Riboflavin Ophthalmic Solution/KXL™ System for the Treatment of Progressive Keratoconus or Corneal Ectasia Following Refractive Surgery

NDA # 203-324

Briefing Package

For the Dermatologic and Ophthalmic Drugs Advisory Committee

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1. EXECUTIVE SUMMARY

Avedro is seeking approval of NDA 203-324 for corneal collagen cross-linking (CXL) with riboflavin ophthalmic solution/KXL® System for the treatment of progressive keratoconus or corneal ectasia following refractive surgery. Avedro was granted orphan drug designation for both keratoconus and corneal ectasia following refractive surgery.

Keratoconus and corneal ectasia are progressive conditions that can result in loss of visual function. The totality of the safety and efficacy data from Avedro's Phase III well-controlled studies provides substantial evidence of safety and effectiveness. The positive benefit to risk ratio of riboflavin ophthalmic solution/KXL System greatly favors approval of this drug-device therapy for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.

Corneal collagen cross-linking is approved for treating keratoconus and corneal ectasia in over 60 countries around the world. The currently available treatment options in the United States (US) for progressive keratoconus and corneal ectasia do not address the underlying problem of compromised corneal biomechanical integrity or prevent or slow progression of the disease. Approval of NDA 203-324 would provide patients in the US the first Food and Drug Administration (FDA) approved therapeutic treatment option that treats the underlying disease.

1.1. Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery

Keratoconus is a devastating, sight-threatening, progressive disease. It is a bilateral asymmetric corneal ectatic disorder, resulting from progressive weakening and thinning of the cornea. The precise organization of the lamellae (bundles of collagen fibers) that make up the corneal stroma is critical for maintaining optical clarity and corneal shape. Microstructural studies have revealed that this precise arrangement is absent in the apical area of the corneal stroma of corneas affected by keratoconus (Meek 2005). In keratoconus, the fibers are more loosely associated, and as the fibers slip apart in a phenomenon known as "creep", the region thins and bulges forward, resulting in the keratoconic "cone," a region of topographic steepening which manifests in irregular astigmatism, increase in higher order aberrations, and consequent decrease in and possible loss of visual function (Meek 2008).

The first functional symptom of keratoconus is often blurred vision, which worsens over time. In addition, the patient may be sensitive to light and experience glare and halo, especially at night. As the condition progresses, ghosting of images and blurring and streaking of light worsen. Headaches, as well as difficulty driving and performing other routine functions may develop. In addition to irregular astigmatism and optical higher order aberrations, visually significant stromal scarring may also be present. In the advanced stages of the disease, the cornea may appear visibly cone-shaped.

Keratoconus has a significant impact on the quality of life. It is a disease of the young and typically healthy (Wagner 2007), with average onset at just 15 years of age (Olivares 1997). With no FDA approved therapy to treat the underlying pathology and halt the progression of this disorder, these patients at the prime of their lives are at risk of suffering a debilitating progressive loss of visual function and face the potential for corneal transplantation (Rabinowitz 1998). In this disease of the young, these effects have life-long impact. Those with keratoconus have increased prevalence of anxiety disorders, poor mental health, difficulty performing social duties and high dependency (Kymes 2004).

Corneal ectasia is a well-described but rare complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy (PRK). It is a condition similar in symptoms to keratoconus, but occurs postoperatively rather than naturally. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual function (Binder 2007, Leccisotti 2007).

1.2. Unmet Medical Need in the US

The currently available disease management options in the US for progressive keratoconus and corneal ectasia do not address the underlying problem of compromised corneal biomechanical integrity, prevent or slow the progression of the disease. They offer temporary relief from visual symptoms in the form of rigid contact lenses and intracorneal ring segments.

When those options no longer provide any relief from symptoms or are not feasible due to advanced disease, corneal transplantation is the only other option. Visual rehabilitation after corneal transplantation is a long and difficult process with a mean time to first fitting of rigid gas permeable lenses of 8 to 18.2 months. (Wietharn 2004, Geerards 2006). Frequent office visits are required to monitor changing corneal curvature and lens fit as corneal sutures are removed over time, representing additional expense and loss of productivity. Recurrence of keratoconus in the graft can occur (Brierly 2000, Pramanik 2006).

The early onset of keratoconus is significant due to the potential for ultimate graft failure and need for secondary transplant. 73% of grafts fail within 20 years (Borderie 2009) and successive grafts are significantly more likely to fail (Inoue 2001). For a keratoconus patient diagnosed at 15 years of age, that means that multiple corneal transplants may be required over their lifetime. By slowing or halting progression in the early stages of the disease, patients have the potential to retain sufficient visual function to lead normal lives, avoid the risks associated with corneal transplantation, and minimize the public health impact and financial burden of the disease (Labiris 2012).

In 2012, keratoconus and corneal ectasia were ranked leading indications for corneal transplants. In addition, keratoconus was the leading indication for anterior lamellar keratoplasty, another form of corneal transplant, in 2012 (43.4%) (Eye Bank Association of America Statistical Report, 2012).

There currently is no (FDA)-approved medical therapy available in the (US) that treats the underlying pathology of progressive keratoconus or corneal ectasia following refractive surgery.

Therefore, a significant unmet medical need exists between the currently available options that only offer temporary relief from visual symptoms and the more-extreme option of corneal transplantation. This treatment gap is profound for patients diagnosed early in their lives who face the possibility of multiple corneal transplants throughout their lifetime. Corneal Collagen Cross-linking with riboflavin/UVA light (CXL) presents patients a much needed therapeutic treatment option and bridges this treatment gap.

1.3. Corneal Collagen Cross-Linking

Corneal collagen cross-linking is a procedure in which the corneal epithelium is debrided followed by administration of riboflavin (vitamin B2) drops to the cornea. The cornea is then exposed to ultraviolet (UV) light at 3.0 mW/cm2 for a treatment time of 30 minutes. Riboflavin and reactive oxygen species interact with corneal proteins to strengthen chemical bonds in the collagen fibrils of the cornea resulting in a shortening and thickening of the collagen fibrils and stiffening of the cornea. As the first therapy to treat the underlying pathology, cross-linking offers a new approach to treating the orphan conditions of progressive keratoconus and corneal ectasia.

The bases for the currently employed corneal collagen cross-linking techniques were developed in Europe by researchers at the University of Dresden in the late 1990's. UV light was used to induce collagen cross-linking in riboflavin soaked porcine and rabbit corneas. The resultant corneas were shown to be stiffer and more resistant to enzymatic digestion. Investigation also proved that the treated corneas contained higher molecular weight polymers of collagen due to fibril crosslinking (Spoerl 2004).

Due to the required debridement of the epithelium prior to administration of riboflavin drops, there is an expected healing process associated with the cross-linking procedure. Additionally, there is an expected timeframe for corneal remodeling following cross-linking. The epithelium healing process could take up to one month with corneal remodeling taking up to three months.

CXL using UVA light with riboflavin has been performed internationally for over a decade with over 500 peer reviewed publications evaluating the procedure. The abundance of data in the public literature demonstrates that cross-linking with riboflavin and UV light stops disease progression, improves corneal curvature on average, and preserves visual acuity in most patients, with actual improvement in a number of individuals. Persistence of effect is seen with three-year data demonstrating the sustained effect of cross-linking in the treated group and the continued progression of disease in the control group (Wollensak 2003a, Wollensak 2006, Hafezi 2007, Wittig-Silva 2008, Raiskup-Wolf 2008, Agrawal 2009, Caporossi 2010, Asri 2011, Henriquez 2011, Hersh 2011, Koller 2011, Vinciguerra 2011, O'Brart 2011, Goldich 2012; Li, 2012). Further, CXL is reported to be safe and associated with few serious complications. (Kolli 2010, Chan 2013; Meek, 2013, Wittig-Silva 2014).

1.4. Description of Drug-Device Combination Product

Avedro's riboflavin ophthalmic solutions are sterile, phosphate buffered saline solutions containing 0.12% riboflavin (Vitamin B2) in either 20% dextran or 0% dextran and act as a photosensitizer. Riboflavin, a water soluble vitamin, is an essential nutrient and a natural

component of many foods. Avedro's riboflavin solutions are manufactured under GMP conditions at Ajinomoto Althea, a registered GMP commercial drug manufacturing facility in the United States.

Avedro's KXL® System is a UVA irradiation system that uses a light emitting diode (LED) to deliver a dose of UVA light to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Avedro's KXL UVA light device is manufactured according to FDA's Quality System Regulations at Avedro in Waltham, MA.

1.5. Regulatory History

Avedro's NDA 203-324 for riboflavin ophthalmic solution/KXL System is based on the results from three Phase III clinical trials (UVX-001, UVX-002, and UVX-003). Study UVX-001 was conducted under the Investigational New Drug (IND) application 78,933, an investigator initiated study submitted by R. Doyle Stulting, M.D., Ph.D., Emory University, Atlanta, GA. All rights to the data generated in UVX-001 were transferred to Avedro in a licensing agreement dated 10 September 2010. Studies UVX-002 and UVX-003 were multi-center studies conducted in the United States under IND 77,882 originally held by Peschke Meditrade GmbH (Hüenenberg, Switzerland). Sponsorship of IND 77,882 was transferred to Avedro on 07 May 2010.

In 2011, Avedro received orphan drug designation for both keratoconus and corneal ectasia following refractive surgery. The inclusion of both indications in the clinical program was discussed with FDA at the onset of the clinical studies.

On 16 September 2013, Avedro submitted NDA 203-324 for Riboflavin ophthalmic solution/KXL System. The proposed indications are for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. The NDA was filed as a 505(b)(2) application because the non-clinical safety of riboflavin ophthalmic solution/ UVA was established based upon data from studies in the published literature on the safety of riboflavin/UVA and its use in corneal collagen cross-linking.

The UV-X Illumination System manufactured by Peschke Meditrade was utilized as the UV light source during the Phase III clinical studies reported in the NDA. Both the UV-X clinical system and the KXL commercial system are LED based illumination systems that deliver an equivalent spectral output of 365 nm with an illumination intensity of 3.0 mW/cm^2 and a treatment time of 30 minutes. The differences between the two systems do not impact the UV light delivered but rather the functionality of the device (Appendix 3). Avedro's KXL device underwent extensive testing to establish equivalency to the UVX device utilized in the clinical studies and to ensure it met relevant consensus standards including IEC 60601-1, IEC 60601-1-2, IEC 60601-1-4, IEC 60601-1-6, and IEC 60825-1. The equivalency testing was discussed with and reviewed by FDA. Therefore, the data collected with the UV-X Illumination System supports approval of the KXL® System.

On 14 March 2014, Avedro received a Complete Response Letter from FDA. On 6 August 2014, Avedro and FDA met to discuss the letter and subsequent resubmission. On 29 September 2014, Avedro resubmitted NDA 203-324.

On 6 November 2014, Avedro received a letter from FDA stating that our submission was "a complete, class 2 response to our March 14th, 2014 action letter" (Appendix 4). The user fee goal date for NDA 203-324 is 29 March 2015.

1.6. Overview of Clinical Study Design

Each of the Phase III studies was a prospective, randomized, parallel-group, open-label, controlled, 12-month trial to determine the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing CXL in the eyes of subjects with progressive keratoconus or corneal ectasia following refractive surgery. In each study, eligible subjects were randomized in a 1:1 ratio into one of two treatment groups: the CXL group and the control group. Subjects with bilateral keratoconus or corneal ectasia had only one eye designated for study treatment (i.e., the study eye). The planned sample size was 160 subjects (80 eyes per treatment group) for each of UVX-002 and UVX-003. For UVX-001, the planned sample size was 320 subjects (160 per indication, with 80 eyes per treatment group).

The clinical trial treatment for all three studies was based upon the Dresden protocol. The study was randomized and a control was used whereby subjects in the control group went through the same procedure but without UVA irradiation or epithelial debridement (Section 5.1.1 Figure 7).

- On Day 0, subjects randomized to the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed. Subjects then received riboflavin ophthalmic solution with dextran in the study eye for 30 minutes (1 drop instilled onto the cornea every 2 minutes, with additional drops as needed to achieve adequate riboflavin saturation). As the Dresden protocol called for the cornea to be at least 400 microns prior to cross-linking, if corneal thickness was < 400 microns in eyes in the CXL group after treatment with riboflavin ophthalmic solution with dextran, a second solution, riboflavin without dextran was instilled into the study eye (2 drops instilled every 5 to 10 seconds until corneal thickness increased to at least 400 microns). After the riboflavin pretreatment regimen was completed, study eyes in the CXL group were exposed to UVA light (365 nm at an irradiance of 3.0mW/cm2) for 30 minutes, with riboflavin ophthalmic solution with dextran continuing to be administered every 2 minutes during this time.
- Subjects randomized to the control group had topical anesthetic administered to the study eye on Day 0 but did not have the corneal epithelium removed. Study eyes were treated with riboflavin ophthalmic solution as described above (both pretreatment and during the simulated irradiation procedure). However, the cornea was not debrided and the UVA light source was not illuminated during the procedure.

In the study design, subjects at Month 3 or later whose eye(s) met the study inclusion/exclusion criteria, were given the option of having CXL performed on their untreated fellow eyes (from the CXL group) and untreated control eye and untreated fellow eye (from the control group). After treatment, these eyes were followed for 12 months according to the same schedule and protocol as the study eye in the CXL group (Section 5).

1.6.1. Primary Efficacy Endpoint

Progressive keratoconus and corneal ectasia following refractive surgery are typified by steepening and irregularity of the cornea. Steepness of the cornea can be quantitatively measured using corneal topography instrumentation. Maximum corneal curvature, as measured by maximum keratometry (K_{max}), quantifies the most pathognomonic feature of progressive keratoconus and corneal ectasia. Based on the etiology and manifestation of ectatic corneal disorders, K_{max} is accepted as a clinically meaningful and reproducible endpoint to be measured in these patient populations (Kolli 2010). For each study, the primary efficacy endpoint was corneal curvature, as measured by K_{max}. K_{max} was evaluated at baseline and at Months 1, 3, 6, and 12. Study success was originally defined as a difference of ≥1 D in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group. In keratoconus and corneal ectasia patients, stabilizing the cornea and stopping progression (no change in Kmax) are clinically meaningful and important factors in measuring the studies' success. A 1D difference is a measurable indicator of not only stabilization but can also indicate improvement. Therefore, 1D was selected as the endpoint.

1.6.2. Primary Efficacy Analysis

1.6.2.1. Change in Timing of Assessment of Primary Efficacy Endpoint

The initial decision to analyze the primary endpoint at 3 months was made by the original IND Sponsor in 2006 (Peschke Meditrade). Over the years, there have been significant advancements in the science of cross-linking. As more has been learned about the natural history of healing after epithelial debridement and corneal remodeling following cross-linking, it has become evident that evaluating effectiveness at the 3 month time period is not clinically appropriate. A 3 month timeframe for analysis of cross-linking is too short of a time to evaluate the benefit of this procedure. The benefit of the corneal cross-linking procedure is best measured at later time-points when the epithelial healing and corneal remodeling processes have been completed. (Caporossi 2010, Wittig-Silva 2014, Mazzotta 2008).

After acquiring the studies from the previous sponsor in 2010, Avedro changed the timing of the primary efficacy analysis from 3 months to 12 months. Avedro selected 12 months as that was the last time point studied and, therefore, would provide the longest-term data on patients treated with the cross-linking procedure. All patients had been treated at the time Avedro acquired the studies, therefore, the change had no impact on study conduct. Additionally, Kmax measured by corneal topography is an objective measurement and, therefore, the change in timing of analysis did not impact this measurement.

The measurement and magnitude of success for the primary endpoint continued to be a ≥1 D difference in the mean change in K_{max} between the CXL group and the control group.

In keratoconus and corneal ectasia patients, stabilizing the cornea and stopping progression is clinically meaningful and an important factor in measuring the studies' success. For patients suffering from these devastating conditions and facing the likelihood of corneal transplantation, halting progression at 12 months is not only clinically meaningful but also life changing.

