STATISTICAL ANALYSIS PLAN

Study Title:	COLLAGEN CROSS-LINKING WITH ULTRAVIOLET-A IN ASYMMETRIC CORNEAS
Sponsor:	CXLUSA, LLC
Protocol No.:	CXL-005
Protocol Version/Date	05-May-2017 (Protocol Version 4.3)
Author Biostatistician:	William Coar, PhD
Analysis Plan Version/Date:	Version 1.0 / 26-Jul-2018

CONFIDENTIAL AND PROPRIETARY INFORMATION

SPONSOR APPROVAL

Collagen Cross-Linking with Ultraviolet-A

in Asymmetric Corneas

William Coar, PhD Biostatistician Axio Research, LLC.	Date
Alan Russell Director, Regulatory Affairs CXL Ophthalmics, LLC	Date
Michael Webb CEO CXL Ophthalmics, LLC	Date

Table of Contents

1. INTRODUCTION

CXL intends to utilize data from the ongoing CXL-005 Phase 2 clinical study to support the design of a Phase 3 trial. In preparation for a meeting with the FDA to propose the Phase 3 design, interim data from CXL-005 will be analyzed to help design the Phase 3 protocol. This version of the SAP describes the analyses planned to support the meeting with FDA.

This SAP is based on Version 4.3 of the study protocol dated 05-May-2017. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. All analyses will be conducted using SAS version 9.4.

1.1 Study Design

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

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

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

In order to provide 12-month data to FDA for Phase 3 planning, sites were instructed to contact patients to request a 12-month assessment. In these cases, patients may have a 6-month visit that suggests they completed study, yet still return for the 12-month assessment. Not all patients that completed study at the 6-month visit will return for a 12-month assessment.

1.1.1 Randomization

Randomization will be stratified by indication and by investigational site among 3 UVA illumination groups consisting of:

Group 1	4 mW/cm2 cycled On/Off at 15 second intervals for 20 minutes (total UVA corneal surface dose of 2.4 J/cm^2)
Group 2	6 mW/cm2 cycled On/Off at 15 second intervals for 20 minutes (total UVA corneal surface dose of 3.6 J/cm^2),
Group 3	4 mW/cm2 cycled On/Off at 15 second intervals for 30 minutes (total UVA corneal surface dose of 3.6 J/cm^2)

1.2 Study Objectives

The objectives of the study are to assess changes in visual acuity and corneal symmetry after corneal collagen cross-linking (CXL) of asymmetric corneas.

1.2.1 Primary Objectives

The primary objective of this study is to assess change in corrected distance visual acuity (CDVA) at months 6 and months 12 using Snellen converted to the LogMAR scale.

1.2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the change in uncorrected distance visual acuity (UCVA) at months 6 and months 12 using Snellen converted to the LogMAR scale
- To assess change in K_{max} at months 6 and months 12.

1.3 Endpoints

1.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the LogMAR of CDVA as defined by:

$$LogMAR = -Log\left[{}^{20}/_{(Snellen\ Acuity\ per\ CRF)}\right]$$

where the log base 10 is used. The usual adjustment for the number of letters read is omitted from the conversion formula since the number of letters read was not captured.

1.3.2 Secondary Endpoints

Secondary endpoints include change from baseline in the following assessments:

- LogMAR of UCVA
- K_{max}

1.3.3 Safety Endpoints

The safety endpoints for this analysis include frequency, intensity, and relationship to study drug of adverse events and serious adverse events.

1.4 Determination of Sample Size

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

The sample size for this ad hoc analysis is partially driven by the enrollment date. All patients with at least one procedure performed are included in the safety analysis. Only patients with a diagnosis of keratoconus, who do not have prior conductive keratoplasty treatment, who are in the study long enough to be eligible for a Month 12 visit are considered for inclusion in the efficacy analysis. Additional details regarding the subset of patients for efficacy analysis can be found in Section 3.2.2

1.5 Timing of Analysis

Analyses will be performed after the interim database lock. The official data for the analysis will be based on SAS datasets subset to include patients eligible for this analysis.

