOINTS ANALYSIS

3.9.1 Anterior Segment Optical Coherence Tomography [redacted]

Data [redacted] will be presented in listings and summarized descriptively.

3.9.2 National Eye Institute Visual Functioning Questionnaire

The NEI-VFQ 25 generates a composite score as well as the following vision-targeted sub-scales: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and color vision, and ocular pain.

In scoring the NEI-VFQ 25, a high score represents better functioning.

The formula for calculating the overall composite score and the sub-scale scores involves 2-steps:

1) Recode the items based on the algorithm in Table 2
2) Take the average items in the sub-scales as specified in Table 3.

Table 2: Recoding of NEI-VFQ 25

Item Number	Original Response Category	Recode Value
1,3,4,15c[(a)]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25	1	0
	2	25
	3	50
	4	75
	5	100

Note: For each item in the original response category a score of "1" is the best functioning response and the highest response category (i.e., either a 5 or 6) represents the lowest functioning response

(a) Item 15c has four-response levels, but is expanded to a five-levels using item 15b.

Note: If 15b=1, then 15c should be recoded to "0"

If 15b=2, then 15c should be recoded to missing.

If 15b=3, then 15c should be recoded to missing.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."
Scoring from Mangione (2000)

Table 3: Sub-Scale Components

Scale	Number of Items	Items to be averaged (after recoding)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Targeted Sub-Scales		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10
The Overall Composite Score is the average of the Vision Targeted Sub-Scale scores		
Note: Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.		

The NEI-VFQ 25 values and change from baseline scores will be summarized using descriptive statistics by treatment group at each of the visits assessed.

3.10 INTERIM ANALYSIS

No interim analysis is planned for this study.

3.11 SAMPLE SIZE JUSTIFICATION

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 forty (240) eyes (160 in the crosslinking treatment group and 80 in the control group) provides [redacted] to detect a difference in the mean change in K_{max} from baseline [redacted] between the crosslinking treatment group and the control group. [redacted]

[redacted] The sample size for this study is determined to be 275 eyes [redacted]

4 REFERENCES

Berglund P., Heeringa S., *Multiple Imputation of Missing Data Using SAS®*, SAS® Institute, 2014.

Mangione C.M., *Version 2000. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25)*. NEI VFQ-25 Scoring Algorithm – August 2000

5 APPENDIX

5.1 SAMPLE SAS CODE FOR PRIMAY ENDPOINT ANALYSIS