1.6.2.2. Utilization of Last Observation Carried Forward (LOCF)

As the study design allowed subjects randomized to the control group to cross over to receive the CXL treatment after Month 3, last observation carried forward (LOCF) was used in order to allow comparisons between the CXL and control groups at the later time points. The primary efficacy analysis used LOCF method for imputing missing data for the control subjects who crossed over and received subsequent CXL in the study eye and for missing data in CXL subjects. The LOCF approach is valid for imputation of study data because keratoconus and post-refractive ectasia are progressive corneal ectatic conditions. Keratoconus and corneal ectasia patients do not experience spontaneous remission or become free of disease, rather a majority continue to progress and become worse as shown in the published literature. The LOCF approach does not account for any continued progression of disease in the control group, making it more difficult to demonstrate differences in mean change from baseline K_{max} with CXL.

As a result, the LOCF approach provides a conservative measure of success of the cross-linking procedure.

In addition to analyses based on LOCF, a series of additional sensitivity analyses with observed data were conducted to explore the bounds of the treatment effect at 1 year based on a variety of different assumptions which included mixed-effects regression models based on linear, log-linear, and nonparametric time trends.

No formal interim analyses were conducted. However, an informal interim analysis of data was conducted in March 2009 by the original IND Sponsor (Peschke Meditrade). Also, Dr. Peter Hersh conducted an informal review of data from patients treated at his site and those findings were published (Hersh 2011).

1.6.3. Safety Endpoints

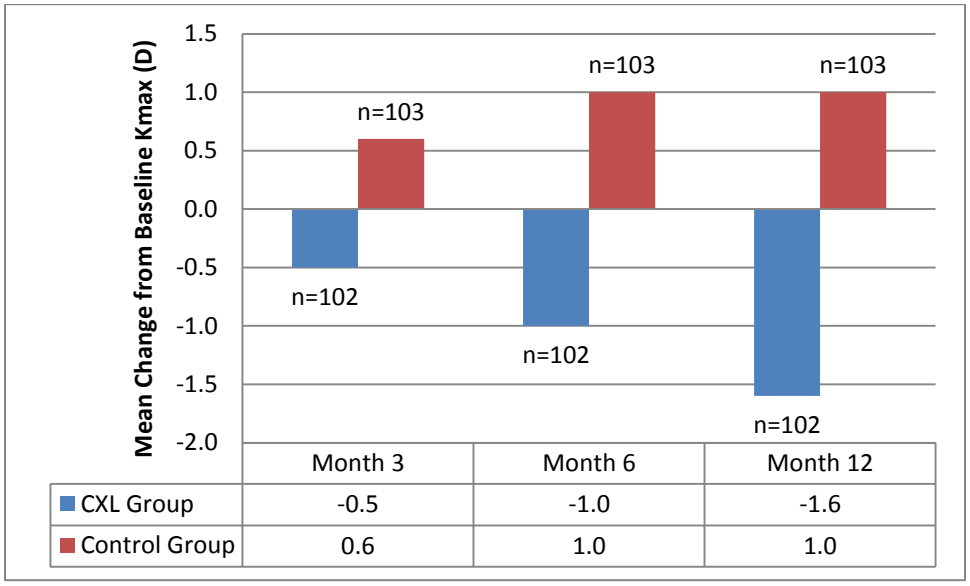
Safety endpoints included the following:

- Number of events and incidence rates of AEs
- Visual acuity (BSCVA and UCVA) using logMar units. LogMar was calculated as the log of the reciprocal of the Snellen fraction.
- Loss of visual acuity
  - Loss of 3 or more lines in BSCVA (+0.3 logMAR change)
  - BSCVA worse than 20/40 (> 0.3 logMAR)
  - Change in endothelial cell density.

1.7. Summary of Efficacy

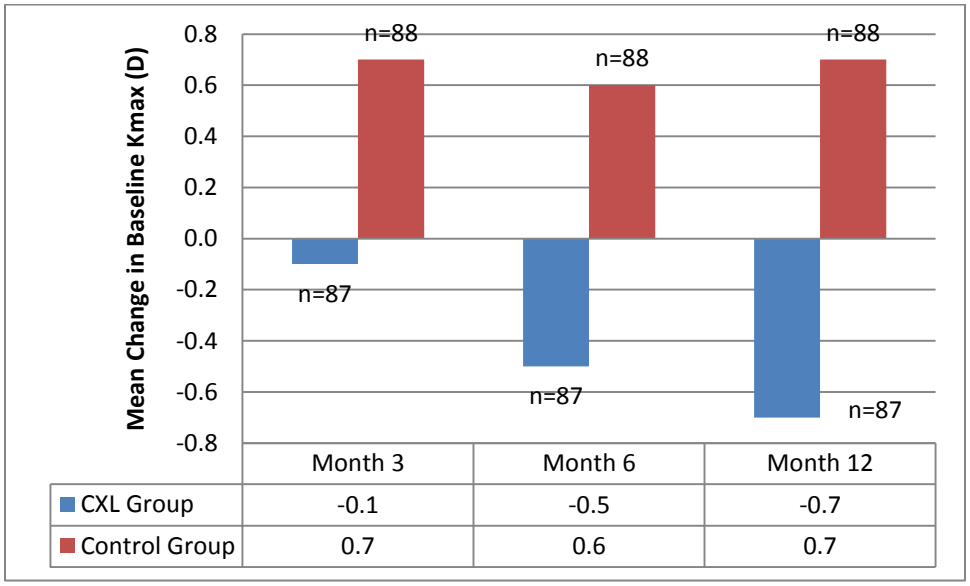
In progressive keratoconus subjects, results of both individual studies and pooled analyses at 12 months meet the primary endpoint of a ≥1 D difference in mean change in K_{max} between CXL and control with clinical and statistical significance. (Figure 1). In the pooled analysis, the difference was 2.6 D (<0.0001).

Figure 1: Differences (Control minus CXL) between Treatment Groups in Mean Changes from Baseline K_{max} (D) in the Randomized Study Eye of Progressive Keratoconus Subjects (LOCF)



In corneal ectasia subjects, results of both individual and pooled analyses at 12 months meet the primary endpoint of a ≥1 D difference in mean change in K_{max} between CXL and control with clinical and statistical significance (Figure 2). In the pooled analysis the difference was 1.4 D ($p<0.0001$).

Figure 2: Differences (Control minus CXL) between Treatment Groups in Mean Changes from Baseline K_{max} (D) in the Randomized Study Eye of Corneal Ectasia Subjects (LOCF)



CXL was effective in not only stopping disease progression but also reversing progression in some subjects, as evidenced by a clinically relevant increase in the proportion of CXL-treated subjects who showed improvement via a reduction in K_{max} over time vs. baseline.

The proportion of progressive keratoconus subjects in the CXL group with either stabilization or improvement in K_{max} over baseline increased over time, reaching over 70% (76% in UVX-001, 70% in UVX-002, and 72% pooled) at Month 12.

The proportion of corneal ectasia subjects in the CXL group with either stabilization or improvement in K_{max} over baseline increased over time, reaching approximately 60% (71% in UVX-001, 59% in UVX-003 and 62% pooled) at Month 12.

CXL provided greater improvements in Visual Acuity compared to Control.

In the pooled progressive keratoconus studies, mean improvement from baseline BSCVA at Month 12 was 5.6 letters in the CXL group versus 2.0 letters in the control groups (p=0.0094).

In the pooled corneal ectasia studies, mean improvement from baseline BSCVA at Month 12 was 5.0 letters in the CXL group versus -0.3 letters in the control group (p<0.0001).

The proportion of subjects in the CXL group with a ≥3-line improvement in BSCVA was more than 2-fold higher in the CXL group than the control group at Month 12 for both indications: progressive keratoconus (19.4% vs. 8.1%) and corneal ectasia (12.5% vs. 4.7%).

1.8. Summary of Safety

The safety evaluation of CXL was based on 512 treated eyes (293 progressive keratoconus; 219 corneal ectasia). Most treated eyes were monitored for a 12 month period following treatment (progressive keratoconus eyes 243/293, 82.9%; corneal ectasia eyes 177/219, 80.8%). Given the large number of eyes treated and length of safety follow-up, the three studies provide a substantial body of evidence of the safety of this product.

1.8.1. Randomized study eyes

A summary of the primary study eye safety data demonstrated that riboflavin ophthalmic solution/KXL System was safe and well tolerated over the 12-month study period. Specifically:

No subjects discontinued due to a treatment emergent adverse event (TEAE).

There was a low incidence rate of Serious Adverse Events (SAEs) associated with CXL.

- No deaths were associated with CXL.
- The incidence of SAEs that occurred from baseline to Month 3 was low in each study group, regardless of indication: progressive keratoconus (0%, CXL; 1.0%, control) and corneal ectasia (1.1%, CXL; 1.1%, control).

- Seven SAE's were reported in six subjects. Of those reported, two were ocular related: ulcerative keratitis (progressive keratoconus subject) and corneal epithelium defect (corneal ectasia subject). Both were considered related to epithelial debridement.

The majority of ocular treatment-emergent adverse events (TEAEs) develop in the short-term, and are of mild/moderate severity.

- As the procedure involved epithelial debridement, it was expected that subjects would experience treatment emergent events related to the debridement and subsequent healing process.
- The most common ocular TEAEs observed in the CXL group (102 progressive keratoconus subjects; 91 corneal ectasia subjects) were expected sequelae following debridement of the cornea or associated with the corneal remodeling process.
- In progressive keratoconus subjects, the most common ocular TEAEs observed in the CXL group (≥10%) from baseline to Month 3 were corneal opacity (haze) (57%), punctate keratitis (25%), corneal striae (24%), corneal epithelium defect (23%), eye pain (17%), vision blurred (16%) and photophobia (11%).
- In corneal ectasia subjects, the most common ocular TEAEs observed in the CXL group (≥10%) from baseline to Month 3 were corneal opacity (haze) (68%), corneal epithelium defect (26%), eye pain (26%), punctate keratitis (20%), photophobia (19%), vision blurred (17%), dry eye (14%) and visual acuity reduced (11%).

Significant loss of visual acuity was not observed in CXL-treated subjects.

- A transient reduction in BSCVA ≥15 letters at the Month 1 visit was observed in a higher proportion of the CXL subjects than control subjects for both indications. This finding is consistent with the effect of epithelial debridement and the expected time course of corneal remodeling. At month 12, 1 CXL subject lost ≥15 letters in BSCVA in UVX-002 and 2 CXL subjects in UVX-003.

Safety data for CXL fellow eyes was similar to that of randomized study eyes

1.8.2. Safety Conclusions

The CXL procedure was safe and well tolerated in both populations. In both keratoconus and ectasia subjects, the most common ocular treatment-emergent adverse events (TEAEs) in any CXL-treated eye were corneal haze, punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision (Sections 6.7 and 6.8). These events are expected sequelae following epithelial debridement. No subjects discontinued due to a treatment emergent adverse event (TEAE). For both indications, most ocular events were mild or moderate in intensity, with most resolved by Month 3 or last study visit. These findings are consistent with the data available in the peer reviewed public literature. Given the large number of eyes treated and length of safety follow-up, the three studies provide a substantial body of evidence of the safety of this product.

1.9. Benefit-Risk Analysis Supports Approval of CXL for the Treatment of Progressive Keratoconus and Corneal Ectasia following Refractive Surgery

Results from the well-controlled studies in the UVX clinical development program provide a positive benefit-to-risk profile for riboflavin ophthalmic solution/KXL® System in the treatment of subjects with the orphan indications of progressive keratoconus or corneal ectasia following refractive surgery.

In these trials, CXL provided clinically meaningful and statistically significant improvements in corneal curvature, as measured by K_{max}, in subjects with these conditions. All three studies met the primary efficacy endpoint of a ≥1 D difference in the mean change in K_{max} between the CXL group and the control group at 12 months. CXL therapy was effective in reversing or stopping disease progression, as evidenced by a clinically relevant increase in the proportion of CXL-treated subjects who showed no progression or improvement and a decrease in CXL subjects who had worsening over time. This finding is particularly relevant since keratoconus and corneal ectasia following refractive surgery are considered to be progressive conditions. In fact, all subjects enrolled in the keratoconus studies had to show significant progression in the 24-month period before randomization. Therefore, stopping progression in these orphan patient populations is an important clinical benefit. CXL treatment not only stopped progression but also reversed disease progression in some subjects. Clinically meaningful improvements over baseline were also observed in visual acuity within 12 months of CXL therapy, indicating that CXL not only corrects corneal curvature but also improves visual function.

Results of the 3 randomized and well-controlled clinical trials showed that CXL was safe and well tolerated over the 12-month study period. As expected, there were no deaths associated with the treatment. The most common events associated with CXL in these studies (e.g., corneal opacity [haze], punctate keratitis, corneal epithelium defect, eye pain, and blurred vision) are expected sequelae following debridement or expected as part of the corneal remodeling process. Most were mild or moderate in intensity and resolved over time.

Currently available treatments for keratoconus and corneal ectasia do not address the underlying problem of compromised corneal biomechanical integrity or prevent the progression of the disease, but rather offer temporary visual rehabilitation in the form of rigid contact lenses and intracorneal ring segments, or require penetrating keratoplasty. As a surgical procedure, corneal transplantation can significantly impact the patient's quality of life, with risk of rejection, lost time from work, and a lengthy vision rehabilitation period.

Patients in the US suffering from keratoconus and corneal ectasia would benefit from another treatment option that bridges the gap in between hard contacts and transplantation. If approved, CXL will be the first drug-device combination product in the US for the treatment of patients with progressive keratoconus or corneal ectasia following refractive surgery.

CXL is the only therapeutic treatment option which slows or prevents disease progression. As such, CXL has the potential to fill a significant unmet medical need for patients suffering from these progressive conditions which may lead to loss of visual function. CXL could redefine the standard of care for these patients in the US.

CXL is approved for use in over 60 countries around the world and is a standard of care for keratoconus and corneal ectasia OUS. In the absence of an FDA approved therapy in the US, the procedure is being performed with devices that are not approved for cross-linking and compounded drug product that is not manufactured according to Good Manufacturing Practices (cGMP's).

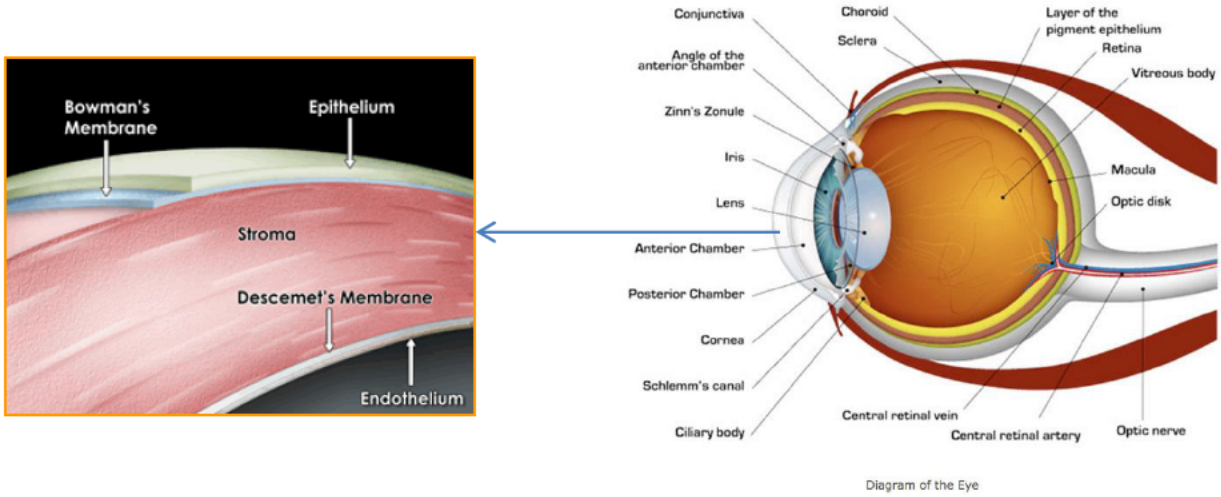
The totality of the safety and efficacy data from Avedro's well-controlled studies provides substantial evidence of safety and efficacy of riboflavin ophthalmic solution/KXL® System for the treatment of progressive keratoconus and corneal ectasia.

The positive benefit to risk ratio of CXL greatly favors approval of riboflavin ophthalmic solution/KXL® System for the treatment of progressive keratoconus and corneal ectasia.