1.6 Changes from Protocol

The protocol states the primary efficacy endpoint of this trial is change in corrected distance visual acuity (CDVA) at the last required study visit (6 months post-op), compared to baseline. For this analysis, the change in CDVA will be estimated at Month 6 as well as Month 12.

The protocol also states that two-sample t-tests will be used for treatment comparisons. Since there are three treatment groups, analysis of variance (ANOVA) will be used instead of conducting separate t-tests on each pairwise combination of treatments. Separate t-tests on each pairwise comparison will be performed as a supportive analysis.

2. DATA

The protocol states that patients complete study at Month 6, and subsequent visits are optional. In planning for the FDA meeting, sites have been instructed to request the Month 12 visit.

2.1 Filtering

Data to be presented in the efficacy analysis are limited to a subset of patients as defined in Section 3.2.3. Filtering will only be done on efficacy data. Baseline and safety data will include all patients randomized and treated as of the data lock date.

Due to database limitations, randomization date is assumed to be the date of the first procedure as determined by the visit date for the Procedure Visit.

Some patients will have longer follow-up data than others. Filtering will not attempt to exclude data from beyond the Month 12 visit. All safety data will be used, but efficacy data beyond Month 12 CRF page will not be analyzed.

2.2 CRF Pages

Not all data will be analyzed in this analysis. Only select CRF pages for key safety and efficacy endpoint to support the Phase III protocol development are considered.

2.3 Unique Patient Identification

Patient number from the CRF does not uniquely identify individual patients. If a patient initially had bilateral treatment, then all data are captured under a single patient number. If a patient initially had unilateral treatment but subsequently had the procedure performed on the untreated eye, data for the newly treated eye were captured under a different patient number. If a patient completed the month 6 assessment and the investigator elected to perform the CXL procedure again, then all data for this repeated procedure are captured under a second patient number.

Sites will provide a list of paired patient numbers that can be used to map all data for each patient to be summarized appropriately.

Patients receiving subsequent CXL therapy were re-randomized. Therefore the subsequent treatment may differ from the initial randomized treatment given during the first procedure. Efficacy summarization will be by individual eye which can accommodate the differing treatments. Adjustments to the safety analysis will need to be considered since that is done overall rather than by individual eye.

3. GENERAL CONSIDERATIONS

3.1 Analysis Considerations

All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA). Only subjects in the appropriate analysis set will be included in summary statistics.

Continuous data will be summarized by treatment using descriptive statistics (number, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized by treatment using frequency tables (number and percentage).

Summaries will be presented by randomized treatment (Group 1, Group 2, Group 3) to allow between treatment comparisons.

3.2 Analysis Sets

Populations for primary analyses of safety and efficacy are defined as follows.

3.2.1 **Randomized and Treated**

The randomized and treated analysis set includes all subjects randomized in the study and have a procedure performed on at least 1 eye prior to the official data lock for this ad hoc analysis. Analysis of the treated analysis set will be by treatment received in the primary eye.

3.2.2 **Safety**

The safety analysis set (SS) includes all subjects enrolled in the treated analysis set. Safety analysis will be performed using the Safety Analysis Set. Analysis of the SS will be performed by the treatment actually received as recorded on the CRF. Subjects with initial unilateral treatment that have a subsequent procedure may appear in the SS under different treatment groups if the subsequent treatment differs from the initial treatment.

3.2.3 **Efficacy Analysis Set**

The efficacy analysis set (EAS) population consists of all patients diagnosed with keratoconus, who do not have prior CK treatment, who do not have a prior corneal crosslinking procedure, and removed contact lenses per protocol as indicated on the CRF. Furthermore, patients must have a measure of change from baseline in at least one of the three efficacy endpoints. Analysis of efficacy endpoints will use the EAS. All EAS analyses will be performed by the treatment received as recorded on the CRF.