2. PROGRESSIVE KERATOCONUS AND CORNEAL ECTASIA FOLLOWING REFRACTIVE SURGERY

The cornea is responsible for approximately 75% of the refractive power of the eye. The orderly structure of the cornea, and particularly the orientation of the collagen fibrils that make up the cornea stroma (Figure 3), enables light to pass through it with minimal disruption or scatter. The cornea can maintain a reasonably constant shape and corneal curvature due to the tensile strength of the collagen fibrils.

Figure 3: Cross Section of the Cornea



In the normal eye, the corneal collagen fibrils lie in orthogonal sheets that are parallel to each other and to the plane of the cornea comprising the extracellular matrix of the corneal stroma. Eyes with progressive ectatic conditions have an abnormal collagen fibril structure. The ectatic cornea is typically marked by thinning and an increase in the anterior and/or posterior curvatures of the cornea, and often lead to high levels of myopia and astigmatism. Keratoconus and ectasia following refractive surgery are both ectatic corneal disorders.

Keratoconus is a devastating, sight-threatening, progressive, orphan disease. It is a naturally-occurring bilateral asymmetric corneal ectatic disorder, resulting from progressive weakening and thinning of the cornea. The organization of the lamellae (bundles of collagen fibers) that make up the corneal stroma is critical for maintaining corneal shape and optical clarity. Microstructural studies have revealed that this precise arrangement is absent in the apical area of the corneal stroma of corneas affected by keratoconus (Meek 2005). In keratoconus, the fibers are more loosely associated, and as the fibers slip apart in a phenomenon known as "creep", the region thins and bulges forward, resulting in the keratoconic "cone," a region of topographic steepening which manifests in irregular astigmatism, increase in higher order aberrations, and consequent decrease in visual function (Meek 2008).

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study (Wagner 2007) is a long term observational study to evaluate the characteristics of keratoconus. The study was

conducted with the support of the National Eye Institute, the National Institutes of Health (NIH) and The Research to Prevent Blindness Foundation. The study enrolled 1,209 keratoconus patients regardless of severity and followed them for 8 years. The study results demonstrated that deterioration was found throughout most of the lifespan of patients, documented by a clear increase in corneal curvature as measured by keratometry (24% of the patients degraded by 3D or more).

The first functional symptom of keratoconus is often blurred vision, which worsens over time (Figure 4). In addition, the patient may be sensitive to light and experience glare and halo, especially at night. As the condition progresses, ghosting of images and blurring and streaking of light worsen. Headaches, as well as difficulty driving and performing other routine functions may develop. In addition to irregular astigmatism and optical higher order aberrations, visually significant stromal scarring may also be present. In the advanced stages of the disease, the cornea may appear visibly cone-shaped (Figure 5).

Figure 4: Vision with Keratoconus

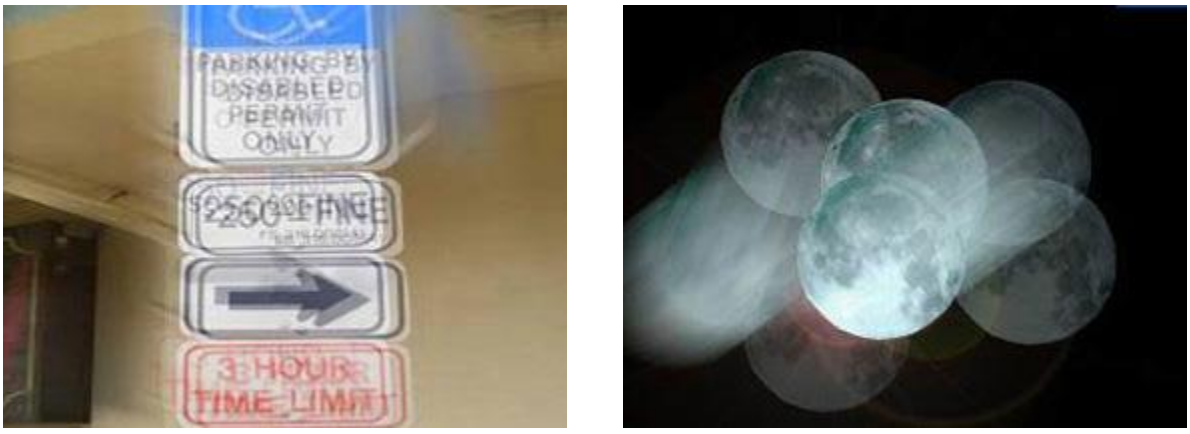
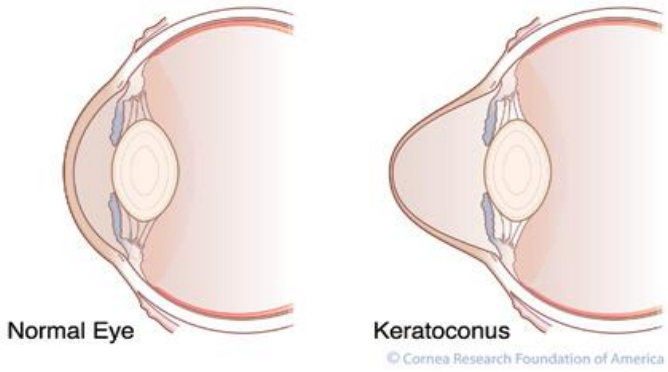


Figure 5: Normal Eye vs. Keratoconus Eye



Keratoconus has a significant impact on quality of life. It is a disease of the young and typically healthy (Wagner 2007), with average onset at just 15 years of age (Olivares 1997). With no FDA approved therapy to treat the underlying pathology and halt or slow the progression of this disorder, patients at the prime of their lives may suffer a debilitating progressive loss of visual function and the potential for eventual corneal transplantation (Rabinowitz 1998). These patients are at a stage in life where the diagnosis of keratoconus may interfere with their ability to complete their education. The result is a significant reduction in quality of life and the devastating knowledge that visual function will continue to decline over the next two decades or longer (Kymes 2004). These effects can have life-long impact. Those with keratoconus have increased prevalence of anxiety disorders, poor mental health, difficulty performing social duties and high dependency (Kymes 2004). Data from the CLEK study documents the devastating impact that keratoconus has on the quality of life of patients (Wagner 2007).

Corneal ectasia is a well-described but rare complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy (PRK). It is an orphan condition similar in symptoms to keratoconus, but occurs postoperatively rather than naturally. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in deterioration of visual function (Binder 2007; Leccisotti 2007).

2.1. Current Standards of Care are Limited

For both keratoconus and corneal ectasia, intervention usually begins with the use of spectacle correction. As corneal protrusion and irregular astigmatism progress, spectacles can no longer adequately correct vision, and the use of rigid, scleral, or hybrid contact lenses is needed to mask the optical irregularity of the cornea and to improve vision. Surgically-implanted intrastromal ring segments (Intacs) are used to improve contact lens wear in patients who are contact lens intolerant. While these provide some symptomatic relief, none of these options treat the underlying disease. When adequate visual function can no longer be achieved with rigid or specialty contact lenses due to corneal scarring or advanced disease state, corneal transplantation is required (Rabinowitz 1998).

The early onset of keratoconus is significant due to the potential for ultimate graft failure and need for secondary transplant. 73% of grafts fail within 20 years (Borderie 2009) and successive grafts are significantly more likely to fail (Inoue 2001). For a keratoconus patient diagnosed at 15 years of age, that means that multiple corneal transplants may be required over their lifetime. In addition, even after transplant, specialty contact lenses are often needed for visual rehabilitation.

In 2012, keratoconus and corneal ectasia were ranked leading indications for corneal transplants. In addition, keratoconus was the leading indication for anterior lamellar keratoplasty, another form of corneal transplant, in 2012 (43.4%) (Eye Bank Association of America Statistical Report, 2012).

Post-keratoplasty astigmatism is the most common complication after corneal transplantation for keratoconus, with many patients unable to tolerate spectacles due to high refractive errors and visual distortion (Mohammadpour 2007). Visual rehabilitation after penetrating keratoplasty is a

long and difficult process. The mean time period to first fitting of rigid gas permeable lens is 8 to 18.2 months (Wietharn 2004; Geerards 2006). Frequent office visits are required to monitor changing corneal curvature and lens fit as corneal sutures are removed over time.

2.2. Unmet Medical Need in the United States

The currently available disease management options in the US for progressive keratoconus and corneal ectasia do not address the underlying problem of compromised corneal biomechanical integrity or prevent or slow the progression of the disease. They offer temporary visual rehabilitation in the form of rigid contact lenses and intracorneal ring segments. When these no longer provide any relief from symptoms, corneal transplantation is the only other option. For a keratoconus patient diagnosed at 15 years of age, that means that multiple corneal transplants may be required over their lifetime. By slowing or halting corneal degeneration in the early stages of the disease, patients have the potential to retain sufficient visual function to lead normal lives, avoid the risks associated with corneal transplantation, and minimize the public health impact and financial burden of the disease (Labiris 2012).

CXL is approved for use in over 60 countries around the world and is a standard of care for keratoconus and corneal ectasia OUS. In the absence of an FDA approved therapy, CXL is occurring in the US outside of the proper regulatory channels. The procedure is being performed with devices that are not approved for cross-linking and compounded drug product that is not manufactured according to Good Manufacturing Practices (cGMP's).

There currently is no Food and Drug Administration (FDA)-approved medical therapy available in the United States (US) for treating the underlying pathology of progressive keratoconus or corneal ectasia following refractive surgery. Therefore, a significant treatment gap exists between the currently available options and corneal transplantation. This treatment gap is profound for patients diagnosed early in their lives who face the possibility of multiple corneal transplants throughout their lifetime. Corneal Collagen Cross-linking with riboflavin ophthalmic solution/KXL system (CXL) presents patients a much needed therapeutic treatment option and bridges this gap.

3. CORNEAL COLLAGEN CROSS-LINKING

3.1. History

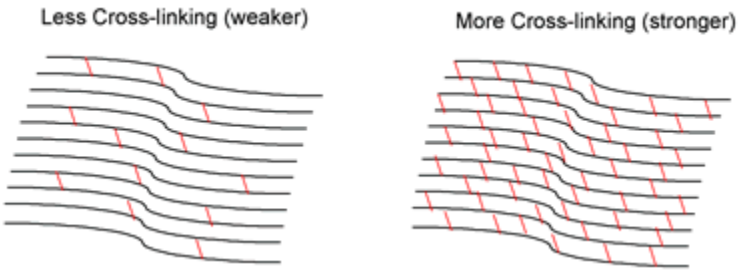
The bases for the currently employed corneal collagen cross-linking techniques were developed in Europe by researchers at the University of Dresden in the late 1990's and are known as the Dresden protocol. UV light was used to induce collagen cross-linking in riboflavin soaked porcine and rabbit corneas. The resultant corneas were shown to be stiffer and more resistant to enzymatic digestion. Investigation also proved that the treated corneas contained higher molecular weight polymers of collagen due to fibril crosslinking (Spoerl 2004).

CXL using UVA light with riboflavin has been performed internationally for over a decade with over 500 peer reviewed publications evaluating the procedure. The abundance of data in the public literature demonstrates that cross-linking with riboflavin and UV light stops disease progression, improves corneal curvature on average, and preserves visual acuity in most patients, with actual improvement in a number of individuals. Persistence of effect is seen with three-year data demonstrating the sustained effect of cross-linking in the treated group and the continued progression of disease in the control group (Wollensak 2003a, Wollensak 2006, Hafezi 2007, Wittig-Silva 2008, Raiskup-Wolf 2008, Agrawal 2009, Caporossi 2010, Asri 2011, Henriquez 2011, Hersh 2011, Koller 2011, Vinciguerra 2011, O'Brart 2011, Goldich 2012, Li 2012). Further, CXL is reported to be safe and associated with few serious complications in the literature (Kolli 2010, Chan 2013, Meek 2013, Wittig-Silva 2014).

3.2. Description of the Procedure

Cross-linking of collagen in the cornea refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. In the cornea, UVA light administered in combination with riboflavin photosensitizer increases the number of corneal collagen cross-links resulting in a shortening and thickening of the collagen fibrils and stiffening of the cornea. In the cross-linking procedure, the corneal epithelium is removed followed by riboflavin administration topically to the eye. After riboflavin saturation into the corneal stroma, exposure to UVA light induces cross-linking: The photochemical reaction is between UVA light and Riboflavin. Riboflavin and reactive oxygen species interact with corneal proteins to create chemical bonds within or between collagen fibrils, thus termed "cross-links". Figure 6 show the parallel corneal layers (white) and the collagen cross-linking (red) which are increased after Corneal Cross-Linking treatment.

Figure 6: Corneal Layers and Collagen Cross-linking



The cross-linking process increases the tensile strength and diameter of the collagen fibrils, prevents further weakening of the cornea, and stiffens and stabilizes the corneal architecture to diminish the progression of corneal ectatic disorders (Wollensak 2003b, Wollensak 2009).

3.2.1. Epithelial Healing and Corneal Remodeling

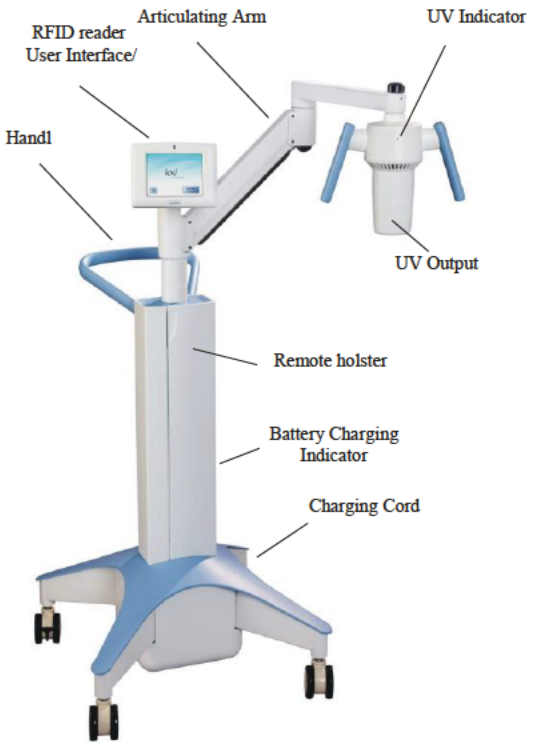
Due to debridement of the epithelium prior to administration of riboflavin drops, there is an expected healing process associated with the cross-linking procedure. Additionally, there is an expected timeframe for corneal remodeling following cross-linking. Confocal studies after cross-linking provide information regarding the mechanism and timeframe for the healing and remodeling processes. The structural and morphological changes that occur after cross-linking can explain correlations between the morphological events and functional data, such as transient effects on visual acuity and keratometry (Mazzotta 2010). It is expected that the re-epithelialization process could take up to one month with corneal remodeling taking up to three months. (Mazzotta 2008 & 2010).

4. DESCRIPTION OF DRUG-DEVICE COMBINATION PRODUCT

Avedro's riboflavin ophthalmic solutions are sterile, phosphate buffered saline solutions containing 0.12% riboflavin (Vitamin B2) in either 20% dextran or 0% dextran and act as a photosensitizer. Riboflavin, a water soluble vitamin, is an essential nutrient and a natural component of many foods. Avedro's riboflavin solutions are manufactured under GMP conditions at Ajinomoto Althea, a registered GMP commercial drug manufacturing facility in the United States.

Avedro's KXL® System is a UVA irradiation system that uses a light emitting diode (LED) to deliver a dose of UVA light to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking (Figure 7). Avedro's KXL UVA light device is manufactured according to FDA's Quality System Regulations at Avedro in Waltham, MA. Avedro's KXL System delivers a spectral output of 365 $\pm$ 10 nm with an illumination intensity of 3.0 mW/cm^2 and a treatment time of 30 minutes.

Figure 7: Overview Illustration of the KXL System



4.1. Regulatory History

Avedro's NDA 203-324 for riboflavin ophthalmic solution/KXL System is based on the results from three Phase III clinical trials (UVX-001, UVX-002, and UVX-003). Study UVX-001 was conducted under the Investigational New Drug (IND) application 78,933, an investigator initiated study submitted by R. Doyle Stulting, M.D., Ph.D., Emory University, Atlanta, GA. All rights to the data generated in UVX-001 were transferred to Avedro in a licensing agreement dated 10 September 2010. Studies UVX-002 and UVX-003 were multi-center studies conducted in the United States under IND 77,882. These studies were conducted by the original sponsor of IND 77,882, Peschke Meditrade GmbH. Sponsorship of IND 77,882 was transferred to Avedro on 07 May 2010 after all patients were enrolled and treated.

In 2011, Avedro received orphan drug designation for both keratoconus and corneal ectasia following refractive surgery. The inclusion of both indications in the clinical program was discussed with FDA at onset of clinical studies.

On 16 September 2013, Avedro submitted NDA 203324 for riboflavin ophthalmic solution/KXL System. The proposed indications are for the treatment of progressive keratoconus or corneal ectasia following refractive surgery. The NDA was filed as a 505(b)(2) application because the non-clinical safety of riboflavin ophthalmic solution/ UVA light was established based upon data from studies in the published literature on the safety of riboflavin/UVA and its ophthalmic use in corneal collagen cross-linking.

The UV-X Illumination System was utilized as the UV light source during the Phase III clinical studies reported in the NDA. Both the UV-X clinical system and the KXL commercial system are LED based illumination systems that deliver an equivalent spectral output of 365 $\pm$ 10 nm with an illumination intensity of 3.0 mW/cm^2 and a treatment time of 30 minutes. The differences between the two systems do not impact the UV light delivered (see Appendix 3). Avedro's KXL device underwent extensive testing to establish equivalency to the UVX device utilized in the clinical studies and to ensure it met relevant consensus standards including IEC 60601-1, IEC 60601-1-2, IEC 60601-1-4, IEC 60601-1-6, and IEC 60825-1. The equivalency testing was discussed with FDA prior to NDA submission. Therefore, the data collected with the UV-X Illumination System supports approval of the KXL® System.

On 14 March 2014, Avedro received a Complete Response Letter from FDA. On 6 August 2014, Avedro and FDA met to discuss the letter and subsequent resubmission. On 29 September 2014, Avedro resubmitted NDA 203-324. On 6 November 2014, Avedro received a letter from FDA stating that our submission was "a complete, Class 2 response to our 14 March 2014 action letter" (Appendix 4). The user fee goal date for the NDA is 29 March 2015.

4.2. Proposed Indications

The proposed indications[1] for use are:

Corneal collagen cross-linking with Photrexa™ Viscous (riboflavin ophthalmic solution) 20% dextran, Photrexa™ (riboflavin ophthalmic solution)/KXL™ System is indicated for the treatment of progressive keratoconus or corneal ectasia following refractive surgery.

[1] Please note that Avedro submitted the trade names Photrexa and Photrexa Viscous for FDA review. These trade names are currently under FDA review and subject to change.

5. PHASE III STUDY DESIGN

The clinical development program for corneal collagen cross-linking in the treatment of progressive keratoconus and corneal ectasia following refractive surgery included three Phase III clinical trials (UVX-001, UVX-002, and UVX-003).

Each study was a prospective, randomized, parallel-group, open-label, controlled, 12-month trial to determine the safety and effectiveness of a single application of riboflavin ophthalmic solution/UVA irradiation for performing corneal cross-linking (CXL) in the eyes of subjects with progressive keratoconus or post-refractive corneal ectasia.

UVX-001 was a single-center investigator-sponsored study conducted by R. Doyle Stulting, M.D., Ph.D. located at Emory Vision in Atlanta, GA. This study enrolled both corneal ectasia subjects and progressive keratoconus subjects. Studies UVX-002 and UVX-003 were multi-center studies each involving the 10 sites listed in Table 1. UVX-002 enrolled only progressive keratcoconus subjects and UVX-003 enrolled only post-refractive corneal ectasia subjects. All sites in the 3 studies were located in the US.

Table 1: Principal Investigators in UVX-002 and UVX-003

Site No.	Principal Investigator	Location of Site	# of Subjects
01[a]	Perry S. Binder, M.D.	Gordon, Binder & Weiss Vision Institute San Diego, CA	UVX-002: 7 UVX-003: 4
02	Eric D. Donnenfeld, M.D.	Ophthalmic Consultants of Long Island Rockville Centre, NY	UVX-002: 11 UVX-003: 19
03	Peter Hersh, M.D.	Cornea and Laser Eye Institute Teaneck, NJ	UVX-002: 54 UVX-003: 30
04	Francis Price, Jr. M.D.	Price Vision Group and Cornea Indianapolis, IN	UVX-002: 26 UVX-003: 21
05	David Schanzlin, M.D.	University of California, San Diego Shiley Eye Center, La Jolla, CA	UVX-002: 7 UVX-003: 4
07	Steven Trokel, M.D.	Columbia University Edward S. Harkness Eye Institute New York City, NY	UVX-002: 4 UVX-003: 5
08	Daniel Durrie, M.D.	Durrie Vision Overland Park, KS	UVX-002: 16 UVX-003: 6
09	William Trattler, M.D.	Center for Excellence in Eye Care Miami, FL	UVX-002: 1 UVX-003: 19
10	David Hardten, M.D., FACS	Minnesota Eye Consultants, P.A. Minneapolis, MN	UVX-002: 16 UVX-003: 15
11	Walter Stark, M.D.	Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD	UVX-002: 5 UVX-003: 7

[a] All outstanding study visits for subjects enrolled by Dr. Perry Binder at site 01 in Studies UVX-002 and UVX-003 were conducted by Dr. David Schanzlin at site 05 following Dr. Binder's retirement on December 9, 2008.

NOTE: For Study UVX-001, the Investigator left the study site prior to study completion and the study was terminated by the study sponsor; as a result several subjects (13 corneal ectasia subjects and 26 keratoconus subjects) at this site were administratively withdrawn from the study prior to completing their participation in the study.

The planned sample size for UVX-001 was 160 eyes (80 per treatment group) with progressive keratoconus and 160 eyes (80 per treatment group) with corneal ectasia. For studies UVX-002 and UVX-003, the planned sample sizes were 160 eyes each (80 per treatment group) with progressive keratoconus and corneal ectasia, respectively. Eligible subjects had one eye randomized into 1 of 2 treatment groups: the CXL group and the control group (one eye per subject became the randomized study eye with the other eye as the fellow eye). Subjects were evaluated at 8 study visits: screening/baseline, Day 0 (randomization/treatment day), and 1 day, 1 week, and 1, 3, 6, and 12 months after treatment (Table 2).

As the initial timing of the primary efficacy endpoint was Month 3, at that time or later, subjects whose eye(s) were eligible for the CXL treatment were given the option of having CXL performed on their randomized control eyes. Additionally, at Month 3 or later, all subjects (from both CXL and control groups) were given the option of having CXL performed on their non-randomized fellow eyes if the fellow eye did not have any contraindications for performing the CXL treatment. After treatment, these eyes were followed for 12 months according to the same schedule and protocol as the study eye in the CXL group (Figure 8).

Figure 8: Study Schematic

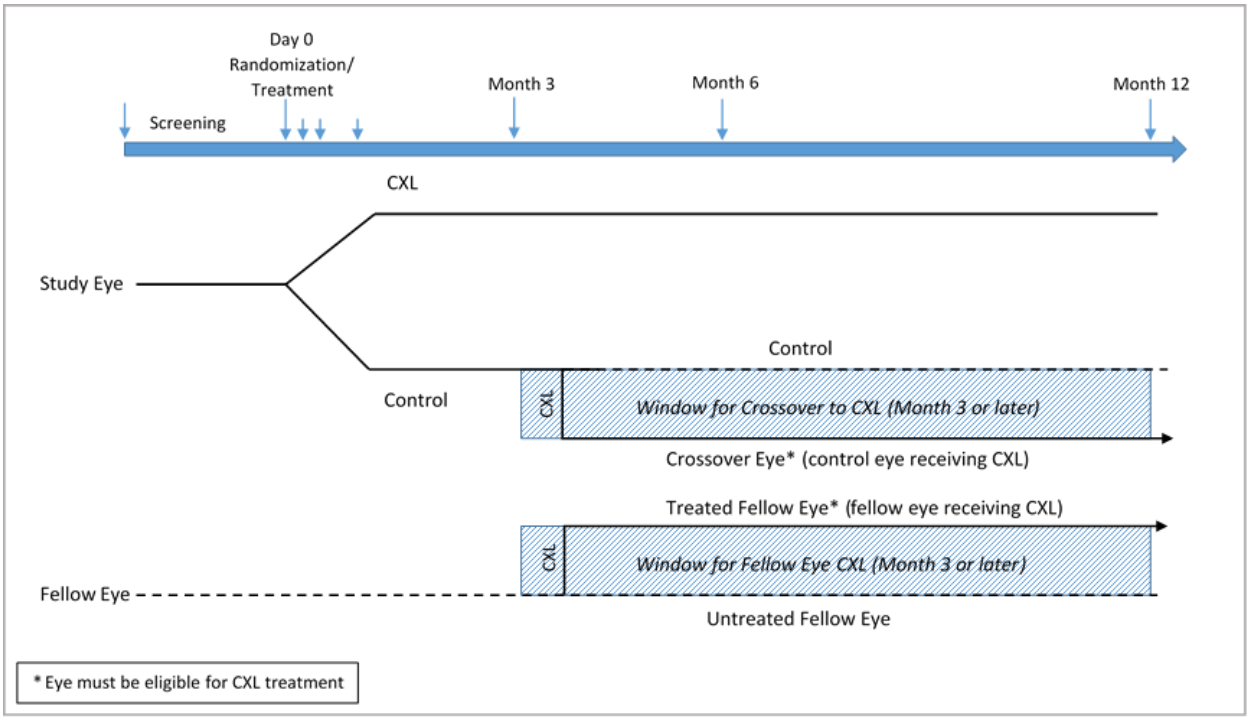


Table 2: Schedule of Visits and Procedures

Procedure	Screen	Treatment Visit[a]	Post-Treatment Visits 1 Day	1 Week	1 Month	3 Months	6 Months	12 Months
Medical History	X	X	X	X	X	X	X	X
Ocular History[b]	X	X	X	X	X	X	X	X
Medication History	X	X	X	X	X	X	X	X
Demographics	X							
BSCVA[c]	X			X	X	X	X	X
UCVA[d]	X		X	X	X	X	X	X
Manifest Refraction	X	X		X	X	X	X	X
Confocal microscopy	X							X
Intraocular Pressure Measurement	X			X	X	X	X	X
Slit Lamp Exam[e]	X		X	X	X	X	X	X
Endothelial cell count	X					X		X
Dilated Fundus Examination	X							X
Pentacam Pachymetry, Keratometry	X				X	X	X	X
Corneal Topography	X				X	X	X	X
Manual keratometry	X				X	X	X	X
OPD scan	X				X	X	X	X
RSVP Questionnaire	X				X	X	X	X
Subjective Complaint Questionnaire	X				X	X	X	X
Sign Consent	X							
Complications		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
CXL or Control Treatment		X						
Ultrasound Pachymetry[f]		X						

[a] Repeat measurements from the screening exam prior to study treatment were allowed if needed to provide accurate baseline measurements before CXL or control treatment.

[b] Ocular history included history of contact lens wear, risk factors for keratoconus or corneal ectasia, and history of refractive surgery. Non-specific questioning was used at each visit to determine other vision-related complaints, complications, or adverse events.

[c] Distance BSCVA was performed using an ETDRS eye chart; the total number of letters that were seen was recorded.

[d] UCVA was performed using an ETDRS eye chart; the total number of letters that were seen was recorded.

[e] The slit lamp exam included a complete survey of the anterior segment. The cornea was examined in detail with specific recordings and gradings (0 to 4+ scale, 0=clear) of the following information: overall corneal clarity and any abnormalities such as corneal infiltrates.

[f] Ultrasound pachymetry was performed at the end of riboflavin dosing (both formulations) and, at the investigator's discretion, could have been repeated at other times during the CXL or control treatment.

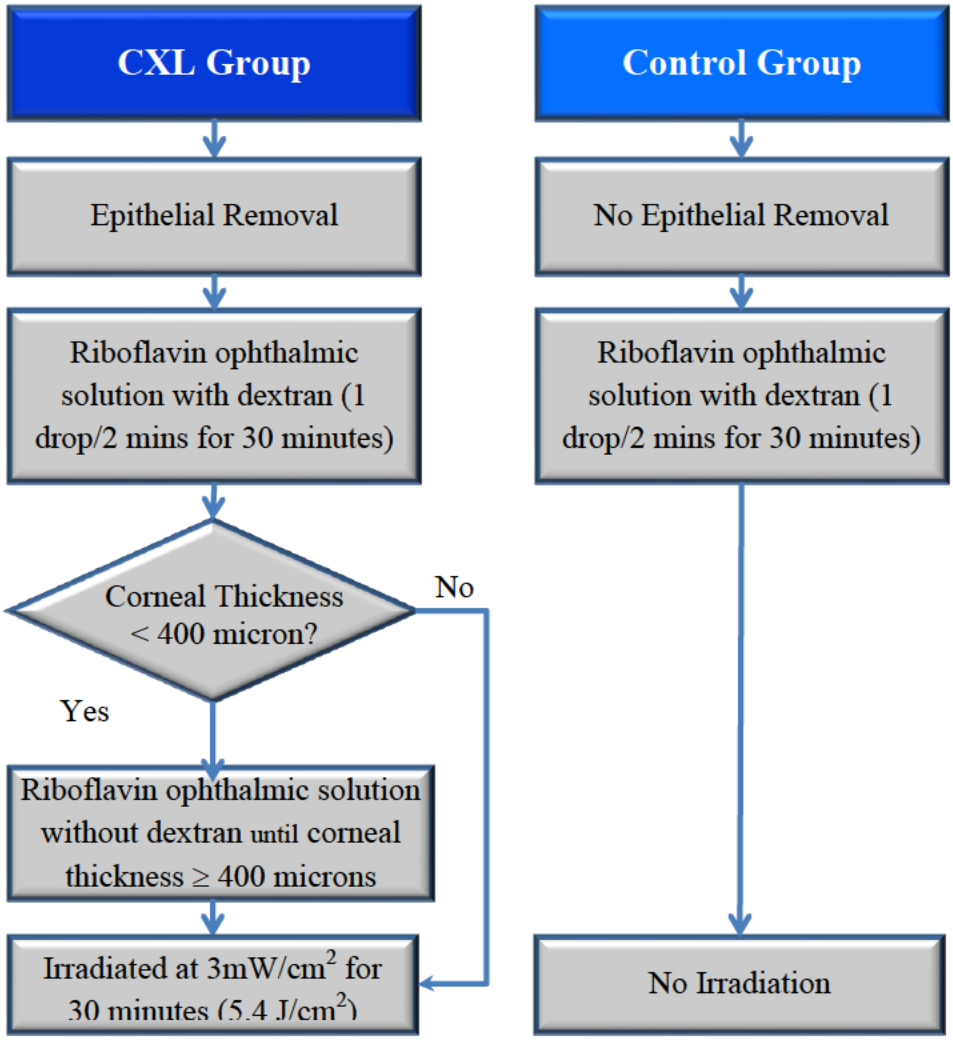
5.1.1. Study Treatments

Corneal collagen cross-linking treatment for all three studies was based upon the Dresden protocol.

On Day 0, subjects randomized to the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed. Subjects then received riboflavin ophthalmic solution with dextran in the study eye for 30 minutes (1 drop instilled onto the cornea every 2 minutes, with additional drops as needed to achieve adequate riboflavin saturation). As the Dresden protocol called for the cornea to be at least 400 microns prior to cross-linking, if corneal thickness was < 400 microns in eyes in the CXL group after treatment with riboflavin ophthalmic solution with dextran, a second solution, riboflavin without dextran was instilled into the study eye (2 drops instilled every 5 to 10 seconds until corneal thickness increased to at least 400 microns). After the riboflavin pretreatment regimen was completed, study eyes in the CXL group were exposed to UVA light (365 nm at an irradiance of 3 mW/cm^2) for 30 minutes, with riboflavin ophthalmic solution with dextran continuing to be administered every 2 minutes during this time.