If the patient's diagnosis per-randomization does not correspond to the diagnosis captured on the medical history page or the diagnosis captured in the procedure page, that patient will be excluded from the EAS.

Determination of the efficacy analysis set may include utilization of patient lists provided by CXL if the criteria set for the EAS can't be directly determined from the CRF data.

3.2.3.1 Justification for Exclusions

The results of the efficacy analysis are strictly to aid in program development. While the exclusions may limit generalizations with interpretation, they are in place to establish estimates

of a treatment effect at month 12 on the set of patients anticipated for the Phase III protocol. No hypotheses are being tested. Point estimates, standard errors, and confidence intervals are to be used for descriptive purposes only.

3.3 Strata and Covariates

Randomization will be stratified by indication and by investigational site. No strata or covariates will be considered in the planned analyses other than for establishing the subset needed for the EAS.

3.4 Examination of Subject Subsets

Additional analyses will be performed in subgroups of patients, including patients under the age of 22, patients with a baseline $K_{max} \geq 47$, and patients with and without pre-procedure corneal scars. Results in male vs. female patients and different ethnicities may also be evaluated.

3.5 Multiple Comparisons

No multiplicity adjustments to control the Type I error rate will be considered.

3.6 Missing Data and Outliers

By definition of the EAS, there are no missing data for the primary endpoint. Missing data will not be imputed for any analysis. If a patient in the EAS has missing data for a secondary endpoint, they will not be included in the analysis of the secondary endpoint.

3.7 Study Eye

For the efficacy endpoints collected on both eyes, only the "worse" eye at randomization will be designated as the study eye and used as the primary eye in the efficacy analyses. The worse eye will be defined as the eye with the lowest CDVA at randomization. If both eyes have the same CDVA, then the eye with the greater Kmax will be chosen. If both eyes have the same Kmax and same CDVA, then the right eye will be designated as the study eye. If only one eye initially receives treatment, then that eye will be designated as the study eye and used in the analyses. The study eye will be labeled as the "Primary Eye" and non-study eye will be labeled as the "Fellow Eye" in the Tables and Listings.

3.8 Visit Windows

3.8.1 Definition of Study Day

Study day is the day relative to the treatment of the first eye. Study day for events on or after the date of the first dose will be defined as the number of days from the date of the first dose of study drug, plus 1 day, so that the date of the first dose will be defined as Day 1.

3.8.2 Definition of Study Baseline

Study baseline is defined as the last observation obtained on or prior to the start of the procedure on the first eye on Study Day 1.

Change from baseline is defined as post-baseline assessment minus baseline assessment. Baseline value will not be carried forward to impute the post-baseline values.

For efficacy measures performed on individual eyes, baseline will be determined for each eye separately based on the date of the procedure on each particular eye.

3.8.3 **Analysis Visits**

The CRF nominal study visits will be used to define analysis visits for each eye based on the expected number of months post-procedure. This allows analysis visits to represent the number of months of post-procedure follow-up associated with each eye.

3.8.4 **Selection of Data in the Event of Multiple Records in a Visit**

If multiple assessments fall within the same analysis visit, the assessment closest to the target visit day specified in the protocol study procedures will be used. If two assessments are equidistant from the target visit day, the earlier assessment will be used.

3.8.5 **Rounding**

The method of rounding for data presentation is provided in Appendix D.

4. BASELINE CHARACTERISTICS AND SUBJECT DISPOSITION

Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, minima, and maxima. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

Summaries will be presented by treatment as recorded on the CRF. Any results presented by diagnosis will be based on diagnosis from medical history.

4.1 Disposition of Subjects

A disposition summary will include

- Number of randomized and treated by primary and fellow eye
- Number of subjects in the Safety analysis set. Subjects may be included in more than one column of the second eye was treated under a different treatment group.
- Number and percentage of subjects with the procedure on the right eye (OD), the left eye (OS) or both eyes (OU) for initial treatment
- Number and percentage of patients that had subsequent CXL treatment on the fellow eye
- Number and percentage of subjects in the efficacy analysis set (EAS)
- Number and percentage of subjects ongoing (per protocol)
- Number and percentage of subjects completing study (at Month 6 per protocol)
- Number and percentage of subjects discontinuing study and the reasons for discontinuation

A subject will be considered discontinued if they have a record that from the end of study CRF page suggesting they did not complete study.

Disposition summaries will be presented by initial treatment received and diagnosis. Percentages will be based on the number of subjects randomized.

A listing of subject disposition will include the date of the procedure for each eye, study completion status, and reason for termination (if applicable).

A separate listing will be provided to identify patients that had re-treatment with CXL.

4.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics summaries, for subjects in the randomized analysis set, will include:

- Age (years at baseline)

- Sex
- Race
- Ethnicity

Demographic and baseline characteristics will be summarized by randomized treatment group for the Treated Analysis Set. No statistical comparisons between the treatment groups will be conducted.

4.3 CXL Procedures

Frequency counts of patients treated with one eye (OS, OD) and with both eyes (OU) will be provided by diagnosis and by randomized treatment group. Continuous statistics for the number of minutes required to achieve corneal saturation with Riboflavin solution for each eye (OS, OD) will also be provided.

4.4 Inclusion and Exclusion Criteria

Data for inclusion and exclusion criteria will not be presented.

4.5 Medical History

Medical history data is used for identification of various subsets of patients but will not be summarized or listed.

4.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary.

Prior medications are defined as any medications that started and stopped prior to the first dose administration on Study Day 1. Concomitant medications are defined as any medications that started or ongoing at time or after the first dose administration on Study Day 1 in each of the study phase.

Where a medication recorded with a partially or fully missing start/stop date or time, and it is unclear as to whether the medication is concomitant, it will be assumed that it is concomitant. Rules for date imputation for classification as prior and/or concomitant are found in Appendix C.

Prior and concomitant medications may be summarized in ad hoc manner.

5. EFFICACY

Efficacy analysis will be performed using the EAS analysis set. All analysis will be based on a change from baseline in the Primary Eye. Point estimates and 95% confidence intervals (CIs) for the mean changes from baseline within each treatment group will be presented.

Only the required CRF nominal study visits (Month 3, Month 6, Month 12) will be used for efficacy analyses of changes from baseline. Analysis will be repeated for both the Primary eye and the Fellow eye. Analysis will be based on months of post-procedure follow-up for the eye being summarized.

Optional visits other than month 12 and unscheduled visits will not be used.

5.1 Primary Efficacy Endpoint

The primary measure of efficacy is the mean change from baseline in LogMAR of Corrected Distance Visual Acuity (CDVA) in the Primary Eye at Month 12 for each treatment group. As supportive analysis to the primary endpoint, the mean change from baseline and treatment differences will be estimated at Month 3 and Month 6.

Separately for each timepoint, analysis of variance (ANOVA) will be used to obtain point estimates and CIs for the change from baseline in LogMAR CDVA for each group. ANOVA will also be used to obtain point estimates and CIs for all pairwise comparisons between the treatment arms. P-values may be provided for descriptive purposes only.

As a sensitivity analysis, separate point estimates and confidence intervals for treatment differences based on a two-sample t-tests for each pairwise comparison will be performed without assuming equal variances. Satterthwaite approximation for degrees of freedom will be used.

Other sensitivity analysis such as mixed models repeated measures to account for the longitudinal nature of the data may be considered in an ad hoc manner.

The primary analysis will be repeated for the Fellow eye.

5.2 Secondary Endpoints

5.2.1 Uncorrected Visual Acuity

The primary analysis will be repeated for LogMAR of UCVA separately for each eye (primary eye and fellow eye).

5.2.2 Maximum Corneal Curvature

The primary analysis will be repeated for K_{max} separately for each eye (primary eye and fellow eye). Additionally, the change from baseline will be categorized defined by: ≤ -2D, -1.99 -1.5D, -1.49D to 1D, .99D to .5D, -.49D to 0D, .01D to .49D, 0.5D to .99D, 1D to 1.49D, 1.5D to 1.99D, ≥2D. Frequency of patients in each category for each eye will be presented at Months 3, 6, and 12.