Subjects randomized to the control group had topical anesthetic administered to the study eye on Day 0 but did not have the corneal epithelium removed. Control study eyes were treated with riboflavin ophthalmic solution as described above (both pretreatment and during the simulated irradiation procedure). However, the cornea was not debrided and the UVA light source was not illuminated during the procedure (Figure 9).

Figure 9: Study Treatments



5.1.2. Patient Population

The inclusion/exclusion criteria used in the completed studies were appropriate to evaluate the efficacy and safety of CXL in the intended target populations (i.e., subjects with progressive keratoconus or corneal ectasia following refractive surgery). In the UVX studies, subjects had to be ≥ 14 years of age and diagnosed with corneal ectasia after refractive surgery (e.g., laser-assisted in-situ keratomileusis [LASIK], photorefractive keratectomy [PRK], or epi-LASIK) or progressive keratoconus and meet all of the inclusion criteria to be eligible for this study. Keratoconus subjects had to demonstrate a history of progression and be diagnosed with progressive keratoconus to be eligible for the study. Progressive keratoconus was defined as demonstrating 1 or more of the following changes over a period of 24 months or less before randomization:

- An increase of ≥ 1.00 diopter (D) in the steepest keratometry value (or simulated keratometry [simK])

- An increase of ≥ 1.00 D in regular astigmatism evaluated by subjective manifest refraction
- A myopic shift (decrease in the spherical equivalent) of ≥ 0.50 D on subjective manifest refraction
- A decrease ≥ 0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.

Subjects had to have axial topography consistent with progressive keratoconus or corneal ectasia and a BSCVA worse than 20/20 (<53 letters [UVX-001 and UVX-002] or <55 letters [UVX-003] on Early Treatment of Diabetic Retinopathy Study chart [EDTRS]). Subjects also had to have adequate corneal thickness to avoid possible endothelial cell damage (≥ 400 microns at the thinnest point when riboflavin with dextran was used alone or ≥ 300 microns when riboflavin without dextran was used).

Subjects were excluded if they had Intacs corneal inserts in the eye to be treated (progressive keratoconus subjects); history of chemical injury in the eye to be treated; or history of corneal disease in the eye to be treated (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc).

The intent-to-treat (ITT) population consisted of all treated subjects, analyzed according to randomized treatment. The Safety population consisted of all treated subjects, analyzed according to the treatment actually received. All efficacy analyses were conducted using the ITT population (unless otherwise indicated); all safety analyses were conducted using the Safety population.

5.1.3. Primary Efficacy Endpoint

For each study, the primary efficacy endpoint was corneal curvature, as measured by K_{max}. K_{max} was evaluated at baseline and at Months 1, 3, 6, and 12. Study success was defined as a difference of ≥1 D in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group.

Progressive keratoconus and corneal ectasia following refractive surgery are typified by steepening and irregularity of the cornea. Steepness of the cornea can be quantitatively measured using corneal topography instrumentation. Maximum corneal curvature, as measured by maximum keratometry (K_{max}), quantifies the most pathognomonic feature of progressive keratoconus and corneal ectasia. Based on the etiology and manifestation of ectatic corneal disorders, K_{max} is accepted as a clinically meaningful and reproducible endpoint to be measured in these patient populations, (Kolli 2010). As previously discussed, for patients suffering from progressive keratoconus, stopping or slowing progression of disease is not only clinically meaningful but also life changing.

5.1.3.1. Change to the timing of assessment of the primary efficacy endpoint

The initial decision to analyze the primary endpoint at 3 months was made by the original IND Sponsor in 2006 (Peschke Meditrade). Over the years, there have been significant advancements in the science of cross-linking. As more has been learned about the natural history of healing after epithelial debridement and corneal remodeling following cross-linking, it has become

evident that evaluating effectiveness at the 3 month time period is not clinically appropriate. A 3 month timeframe for analysis of cross-linking is too short of a time to evaluate the benefit of this procedure. The benefit of the corneal cross-linking procedure is best measured at later time-points when the epithelial healing and corneal remodeling processes have been completed. (Caporossi 2010, Wittig Silva 2014, Mazzotta 2008 and 2010).

After acquiring the studies from the previous sponsor in 2010, Avedro changed the timing of the primary efficacy analysis from 3 months to 12 months. Avedro selected 12 months as that was the last time point studied and, therefore, would provide the longest-term data on patients treated with the cross-linking procedure. All patients had been treated at the time Avedro acquired the studies, therefore, the change had no impact on study conduct. Additionally, Kmax measured by corneal topography is an objective measurement and, therefore, the change in timing of analysis did not impact this measurement.

The measurement and magnitude of success for the primary endpoint continued to be a ≥1 D difference in the mean change in K_{max} between the CXL group and the control group.

In keratoconus and corneal ectasia patients, stabilizing the cornea and stopping progression is clinically meaningful and an important factor in measuring the studies' success. For patients suffering from these devastating conditions and facing the likelihood of corneal transplantation, halting progression at 12 months is not only clinically meaningful but also life changing.

5.1.4. Statistical Analysis of the Primary Endpoint

As the study design allowed subjects randomized to the control group to cross over to receive the CXL treatment after Month 3, last observation carried forward (LOCF) was used in order to allow comparisons between the CXL and control groups at the later time points. The primary efficacy analysis used LOCF method for imputing missing data for the control subjects who crossed over and received subsequent CXL in the study eye and for missing data in CXL subjects. The LOCF approach is valid for imputation of study data because keratoconus and post-refractive ectasia are progressive corneal ectatic conditions. Keratoconus and corneal ectasia patients do not experience spontaneous remission or become free of disease, rather a majority continue to progress and become worse as shown in the published literature. The studies in the published literature coupled with Avedro's observed clinical data provide confirmation of progression in these patient populations and support the validity of the use of LOCF method to impute missing data. The LOCF approach does not account for any continued progression of disease in the control group, making it more difficult to demonstrate differences in mean change from baseline K_{max} with CXL.

As a result, the LOCF approach provides a conservative measure of success of the cross-linking procedure.

In addition to analyses based on LOCF, a series of additional sensitivity analyses with observed data were conducted to explore the bounds of the treatment effect at 1 year based on a variety of different assumptions which included mixed-effects regression models based on linear, log-linear, and nonparametric time trends.

The change in K_{max} from baseline was evaluated for all eyes randomized to the CXL and control groups. Data were summarized using descriptive statistics, and the differences in mean changes

between the CXL group and the control group at each time point were evaluated using a 2-sample t-test.

Further, categorical changes from baseline K_{max} were evaluated in randomized CXL eyes to evaluate the distribution of K_{max} values. Data were tabulated as the proportion of subjects within each category. The change in K_{max} from baseline was evaluated for all eyes randomized to the CXL and control groups. Data were summarized using descriptive statistics, and the differences in mean changes between the CXL group and the control group at each time point were evaluated using a 2-sample t-test.

No formal interim analyses were conducted. However, an informal interim analysis of data was conducted in March 2009 by the original IND Sponsor (Peschke Meditrade). Also, Dr. Peter Hersh conducted an informal review of data from patients treated at his site and only those findings were published (Hersh 2011).

Based upon the informal analysis described above, the overall alpha-level for analysis of the primary efficacy endpoint was 0.049.

5.1.5. Secondary and Other Endpoints

Secondary efficacy endpoints included analysis of the mean change in K_{max} from baseline to Months 1, 3, 6, and 12 for all CXL treated eyes (study eyes randomized to CXL group, study eyes randomized to control group and subsequently receiving CXL treatment [crossover eyes], and non-study fellow eyes receiving CXL treatment). The categorical distribution of K_{max} values was evaluated, including the proportion of subjects who experienced a ≥1 D decrease from baseline in K_{max}. Mean change from baseline K_{max} was evaluated for subjects who only received riboflavin with dextran and subjects who did not achieve a corneal thickness < 400 microns after treatment with riboflavin with dextran and subsequently received riboflavin without dextran. Mean changes from baseline in BSCVA and UCVA and categorical changes from baseline in BSCVA were evaluated by treatment group.

5.1.6. Safety Endpoints

For all AEs, the number of distinct treatment emergent events (TEAE) and the number and percent of subjects who experienced the event were summarized by treatment group and categorized by system organ class (SOC) and preferred term (PT) for the Safety population.

Changes from baseline in BSCVA and UCVA (using logMar units) were evaluated at Months 1, 3, 6, and 12 for all eyes randomized to the CXL and control groups. Data were summarized using descriptive statistics, and differences in mean changes between treatment groups were evaluated using a 2-sample t-test. The proportions of subjects with categorical gains and losses in BSCVA were also tabulated by treatment group and study visit for the Safety population.

Changes from baseline in endothelial cell counts were evaluated at Months 1, 3, 6, and 12 for the Safety population. (Note: Months 1 and 6 were not planned visits for endothelial cell count determinations; therefore, the number of subjects with evaluations at these time points was small). Data were summarized using descriptive statistics; differences between treatment groups for mean changes from baseline were analyzed using a 2-sample t-test.

6. PHASE III STUDY RESULTS

6.1. Subject Disposition

Subjects who were diagnosed with corneal ectasia after refractive surgery or progressive keratoconus and met all of the inclusion criteria were considered eligible for these studies. Keratoconus subjects had to demonstrate a history of progression over a 24 month period and be diagnosed with progressive keratoconus to be eligible for the study.

For Study UVX-002 (all subjects) and Study UVX-001 (keratoconus subjects only), a total of 205 progressive keratoconus subjects were randomized. Of the 205 subjects, 102 subjects were randomized to the CXL group, and 103 subjects were randomized to the control group (Table 3). Most subjects (78%) completed the study, and 46 subjects (22%) discontinued. Reasons for discontinuation were administrative reasons (13%), voluntarily withdrawal (5%), and loss to follow-up (4%). All of the subjects who discontinued based on "administrative/other" reasons were due to the early termination of Study UVX-001 by the investigator-sponsor. None of the subjects discontinued due to an adverse event.

Table 3: Keratoconus Subject Disposition

	UVX-001*		UVX-002		Pooled Studies	
Category	**CXL Group (N=29)**	**Control Group (N=29)**	**CXL Group (N=73)**	**Control Group (N=74)**	**CXL Group (N=102)**	**Control Group (N=103)**
Received Randomized Treatment (n)	29	29	73	74	102	103
Completed: n (%)	20 (69.0)	12 (41.4)	65 (89.0)	62 (83.8)	85 (83.3)	74 (71.8)
Discontinued: n (%)	9 (31.0)	17 (58.6)	8 (11.0)	12 (16.2)	17 (16.7)	29 (28.2)
Administrative/other[a]	9 (31.0)	17 (58.6)	0	0	9 (8.8)	17 (16.5)
Voluntary Withdrawal (unrelated to safety)	0	0	3 (4.1)	8 (10.8)	3 (2.9)	8 (7.8)
Lost to Follow-up	0	0	5 (6.8)	4 (5.4)	5 (4.9)	4 (3.9)
Adverse Event	0	0	0	0	0	0

[a] In UVX-001, all cases of "administrative" discontinuation were due to the investigator leaving the site and the study being terminated by the Sponsor.
* Progressive keratoconus subjects only

For Study UVX-003 (all subjects) and Study UVX-001 (corneal ectasia subjects only), a total of 179 corneal ectasia subjects were randomized. Of the 179 subjects, 91 subjects were randomized to the CXL group, and 88 subjects were randomized to the control group (Table 4). Most subjects (75%) completed the study, and 44 subjects (25%) discontinued. Reasons for discontinuation were "administrative/other" (9%), lost to follow-up (7%), voluntarily withdrawal (3%), and administrative reasons (1%). All of the subjects who discontinued based on "administrative/other" reasons were due to the early termination of Study UVX-001 by the investigator-sponsor.

None of the subjects discontinued due to an adverse event.

Table 4: Corneal Ectasia Subject Disposition

Category	UVX-001*		UVX-003		Pooled Studies	
	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=91)	Control Group (N=88)
Received Randomized Treatment (N)	24	25	67	63	91	88
Completed: n (%)	20 (83.3)	11 (44.0)	56 (83.6)	48 (76.2)	76 (83.5)	59 (67.0)
Discontinued: n (%)	4 (16.7)	14 (56.0)	11 (16.4)	15 (23.8)	15 (16.5)	29 (33.0)
Administrative/Other[a]	3 (12.5)	11 (44.0)	5 (7.5)	7 (11.1)	8 (8.8)	18 (20.4)
Lost to Follow-Up	1 (4.2)	3 (12.0)	6 (9.0)	3 (4.8)	7 (7.7)	6 (6.8)
Voluntary Withdrawal (unrelated to safety)	0	0	0	5 (7.9)	0	5 (5.7)
Adverse Event	0	0	0	0	0	0

[a] In UVX-001, all cases of "other" were due to the investigator leaving the site and the study being terminated by the Sponsor.
*Corneal ectasia subjects only

6.2. Subject Demographics

As depicted in Table 5 and Table 6, demographic characteristics were generally comparable between studies and between treatment groups within each study. In the pooled progressive keratoconus studies, mean age of the total study population was 33.0 years (range of 14 to 63 years). Most subjects were Caucasian (75.4%), and the majority were male (69.8%). Approximately 12% of subjects were Hispanic/Latino. In corneal ectasia subjects, mean age was 42.7 years (range of 22 to 63 years). Most subjects were Caucasian (79.3%), and the majority were male (68.2%). Approximately 20% of subjects were Hispanic/Latino.

Table 5: Demographics (ITT Population): Progressive Keratoconus Subjects

		UVX-001*		UVX-002		Pooled Studies	
Parameter	**Statistic**	**CXL Group (N=29)**	**Control Group (N=29)**	**CXL Group (N=73)**	**Control Group (N=74)**	**CXL Group (N=102)**	**Control Group (N=103)**
Age (yrs)	N	29	29	73	74	102	103
	Mean	33.3	36.9	30.2	34.2	31.1	35.0
	SD	7.59	12.53	10.08	11.52	9.51	11.82
	Median	33.9	37.5	29.0	31.9	29.7	33.8
	Min, Max	20, 50	16, 60	14, 57	15, 63	14, 57	15, 63
Gender	N	29	29	73	74	102	103
	Female - n (%)	8 (27.6)	11 (37.9)	19 (26.0)	24 (32.4)	27 (26.5)	35 (34.0)
	Male - n (%)	21 (72.4)	18 (62.1)	54 (74.0)	50 (67.6)	75 (73.5)	68 (66.0)
Ethnicity	N[a]	29	29	38	39	67	68
	Hispanic/Latino - n (%)	3 (10.3)	3 (10.3)	7 (18.4)	3 (7.7)	10 (14.9)	6 (8.8)
	Not Hispanic/Latino - n (%)	26 (89.7)	26 (89.7)	31 (81.6)	36 (92.3)	57 (85.1)	62 (91.2)
Race[b]	N[c]	29	29	71	74	100	103
	White - n (%)	19 (65.5)	19 (65.5)	54 (76.1)	61 (82.4)	73 (73.0)	80 (77.7)
	Black/African-American - n (%)	4 (13.8)	4 (13.8)	7 (9.9)	7 (9.5)	11 (11.0)	11 (10.7)
	Asian - n (%)	1 (3.4)	2 (6.9)	0	1 (1.4)	1 (1.0)	3 (2.9)
	Other Race[d] - n (%)	5 (17.2)	4 (13.8)	10 (14.1)	5 (6.8)	15 (15.0)	9 (8.7)

[a]Percentages are based on the number of subjects who reported ethnicity.
[b]As reported by the subject.
[c]Percentages are based on the number of subjects who reported race.
[d]In the pooled studies, race was reported as "other" for 10 Hispanics, 6 Indians, 2 Spanish, 1 Indian/South Asian, 1 Black/Asian, 1 Brazilian, 1 Latino, 1 Ethiopian, and 1 Moroccan.
*Progressive keratoconus subjects only

Table 6: Demographics (ITT Population): Corneal Ectasia Subjects

		UVX-001*		UVX-003		Pooled Studies	
Parameter	**Statistic**	**CXL Group (N=24)**	**Control Group (N=25)**	**CXL Group (N=67)**	**Control Group (N=63)**	**CXL Group (N=91)**	**Control Group (N=88)**
Age (yrs)	N	24	25	67	63	91	88
	Mean	45.0	40.0	43.0	42.5	43.5	41.8
	SD	8.95	7.67	8.72	9.08	8.78	8.73
	Median	42.7	38.6	44.2	41.4	43.6	39.7
	Min, Max	28, 63	24, 57	22, 60	24, 62	22, 63	24, 62
Gender	N	24	25	67	63	91	88
	Female - n (%)	10 (41.7)	8 (32.0)	23 (34.3)	16 (25.4)	33 (36.3)	24 (27.3)
	Male - n (%)	14 (58.3)	17 (68.0)	44 (65.7)	47 (74.6)	58 (63.7)	64 (72.7)
Ethnicity	N[a]	24	24	27	27	51	51
	Hispanic/Latino - n (%)	2 (8.3)	1 (4.2)	9 (33.3)	9 (33.3)	11 (21.6)	10 (19.6)
	Not Hispanic/Latino - n (%)	22 (91.7)	23 (95.8)	18 (66.7)	18 (66.7)	40 (78.4)	41 (80.4)
Race[b]	N[c]	24	25	63	57	87	82
	White - n (%)	18 (75.0)	21 (84.0)	50 (79.4)	45 (78.9)	68 (78.2)	66 (80.5)
	Black/African-American - n (%)	3 (12.5)	2 (8.0)	7 (11.1)	5 (8.8)	10 (11.5)	7 (8.5)
	Asian - n (%)	0	0	3 (4.8)	4 (7.0)	3 (3.4)	4 (4.9)
	Other Race[d] - n (%)	3 (12.5)	2 (8.0)	3 (4.8)	3 (5.3)	6 (6.9)	5 (6.1)

[a]Percentages are based on the number of subjects who reported ethnicity.
[b]As reported by the subject.
[c]Percentages are based on the number of subjects who reported race.
[d]In the pooled studies, race was reported as "other" for 6 Hispanics, 2 Middle Easterners; 1 Indian, 1 Latino, and 1 mixed.
*Corneal ectasia subjects only

6.3. Baseline Characteristics

The majority (69.2%) of progressive keratoconus subjects were classified as having mild disease (disease severity was not reported for corneal ectasia).

In the pooled progressive keratoconus population, at baseline, pre-treatment, the mean K_{max} was similar in the CXL (60.9 D) and control (60.4 D) groups (Table 8).

In the pooled corneal ectasia population, at baseline, pre-treatment, the mean K_{max} was similar in the CXL (55.4) and control (54.8 D) groups (Table 17).

Mean BSCVA at baseline was comparable between treatment groups in the pooled progressive keratoconus (33.2 letters, CXL; 32.8 letters, control) and corneal ectasia (37.0 letters, CXL; 38.1 letters, control) subjects (Table 14 and Table 23, respectively).

6.4. Time of Cross-over in the Control Group

Table 7 presents a tabulation of the number of keratoconus and ectasia subjects remaining in the study and the timing of crossover in the control group for the study eye.

In the pooled progressive keratoconus analysis, it is notable that at Month 12, 99% of subjects remaining in the study in the control group crossed-over to be treated.

In the pooled corneal ectasia analysis, it is notable that at Month 12, 97% of subjects remaining in the study in the control group crossed over to have the study eye treated with CXL.

Table 7: Timing of CXL Cross-over

Visit	CXL Group	Control Group	
	# of Subjects Remaining in the Study	# of Subjects Remaining in the Study	# of Subjects Remaining that Crossed-over
Progressive Keratoconus			
	N=102	**N=103**	
Month 1	102 (100%)	103 (100%)	0
Month 3	101 (99%)	101 (98%)	0
Month 6	100 (98%)	96 (93%)	57 (59%)
Month 12	90 (88%)	76 (74%)	75 (99%)
Corneal Ectasia			
	N=91	**N=88**	
Month 1	91(100%)	88 (100%)	0
Month 3	91 (100%)	87 (99%)	0
Month 6	88 (97%)	80 (91%)	48 (60%)
Month 12	76 (84%)	60 (68%)	58 (97%)

6.5. Efficacy in Progressive Keratoconus – Randomized Study Eye

6.5.1. Analysis Populations

In UVX-002, the ITT population consisted of all treated subjects, analyzed according to randomized treatment. In UVX-002, 2 subjects, 1 per treatment group, inadvertently received the incorrect randomized study treatment on Day 0. Therefore, the ITT population consisted of subjects as randomized and the Safety population consisted of all treated subjects, analyzed according to the treatment actually received. Most of the efficacy analyses were conducted using the ITT population. Since the K_{max} analyses of all CXL-treated eyes and non-study CXL-treated eyes involved crossover from control to CXL treatment, these analyses were conducted using the Safety (as treated) population (see Section 6.8). Exposure results were also summarized using the Safety population.

In the pooled keratoconus studies, the ITT population consisted of 205 randomized eyes (102, CXL group; 103, control group).

6.5.2. Primary Endpoint - Mean Change from Baseline K_{max} in the Randomized Eye

6.5.2.1. Primary Analysis – LOCF Analysis

Table 8 presents mean changes from baseline K_{max} (LOCF) in randomized study eyes over time. The efficacy data were analyzed 3 ways: (1) the UVX-001 progressive keratoconus data alone 2) the UVX-002 data alone and 3) the UVX-001 progressive keratoconus data pooled with the UVX-002 data. In progressive keratoconus patients, all three analyses met the primary endpoint of ≥1D difference in mean change in baseline Kmax between the cross-linked group and the control group at month 12.

UVX-001 (Progressive Keratoconus Subjects)

The difference between the CXL and control groups in mean change from baseline in K_{max} progressively improved, in favor of CXL, from Month 3 through Month 12. The CXL group improved over control at Month 3 (0.4 D) but not enough to meet the ≥ 1.0 D threshold specified and exceeded 1.0 D, meeting the endpoint at Month 6 (1.4 D) and Month 12 (1.9 D). The difference between treatment groups in mean change from baseline K_{max} was statistically significant at Month 12 (p=0.0175).

UVX-002

The difference between the CXL and control groups in mean change from baseline K_{max} progressively improved, in favor of CXL, from Month 3 through Month 12. The difference between treatment groups exceeded the endpoint of 1.0 D at Month 3 (1.3 D), Month 6 (2.3 D), and Month 12 (2.9 D). The difference between treatment groups in mean change from baseline K_{max} was statistically significant at Month 12 (p=0.0010).

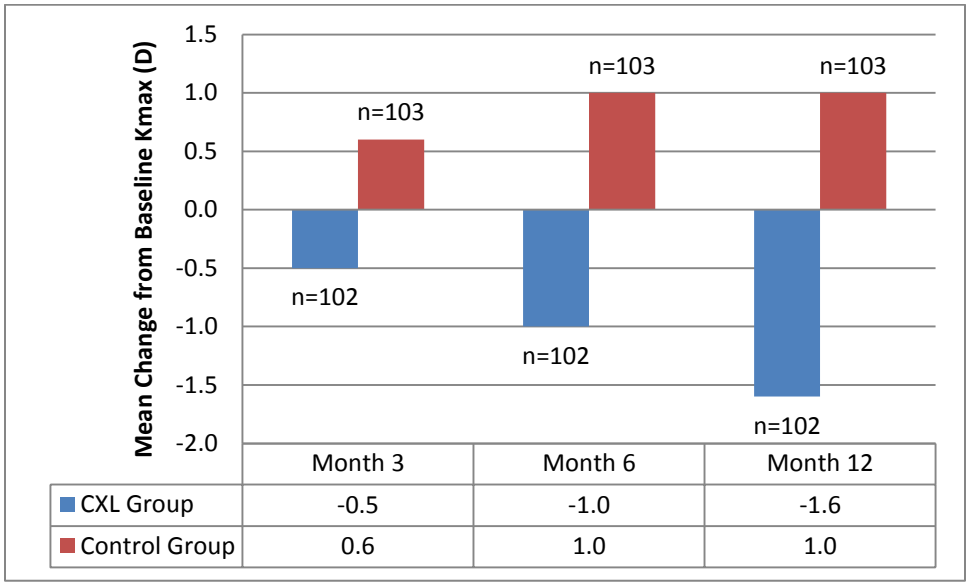
Pooled

Similar results were observed in the pooled studies. The difference between the CXL and control groups in mean change from baseline K_{max} progressively improved, in favor of CXL, from Month 3 through Month 12 (Figure 10). The difference between treatment groups was ≥ 1.0

D at Month 3 (1.1 D), Month 6 (2.0 D), and Month 12 (2.6 D). The difference between treatment groups in mean change from baseline K_{max} was highly statistically significant at Month 12 (<0.0001).

Given that 1 D is generally accepted as a meaningful difference, the aforementioned finding of treatment effects ≥1.0 D in favor of CXL is clinically and statistically significant.

Figure 10: Mean Changes from Baseline K_{max} (D) in the Randomized Study Eye of Progressive Keratoconus Subjects (LOCF)



For patients suffering from these devastating conditions and facing the possibility of corneal transplantation, halting progression (no change in curvature) at 6 or 12 months is clinically meaningful. The data demonstrates that cross-linking not only halted progression but also improved corneal curvature in many treated subjects. This outcome is especially meaningful because it may prevent or delay corneal transplantation and allows patients to better manage their disease symptoms.

Table 8: Progressive Keratoconus: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF)

		UVX-001*			UVX-002			Pooled Studies		
Visit	**Statistic**	**CXL Group (N=29)**	**Control Group (N=29)**	**P-value[a]**	**CXL Group (N=73)**	**Control Group (N=74)**	**P-value[a]**	**CXL Group (N=102)**	**Control Group (N=103)**	**P-value[a]**
Baseline	N	29	29		73	74		102	103	
	Mean	60.6	61.9		61.0	59.8		60.9	60.4	
	SD	7.34	8.32		9.81	9.16		9.14	8.94	
Month 1[b]	N	29	29		73	74		102	103	
	Mean Change from Baseline	1.4	–2.9	0.0563	1.2	–0.5	0.0678	1.3	–1.2	0.0081
	SD	2.68	11.66		3.36	7.18		3.17	8.68	
Month 3	N	29	29		73	74		102	103	
	Mean Change from Baseline	–0.3	0.1	0.5085	–0.6	0.7	0.1142	–0.5	0.6	0.0867
	SD	2.68	2.61		4.44	5.58		4.01	4.92	
Month 6	N	29	29		73	74		102	103	
	Mean Change from Baseline	–0.9	0.5	0.0674	–1.1	1.2	0.0129	–1.0	1.0	0.0032
	SD	2.61	2.99		5.06	5.71		4.49	5.09	
Month 12	N	29	29		73	74		102	103	
	Mean Change from Baseline	–1.4	0.5	0.0175	–1.7	1.2	0.0010	–1.6	1.0	<0.0001
	SD	2.84	2.99		4.69	5.70		4.23	5.08	

*Progressive keratoconus subjects only

[a] P-value is based on the difference between CXL and Control using a 2-sided t-test. Per the SAP, while p-values are reported for all visits, the only one reported in this table that was used for statistical inference was the analysis of Month 12 (alpha=0.049 due to the unplanned analysis at Month 3).

[b] The Month 1 K_{max} summary statistics for the UVX-001 Keratoconus Control Group contains an incorrect K_{max} value for one patient (due to a Pentacam output error where the printout showed a K_{max} value of -0.3 D instead of the correct K_{max} value of 64.4 D). The Month 1 K_{max} summary statistics for the UVX-002 Control Group contains an incorrect value for one patient whereby a K_{max} value of 0 was incorrectly entered in the database instead of the actual Kmax value of 58.9 D.

6.5.2.2. Observed Data Analysis

K_{max} results were summarized using observed values at each visit through Month 12; however, the number of observations in the randomized study eye dropped after Month 3 in the control group when the study eye could cross-over to receive CXL treatment. As a result, none of the subjects in the control group of UVX-001 and only 2 subjects in the control group of UVX-002 had an observation for the randomized study eye at Month 12. Therefore, for analyses comparing the CXL and control groups, the discussion below focuses on Month 6 results, the last time point with an evaluable number of subjects in the control group.

Table 9 presents mean changes from baseline K_{max} in randomized study eyes over time using observed values for UVX-001 (progressive keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects)

At baseline, the mean K_{max} was similar in the CXL (60.6 D) and control (61.9 D) groups. After CXL treatment, mean K_{max} observed values progressively decreased from baseline at Month 3 (–0.3 D), Month 6 (–1.0 D), and Month 12 (–1.6 D). In the control group, mean K_{max} observed values increased from baseline at Month 3 (N=29, 0.1 D) and Month 6 (N=18, 0.2 D), indicative of a worsening in K_{max}.

The CXL group improved over control at Month 3 but did not meet the ≥ 1.0 D threshold specified (–0.3 D vs. 0.1 D, p=0.5085) and exceeded 1.0 D at Month 6 (–1.0 D vs. 0.2 D, p=0.1517). The difference between treatment groups at Month 12 could not be evaluated with observed case analysis.

UVX-002

K_{max} at baseline was 61.0 D in the CXL group and 59.8 D in the control group. After CXL treatment, mean K_{max} observed values progressively decreased (i.e., improved) from baseline to Month 3 (–0.7 D), Month 6 (–1.3 D), and Month 12 (–1.8 D). In comparison, in the control group, mean K_{max} increased at Month 3 (N=67, 0.8 D), Month 6 (N=21, 1.8 D), and Month 12 (N=2, 0.8 D), indicative of a worsening in K_{max}.

The difference in mean changes from baseline K_{max} between the CXL and control groups exceeded 1.0 D, in favor of CXL, at Month 3 (–0.7 D vs. 0.8 D, p=0.1051) and Month 6 (–1.3 D vs. 1.8 D, p=0.0151). Given that there were only 2 subjects in the control group with an observed value at Month 12, the difference between treatment groups at that time point is not meaningful.

Pooled

Figure 11 presents mean changes from baseline K_{max} in randomized study eyes over time using observed values from the pooled studies. K_{max} results were summarized using observed values at each visit through Month 12; however, the number of observations in the randomized control eye began decreasing after Month 3 when the control eye could cross-over to receive CXL treatment.

After CXL treatment, mean K_{max} observed data demonstrated a consistent improvement from baseline at Month 3 (–0.6 D), Month 6 (–1.2 D), and Month 12 (–1.8 D). By comparison, in the control group, mean K_{max} observed data demonstrated worsening from baseline at Month 3

(N=96, 0.6 D), Month 6 (N=39, 1.1 D), and Month 12 (N=2, 0.8 D). The difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor of CXL, at Month 3 (1.2 D), Month 6 (2.3 D) and Month 12 (2.6 D).

Observed case data supports the treatment effect of cross-linking and progression of disease in untreated subjects. The observed data in progressive keratoconus subjects exceeded the endpoint of ≥1 D difference in the mean change in K_{max} between CXL and control groups at all timepoints. These observed case data are profoundly meaningful and demonstrate cross-linking not only halts progression but also can improve corneal curvature in subjects with progressive keratoconus.