6. SAFETY

Safety data will be summarized using the safety population. Missing data will not be imputed for safety analyses. In the presence of partial dates, the available data (month and/or year) will be compared to the appropriate study reference dates to identify the most likely treatment received.

6.1 Treatment Emergent Adverse Events

6.1.1 General Considerations for Analysis of Adverse Events

General considerations for AE summaries and calculations are:

- Multiple events by preferred term (PT) and system organ class (SOC) will be counted once only per subject.

6.1.2 Adverse Event Dictionary

AEs will be coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 16.0 or higher. In MedDRA, each verbatim term is mapped to a preferred term and high level term (HLT), which is then mapped to a system organ class. Tables and listings will present data at the SOC and PT level.

6.1.3 Definition of Treatment-Emergent

Treatment-emergent adverse events are events that

- Began on or after the date of the date of the first procedure.
- Had no recorded start date with a stop date after the first procedure.
- Had no recorded start date or stop date

For patients that received multiple treatments, treatment emergent adverse events will be attributed to the last treatment received.

Rules for date imputation to determine treatment emergent status can be found in Appendix C.

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used to classify all adverse events reported during the study by system organ class (SOC) and preferred term (PT). Adverse events will be summarized by SOC and PT.

Treatment Emergent adverse events by SOC, PT will be summarized and listed.

6.2 Anticipated Adverse Events

Adverse events that are anticipated will be summarized by SOC, PT. An adverse event is considered anticipated based solely on the CRF field that captures if the adverse event is expected.

7. REFERENCES

None

8. APPENDICES

8.1 Appendix A: Schedule of Assessments

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

[1]Or documented dilated fundus exam by another provider

[2]By ultrasound or other scanning device such as Pentacam

[3]Optional assessment procedures

[4]Other Assessments include corneal wavefront, optical coherence tomography (OCT), Brillouin microscopy, iTrace wavefront aberrometry/topography, Orbscan corneal topography, tomography, contrast sensitivity testing, or other non-invasive diagnostic tools that may be available to an investigator.

8.2 Appendix B: Tables, Listings, and Figures

Table 1	Disposition	Treated Analysis Set
Table 2.1	Demographics	Treated Analysis Set
Table 2.2	Demographics	Efficacy Analysis Set
Table 3	CXL Procedures	Safety Analysis Set
Table 4.1.1	Summary of Corrected Distance Visual Acuity	Efficacy Analysis Set
Figure 4.1.1	Mean +/- SE of Changes in Corrected Distance Visual Acuity	Efficacy Analysis Set
Table 4.1.2	Analysis of Changes in Corrected Distance Visual Acuity	Efficacy Analysis Set
Table 4.2.1	Summary of Corrected Distance Visual Acuity in Patients < 22 Years Old	Efficacy Analysis Set
Figure 4.2.1	Mean +/- SE of Changes in Corrected Distance Visual Acuity in Patients < 22 Years Old	Efficacy Analysis Set
Table 4.2.2	Analysis of Changes in Corrected Distance Visual Acuity in Patients < 22 Years Old	Efficacy Analysis Set
Table 4.3.1	Summary of Corrected Distance Visual Acuity in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Figure 4.3.1	Mean +/- SE of Changes in Corrected Distance Visual Acuity in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Table 4.3.2	Analysis of Changes in Corrected Distance Visual Acuity in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Table 5.1.1	Summary of Uncorrected Visual Acuity	Efficacy Analysis Set
Figure 5.1.1	Mean +/- SE of Changes in Uncorrected Visual Acuity	Efficacy Analysis Set
Table 5.1.2	Analysis of Changes in Uncorrected Visual Acuity	Efficacy Analysis Set
Table 5.2.1	Summary of Uncorrected Visual Acuity in Patients < 22 Years Old	Efficacy Analysis Set
Figure 5.2.1	Mean +/- SE of Changes in Uncorrected Visual Acuity in Patients < 22 Years Old	Efficacy Analysis Set
Table 5.2.2	Analysis of Changes in Uncorrected Visual Acuity in Patients < 22 Years Old	Efficacy Analysis Set
Table 5.3.1	Summary of Uncorrected Visual Acuity in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Figure 5.3.1	Mean +/- SE of Changes in Uncorrected Visual Acuity in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Table 5.3.2	Analysis of Changes in Uncorrected Visual Acuity in Patients with Baseline Kmax ≥47	Efficacy Analysis Set