Figure 11: Mean Changes from Baseline K_{max} (D) in the Randomized Study Eye of Progressive Keratoconus Subjects (Observed)

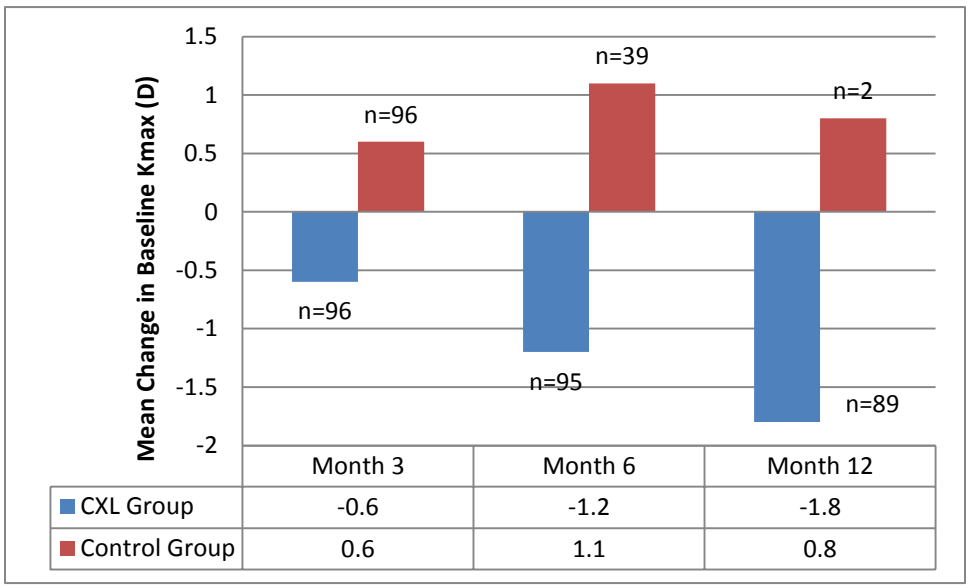


Table 9: Progressive Keratoconus: Mean Changes from Baseline K_{max} in the Randomized Study Eye (Observed Values)

		UVX-001*			UVX-002			Pooled Studies		
Visit	**Statistic**	**CXL Group (N=29)**	**Control Group (N=29)**	**P-value[a]**	**CXL Group (N=73)**	**Control Group (N=74)**	**P-value[a]**	**CXL Group (N=102)**	**Control Group (N=103)**	**P-value[a]**
Baseline	N	29	29		73	74		102	103	
	Mean	60.6	61.9		61.0	59.8		60.9	60.4	
	SD	7.34	8.32		9.81	9.16		9.14	8.94	
Month 1	N	29	28		70	73		99	101	
	Mean Change from Baseline	1.4	–3.0	0.0547	1.3	–0.5	0.0662	1.3	–1.2	0.0081
	SD	2.68	11.86		3.42	7.23		3.21	8.77	
Month 3	N	29	29		67	67		96	96	
	Mean Change from Baseline	–0.3	0.1	0.5085	–0.7	0.8	0.1051	–0.6	0.6	0.0798
	SD	2.68	2.61		4.60	5.83		4.11	5.07	
Month 6	N	28	18		67	21		95	39	
	Mean Change from Baseline	–1.0	0.2	0.1517	–1.3	1.8	0.0151	–1.2	1.1	0.0067
	SD	2.60	3.24		5.23	3.85		4.60	3.62	
Month 12	N	20	0		69	2		89	2	
	Mean Change from Baseline	–1.6	----	----	–1.8	0.8	0.4382	–1.8	0.8	0.4048
	SD	2.40	----		4.76	1.41		4.33	1.41	

*Progressive keratoconus subjects only

[a] P-value is based on the difference between CXL and Control using a 2-sided t-test. Per the SAP, while p-values are reported for all visits, the only one reported in this table that was used for statistical inference was the analysis of Month 12 (alpha=0.049 due to the unplanned analysis at Month 3).

6.5.2.3. Sensitivity Analyses Support Primary Efficacy Results

In support of the clinical efficacy results presented in NDA 203-324, Avedro conducted additional statistical analyses. The sensitivity analyses explored the bounds of the treatment effect at 1 year based on a variety of assumptions which included mixed-effects regression models based on linear, log-linear, and nonparametric time trends. The analyses were robust, consistent and support the primary efficacy analyses (Appendix 5).

Among patients with keratoconus, the log-linear model provided the best fit of pooled results (BIC= 3770.60). After one year, there was a 2.68D magnitude in treatment difference between the CXL and control groups (SE= 0.64, p<0.0001). An analysis of site-specific time trends showed that the overall variability was about 16%; though there was considerable variability at baseline and in terms of rate of change, the estimated magnitude of treatment effect was consistent across all sites. In a between subjects analysis among the CXL group, a log-linear model was the best fit with a 2.68D effect at 1 year (SE=0.64, p<0.0001). In a within subject analysis among control subjects who crossed over to receive treatment in the primary eye, a linear model was the best fit with an estimated 3.87D within-subject effect (SE=1.23, p=0.0016). Lastly, in a within subject analysis comparing control subjects for treated and untreated eyes, a linear model was the best fit with an estimated 5.81D treatment effect (SE=2.02, p=0.0041) at 1 year.

6.5.3. Distribution of Change from Baseline K_{max} in the Randomized Eye

6.5.3.1. LOCF

Table 10 presents the categorical distribution of change from baseline K_{max} (LOCF) in randomized CXL eyes for UVX-001 (progressive keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects)

The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 65.5% (19/29) at Month 3; 72.4% (21/29) at Month 6; and 75.9% (22/29) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} was 44.8% (13/29) at Month 3, 51.7% (15/29) at Month 6, and 51.7% (15/29) at Month 12.

UVX-002

The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 24.7% (18/73) at Month 1; 49.3% (36/73) at Month 3; 61.6% (45/73) at Month 6; and 69.9% (51/73) at Month 12. Further, the proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} progressively increased through Month 12: 12.3% (9/73) at Month 1; 30.1% (22/73) at Month 3; 43.8% (32/73) at Month 6; and 50.7% (37/73) at Month 12.

Pooled

Figure 15 presents the categorical distribution of change from baseline K_{max} for the UVX-001 progressive keratoconus data pooled with the UVX-002 data at Month 12.

72 % of subjects who received cross-linking experienced stopping of progression (no change) or improvement by Month 12. In a patient population struggling with a progressive sight threatening disease, this result is profoundly meaningful.

Figure 12: Progressive Keratoconus: Distribution of Change from Baseline in K_{max} in Randomized CXL Eyes (Month 12 LOCF)

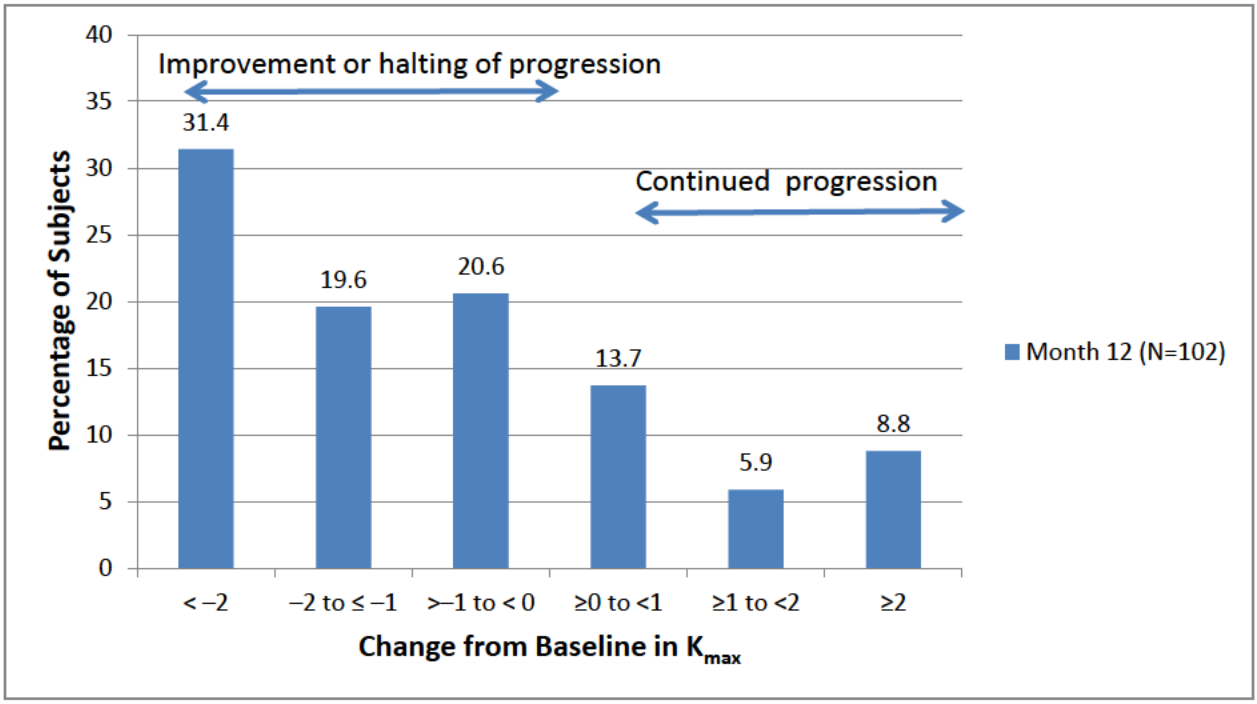


Table 10: Progressive Keratoconus: Distribution of Change from Baseline in K_{max} in Randomized CXL Eyes (LOCF)

	Change from Baseline in K_{max}											
	< –2		–2 to ≤ –1		>–1 to < 0		≥0 to <1		≥1 to <2		≥2	
Visit	**n**	**%**	**N**	**%**	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
UVX-001*												
Month 1 (N=29)	0	0	1	3.4	5	17.2	12	41.1	3	10.3	8	27.6
Month 3 (N=29)	5	17.2	8	27.6	6	20.7	5	17.2	2	6.9	3	10.3
Month 6 (N=29)	9	31.0	6	20.7	6	20.7	2	6.9	2	6.9	4	13.8
Month 12 (N=29)	9	31.0	6	20.7	7	24.1	4	13.8	1	3.4	2	6.9
UVX-002												
Month 1 (N=73)	8	11.0	1	1.4	9	12.3	18	24.7	6	8.2	31	42.5
Month 3 (N=73)	16	21.9	6	8.2	14	19.2	14	19.2	12	16.4	11	15.1
Month 6 (N=73)	18	24.7	14	19.2	13	17.8	11	15.1	7	9.6	10	13.7
Month 12 (N=73)	23	31.5	14	19.2	14	19.2	10	13.7	5	6.8	7	9.6
Pooled Studies												
Month 1 (N=102)	8	7.8	2	2.0	14	13.7	30	29.4	9	8.8	39	38.2
Month 3 (N=102)	21	20.6	14	13.7	20	19.6	19	18.6	14	13.7	14	13.7
Month 6 (N=102)	27	26.5	20	19.6	19	18.6	13	12.7	9	8.8	14	13.7
Month 12 (N=102)	32	31.4	20	19.6	21	20.6	14	13.7	6	5.9	9	8.8

*Progressive keratoconus subjects only

6.5.3.2. Observed Case Analysis

Table 11 presents the categorical distribution of change from baseline K_{max} in randomized CXL eyes using observed case data for UVX-001 (progressive keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects) and UVX-002

In both studies, the proportion of CXL subjects who had any improvement in K_{max} progressively increased over time, ranging from 20.7% (Month 1) to 75.0% (Months 6 and 12) in UVX-001 and from 25.7% (Month 1) to 72.5% (Month 12) in UVX-002. In UVX-001, the proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} ranged from 3.4% (1/29) at Month 1 to 53.6% (15/28) at Month 6. In UVX-002, these values ranged from 12.9% (9/70) at Month 1 to 52.2% (36/69) at Month 12.

Pooled

Similar results were observed in the pooled studies.

Figure 13 presents the categorical distribution of change from baseline K_{max} for the UVX-001 progressive keratoconus data pooled with the UVX-002 data.

73% of subjects who received cross-linking experienced stopping of progression (no change) or improvement by Month 12. In a patient population struggling with a progressive sight threatening disease, this result is profoundly meaningful.

Since K_{max} is expected to increase over time in subjects with progressive keratoconus, stopping progression is considered to be a clinically meaningful outcome. The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 56.3% (54/96) at Month 3; 68.4% (65/95) at Month 6; and 73.0% (65/89) at Month 12.

Figure 13: Progressive Keratoconus: Distribution of Change from Baseline in K_{max} in Randomized CXL Eyes (Month 12 Observed)

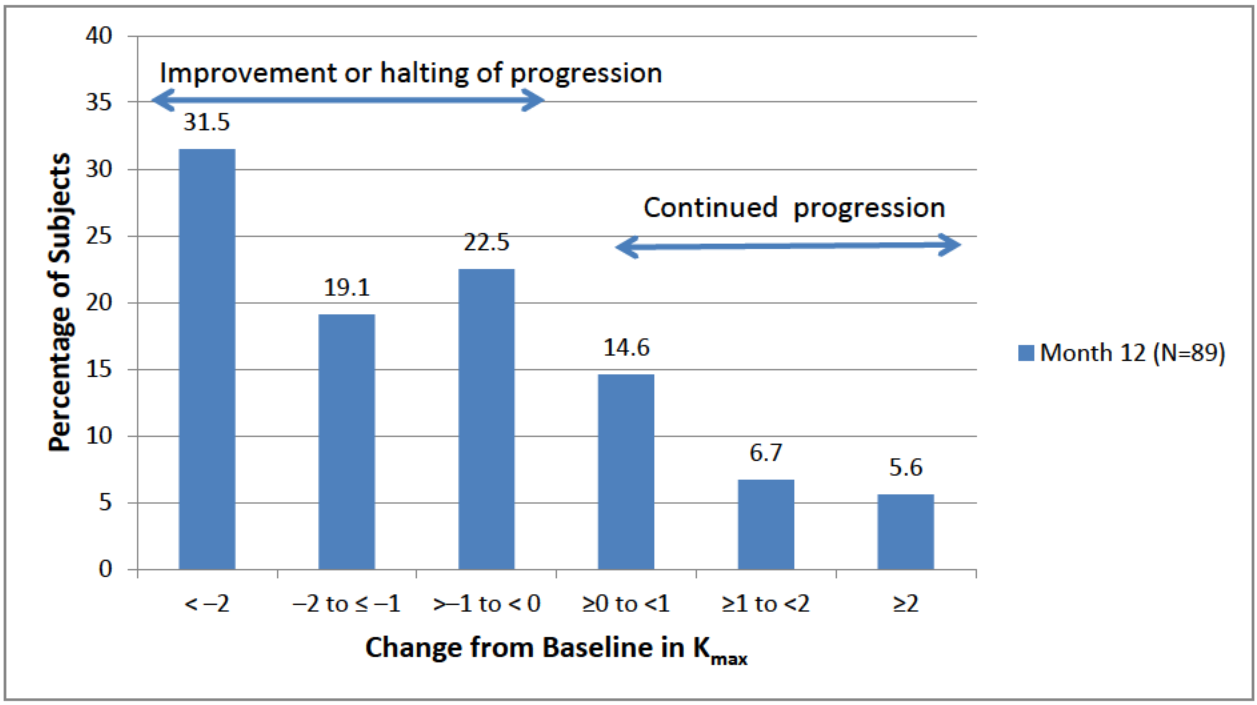


Table 11: Distribution of Change from Baseline in K_{max} in Randomized CXL Eyes (ITT Population, Observed Values): UVX-001 (Progressive Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002

	Change from Baseline in K_{max}											
	< –2		–2 to ≤ –1		>–1 to < 0		≥0 to <1		≥1 to <2		≥2	
Visit	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
UVX-001*												
Month 1 (N=29)	0	0	1	3.4	5	17.2	12	41.4	3	10.3	8	27.6
Month 3 (N=29)	5	17.2	8	27.6	6	20.7	5	17.2	2	6.9	3	10.3
Month 6 (N=28)	9	32.1	6	21.4	6	21.4	2	7.1	2	7.1	3	10.7
Month 12 (N=20)	5	25.0	4	20.0	6	30.0	4	20.0	1	5.0	0	0
UVX-002												
Month 1 (N=70)	8	11.4	1	1.4	9	12.9	15	21.4	6	8.6	31	44.3
Month 3 (N=67)	16	23.9	6	9.0	13	19.4	11	16.4	12	17.9	9	13.4
Month 6 (N=67)	18	26.9	14	20.9	12	17.9	8	11.9	7	10.4	8	11.9
Month 12 (N=69)	23	33.3	13	18.8	14	20.3	9	13.0	5	7.2	5	7.2
Pooled Studies												
Month 1 (N=99)	8	8.1	2	2.0	14	14.1	27	27.3	9	9.1	39	39.4
Month 3 (N=96)	21	21.9	14	14.6	19	19.8	16	16.7	14	14.6	12	12.5
Month 6 (N=95)	27	28.4	20	21.1	18	18.9	10	10.5	9	9.5	11	11.6
Month 12 (N=89)	28	31.5	17	19.1	20	22.5	13	14.6	6	6.7	5	5.6

*Progressive keratoconus subjects only

6.5.4. Mean Changes from Baseline K_{max} in the Randomized Study Eye by Use of Riboflavin with and without Dextran

Subjects in the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed. Subjects then received riboflavin ophthalmic solution with dextran in the study eye for 30 minutes. If corneal thickness was < 400 microns in eyes in the CXL group after treatment with riboflavin ophthalmic solution with dextran, a second solution was instilled into the study eye: riboflavin without dextran.