Table 6.1.1	Summary of Maximum Corneal Curvature	Efficacy Analysis Set
Figure 6.1.1	Mean +/- SE of Maximum Corneal Curvature	Efficacy Analysis Set
Table 6.1.2	Analysis of Changes in Maximum Corneal Curvature	Efficacy Analysis Set
Table 6.1.3	Categorical Shifts in Maximum Corneal Curvature	Efficacy Analysis Set
Table 6.2.1	Summary of Maximum Corneal Curvature in Patients < 22 Years Old	Efficacy Analysis Set
Figure 6.2.1	Mean +/- SE of Maximum Corneal Curvature in Patients < 22 Years Old	Efficacy Analysis Set
Table 6.2.2	Analysis of Changes in Maximum Corneal Curvature in Patients < 22 Years Old	Efficacy Analysis Set
Table 6.2.3	Categorical Shifts in Maximum Corneal Curvature in Patients < 22 Years Old	Efficacy Analysis Set
Table 6.3.1	Summary of Maximum Corneal Curvature in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Figure 6.3.1	Mean +/- SE of Maximum Corneal Curvature in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Table 6.3.2	Analysis of Changes in Maximum Corneal Curvature in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Table 6.3.3	Categorical Shifts in Maximum Corneal Curvature in Patients with Baseline Kmax ≥47	Efficacy Analysis Set
Table 7.1	Overview of Adverse Events	Safety Analysis Set
Table 7.2	Treatment Emergent Adverse Events by SOC and PT	Safety Analysis Set
Table 7.3	Treatment Emergent Anticipated Adverse Events by SOC and PT	Safety Analysis Set
Listing 1	Subject Disposition	Treated Analysis Set
Listing 2	Listing of Patients with Re-Treatment with CXL	Treated Analysis Set
Listing 3	Listing of Aes	Safety Analysis Set

8.3 Appendix C: Imputation Rules for Missing Dates

Incomplete diagnosis or treatment date

- If day is missing, day will be set to 15th of the month.
- If month and day are missing, month and day will be set to July 1st.
- If year and month and day are missing, date will be set to missing.

Adverse Event

- If onset date is completely missing, onset date is set to date of first treatment.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
  - If year = year of first treatment, then set month and day to month and day of first treatment
  - If year < year of first treatment, then set month and day to December 31st.
  - If year > year of first treatment, then set month and day to January 1st.
- If month and year are present and day is missing:
  - If year=year of first treatment and month = month of first treatment then set day to day of first treatment date month < month of first treatment then set day to last day of month > month of first treatment then set day to first day of month
  - If year < year of first treatment then set day to last day of month
  - If year > year of first treatment then set day to first day of month
- For all other cases, set onset date to date of first treatment.

Concomitant Medications

- If start date is completely missing, start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
- If year and month are present and day is missing, set day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.
- If year and month are present and day is missing, set day to last day of the month.

8.4 Appendix D: Programming Specifications

Continuous data will be listed corresponding to the precision measured or calculated. Variability summaries will be presented using one additional significant digit relative to the precision of the underlying data.

All percentages are to be expressed as integers with one decimal place. The convention for rounding percentages is as follows:

- Values greater than or equal to x.x5% are rounded up
- Values between 0 and x.x5% are rounded down
- Values between –x.x5% and 0 are rounded up
- Values less than or equal to –x.x5% are rounded down