Subjects in the sham treatment group had topical anesthetic administered to the study eye but did not have the corneal epithelium removed. Study eyes were treated with riboflavin ophthalmic solution as described above.

6.5.4.1. Observed Case Analysis

For subjects who received riboflavin with dextran alone, mean K_{max} at baseline tended to be lower in the CXL group in UVX-001 and was comparable between treatment groups in UVX-002. In the CXL group of UVX-001, mean K_{max} values decreased from baseline at Months 3, 6, and 12; in UVX-002, mean K_{max}, showed no change from baseline at Month 3, and decreased from baseline at Months 6 and 12. In the control group of both studies, mean K_{max} increased from baseline at Months 3 and 6. In both studies, the difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor of CXL, at Month 6 (UVX-001: difference of 1.4 D, p=0.1067; UVX-002: difference of 2.4 D, p=0.0162).

For subjects who received riboflavin with dextran followed by riboflavin without dextran, mean K_{max} at baseline tended to be higher in the CXL group in UVX-001 and was comparable between treatment groups in UVX-002. In the CXL group of UVX-001, mean K_{max} values showed no change from baseline at Month 3, and decreased from baseline at Months 6 and 12; in UVX-002, mean K_{max} values increased from baseline at Month 1 and decreased from baseline at Months 3, 6, and 12. In the control group of both studies, mean K_{max} increased from baseline at Months 3 and 6. In UVX-001, the difference in mean changes from baseline K_{max} between the CXL and control groups did not reach ≥ 1.0 D, in favor of CXL, at any time point through Month 6. In UVX-002, the difference was ≥ 1.0 D, in favor of CXL, at Month 3 (difference of 2.2 D, p=0.0789) and Month 6 (difference of 3.6 D, p=0.0246).

In the pooled studies, mean K_{max} at baseline was 59.3 D in the CXL group and 60.4 D in the control group for subjects who received riboflavin with dextran alone (Table 12). After CXL treatment, mean K_{max} values decreased from baseline at Month 3 (–0.1 D), Month 6 (–0.7 D) and Month 12 (–1.1 D). In comparison, in the control group, mean K_{max} increased from baseline at Month 3 (N=96, 0.6 D) and Month 6 (N=39, 1.1 D). The difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor of CXL, at Month 6 (difference of 1.8 D, p=0.0107).

For subjects in the pooled studies who received riboflavin with dextran followed by riboflavin without dextran, mean K_{max} at baseline was 63.0 D in the CXL group and 60.4 D in the control group (Table 12). After CXL treatment, mean K_{max} progressively decreased from baseline at Month 3 (–1.2 D), Month 6 (–1.8 D), and Month 12 (–2.6 D). In comparison, in the control group, mean K_{max} increased from baseline at Month 3 (N=96, 0.6 D) and Month 6 (N=39, 1.1 D). The difference in mean changes from baseline K_{max} between the CXL and control groups was

≥ 1.0 D, in favor of CXL, at Month 3 (difference of 1.8 D, p=0.0727) and Month 6 (difference of 2.9 D, p=0.0120).

Table 12: Mean Changes from Baseline K_{max} in the Randomized Study Eye by Use of Riboflavin with and without Dextran (ITT Population, Observed Values): Pooled UVX-001 and UVX-002

		Riboflavin with Dextran			Riboflavin with Dextran Followed by Riboflavin Without Dextran		
Visit	**Statistic**	**CXL (N=58)**	**Control (N=103)**	**P-value[a]**	**CXL (N=44)**	**Control (N=103)[b]**	**P-value**
Baseline	N	58	103		44	103	
	Mean	59.3	60.4		63.0	60.4	
	SD	7.69	8.94		10.49	8.94	
Month 1	N	56	101		43	101	
	Mean Change from Baseline	1.8	–1.2	0.0138	0.7	–1.2	0.1775
	SD	2.16	8.77		4.15	8.77	
Month 3	N	54	96		42	96	
	Mean Change from Baseline	–0.1	0.6	0.3271	–1.2	0.6	0.0727
	SD	1.94	5.07		5.80	5.07	
Month 6	N	53	39		42	39	
	Mean Change from Baseline	–0.7	1.1	0.0107	–1.8	1.1	0.0120
	SD	3.00	3.62		6.04	3.62	
Month 12	N	48	2		41	2	
	Mean Change from Baseline	–1.1	0.8	0.2073	–2.6	0.8	0.4255
	SD	2.03	1.41		5.92	1.41	

[a] P-value is based on the difference between CXL and Control using a 2-sided t-test. Per the SAP, while p-values are reported for all visits, the only one reported in this table that was used for statistical inference was the analysis of Month 12 (alpha=0.049 due to the unplanned analysis at Month 3).

[b] Per protocol, none of the subjects in the control group were to receive riboflavin with dextran followed by riboflavin without dextran in the primary eye on Day 0. Therefore, the riboflavin with dextran only data were used for the control group in this analysis.

6.5.5. Improvements in Visual Acuity in Progressive Keratoconus Subjects

6.5.5.1. Mean Change from Baseline in BSCVA

6.5.5.1.1. LOCF Analysis

Table 13 summarizes mean changes from baseline in BSCVA in the randomized eye using LOCF for UVX-001 (progressive keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects)

Mean BSCVA was comparable between treatment groups at baseline. At Month 6, the mean change from baseline in BSCVA was 5.7 letters in the CXL group and 3.4 letters in the control group (p=0.4157). At Month 12, the mean change from baseline in BSCVA was 7.2 letters in the CXL group and 3.4 letters in the control group; this difference between treatments was not statistically significant (p=0.1685).

UVX-002

Mean BSCVA was comparable between treatment groups at baseline. At Month 6, the mean change from baseline in BSCVA was 4.5 letters for the CXL group and 1.5 letters in the control group (p=0.0750). At Month 12, the mean change from baseline in BSCVA was 5.0 letters and 1.4 letters in the CXL and control groups, respectively (p=0.0280).

Pooled Studies

In the pooled studies, mean BSCVA was comparable between treatment groups at baseline. The mean change from baseline ranged from –0.3 letters to 5.6 letters in the CXL group and from 2.0 to 2.3 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 4.8 letters in the CXL group versus 2.0 letters in the control group (p=0.0519). At Month 12, these values were 5.6 letters and 2.0 letters in the CXL and control groups, respectively (p=0.0094).

Table 13: Progressive Keratoconus: Best Spectacle-Corrected Visual Acuity (ETDRS Letters Read) in the Randomized Eye - LOCF)

		UVX-001*		UVX-002		Pooled Studies	
Visit	**Statistic**	**CXL Group (N=29)**	**Control Group (N=29)**	**CXL Group (N=73)**	**Control Group (N=74)**	**CXL Group (N=102)**	**Control Group (N=103)**
Baseline	N	29	29	73	73	102	102
	Mean	32.4	31.7	33.5	33.2	33.2	32.8
	SD	11.64	13.03	14.06	13.99	13.37	13.68
Month 1	N	29	29	73	73	102	102
	Mean Change from Baseline	–1.0	3.9	–0.0	1.6	–0.3	2.3
	SD	9.87	10.36	9.35	7.20	9.46	8.24
Month 3	N	29	29	73	74	102	102
	Mean Change from Baseline	6.5	3.8	3.3	1.4	4.2	2.1
	SD	10.56	9.43	9.91	8.13	10.15	8.53
Month 6	N	29	29	73	73	102	102
	Mean Change from Baseline	5.7	3.4	4.5	1.5	4.8	2.0
	SD	10.84	9.96	11.76	8.13	11.46	8.68
Month 12	N	29	29	73	73	102	102
	Mean Change from Baseline	7.2	3.4	5.0	1.4	5.6	2.0
	SD	10.37	9.96	11.20	8.18	10.96	8.72

*****Progressive keratoconus subjects only

6.5.5.1.2. Observed Case Analysis

Table 14 summarizes mean changes from baseline in BSCVA in the randomized eye using observed values for UVX-001 (keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects)

When observed case data were used, the mean change from baseline in BSCVA ranged from –1.0 to 9.6 letters in the CXL group and from 3.5 to 4.4 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 6.1 letters in the CXL group and 4.4 letters in the control group.

UVX-002

When observed case data were used, the mean change from baseline in BSCVA ranged from 0.3 letters to 5.7 letters in the CXL group and from –2.0 to 1.6 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 5.7 letters for the CXL group and –2.0 letters in the control group (Table 14). This difference between treatments was clinically relevant and statistically significant (p=0.0064).

Pooled

In the pooled studies, mean BSCVA was comparable between treatment groups at baseline. The mean change from baseline in BSCVA ranged from –0.1 letters to 5.9 letters in the CXL group and from 0.0 to 2.1 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 5.8 letters for the CXL group versus 1.1 letters in the control group (p=0.0241).

Table 14: Progressive Keratoconus: Best Spectacle-Corrected Visual Acuity (ETDRS Letters Read) in the Randomized Eye (Observed Values)

		UVX-001*		UVX-002		Pooled Studies	
Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=102)	Control Group (N=103)
Baseline	N	29	29	73	73	102	102
	Mean	32.4	31.7	33.5	33.2	33.2	32.8
	SD	11.64	13.03	14.06	13.99	13.37	13.68
Month 1	N	29	28	72	70	101	98
	Mean Change from Baseline	–1.0	3.5	0.3	1.6	–0.1	2.1
	SD	9.87	10.24	9.04	7.35	9.25	8.26
Month 3	N	29	29	69	68	98	97
	Mean Change from Baseline	6.5	3.8	4.1	1.2	4.8	1.9
	SD	10.56	9.43	8.72	8.21	9.31	8.62
Month 6	N	28	18	68	20	96	38
	Mean Change from Baseline	6.1	4.4	5.7	–2.0	5.8	1.1
	SD	10.84	10.61	10.70	10.89	10.68	11.09
Month 12	N	20	0	66	2	86	2
	Mean Change from Baseline	9.6	----	4.8	0.0	5.9	0.0
	SD	8.80	----	10.55	8.49	10.32	8.49

*****Progressive keratoconus subjects only

6.5.5.2. Categorical Changes from Baseline in BSCVA

6.5.5.2.1. LOCF Analysis

Table 15 summarizes categorical changes from baseline in BSCVA in the randomized eye using LOCF for UVX-001 (keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects)

In UVX-001, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 69.0% (20/29) and 60.7% (17/28) in the CXL and control groups, respectively. At Month 12, these values were 79.3% and 60.7%, respectively. The proportion of subjects with a ≥15-letter improvement in BSCVA was comparable between treatment groups at Month 6 (17.2% vs. 21.4%) and Month 12 (24.1% vs. 21.4%).

UVX-002

In UVX-002, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 62.3% (43/69) and 59.2% (42/71) in the CXL and control groups, respectively. At Month 12, these values were 65.2% and 59.2%, respectively. The proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group compared with the control group, both at Month 6 (14.5% vs. 2.8%) and Month 12 (17.4% vs. 2.8%).

Pooled

In the pooled studies, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 64.3% (63/98) and 59.6% (59/99) in the CXL and control groups, respectively. At Month 12, these values were 69.4% and 59.6%, respectively. The proportion of subjects with a ≥15-letter improvement in BSCVA was approximately 2-fold higher in the CXL group compared with the control group, both at Month 6 (15.3% vs. 8.1%) and Month 12 (19.4% vs. 8.1%).

Table 15: Categorical Changes from Baseline in Best Spectacle-Corrected Visual Acuity in the Randomized Eye (ITT Population, LOCF): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002

			UVX-001*		UVX-002		Pooled Studies	
Visit	Category		CXL Group (N=29)	Control Group (N=29)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=102)	Control Group (N=103)
Month 1	N		29	28	69	71	98	99
	Gain ≥ 15 letters	n (%)	1 (3.4)	6 (21.4)	4 (5.8)	4 (5.6)	5 (5.1)	10 (10.1)
	Gain of 10 to 14 letters	n (%)	3 (10.3)	1 (3.6)	3 (4.3)	7 (9.9)	6 (6.1)	8 (8.1)
	Gain of 5 to 9 letters	n (%)	2 (6.9)	4 (14.3)	7 (10.1)	9 (12.7)	9 (9.2)	13 (13.1)
	Gain of 1 to 4 letters	n (%)	9 (31.0)	5 (17.9)	14 (20.3)	21 (29.6)	23 (23.5)	26 (26.3)
	Loss of 0 to 4 letters	n (%)	7 (24.1)	7 (25.0)	22 (31.9)	18 (25.4)	29 (29.6)	25 (25.3)
	Loss of 5 to 9 letters	n (%)	1 (3.4)	2 (7.1)	11 (15.9)	6 (8.5)	12 (12.2)	8 (8.1)
	Loss of 10 to 14 letters	n (%)	4 (13.8)	2 (7.1)	5 (7.2)	4 (5.6)	9 (9.2)	6 (6.1)
	Loss ≥ 15 letters	n (%)	2 (6.9)	1 (3.6)	3 (4.3)	2 (2.8)	5 (5.1)	3 (3.0)
Month 3	N		29	28	69	71	98	99
	Gain ≥ 15 letters	n (%)	6 (20.7)	6 (21.4)	9 (13.0)	2 (2.8)	15 (15.3)	8 (8.1)
	Gain of 10 to 14 letters	n (%)	4 (13.8)	3 (10.7)	6 (8.7)	9 (12.7)	10 (10.2)	12 (12.1)
	Gain of 5 to 9 letters	n (%)	7 (24.1)	3 (10.7)	13 (18.8)	11 (15.5)	20 (20.4)	14 (14.1)
	Gain of 1 to 4 letters	n (%)	7 (24.1)	6 (21.4)	14 (20.3)	20 (28.2)	21 (21.4)	26 (26.3)
	Loss of 0 to 4 letters	n (%)	2 (6.9)	5 (17.9)	14 (20.3)	19 (26.8)	16 (16.3)	24 (24.2)
	Loss of 5 to 9 letters	n (%)	2 (6.9)	4 (14.3)	7 (10.1)	4 (5.6)	9 (9.2)	8 (8.1)
	Loss of 10 to 14 letters	n (%)	0	1 (3.6)	3 (4.3)	2 (2.8)	3 (3.1)	3 (3.0)
	Loss ≥ 15 letters	n (%)	1 (3.4)	0	3 (4.3)	4 (5.6)	4 (4.1)	4 (4.0)

Table 15: Categorical Changes from Baseline in Best Spectacle-Corrected Visual Acuity (ITT Population, LOCF): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002 (Continued)

			UVX-001*		UVX-002		Pooled Studies	
Visit	Category		CXL Group (N=29)	Control Group (N=29)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=102)	Control Group (N=103)
Month 6	N		29	28	69	71	98	99
	Gain ≥ 15 letters	n (%)	5 (17.2)	6 (21.4)	10 (14.5)	2 (2.8)	15 (15.3)	8 (8.1)
	Gain of 10 to 14 letters	n (%)	4 (13.8)	2 (7.1)	6 (8.7)	8 (11.3)	10 (10.2)	10 (10.1)
	Gain of 5 to 9 letters	n (%)	7 (24.1)	3 (10.7)	14 (20.3)	13 (18.3)	21 (21.4)	16 (16.2)
	Gain of 1 to 4 letters	n (%)	4 (13.8)	6 (21.4)	13 (18.8)	19 (26.8)	17 (17.3)	25 (25.3)
	Loss of 0 to 4 letters	n (%)	4 (13.8)	4 (14.3)	16 (23.2)	19 (26.8)	20 (20.4)	23 (23.2)
	Loss of 5 to 9 letters	n (%)	2 (6.9)	5 (17.9)	6 (8.7)	5 (7.0)	8 (8.2)	10 (10.1)
	Loss of 10 to 14 letters	n (%)	3 (10.3)	2 (7.1)	0	2 (2.8)	3 (3.1)	4 (4.0)
	Loss ≥ 15 letters	n (%)	0	0	4 (5.8)	3 (4.2)	4 (4.1)	3 (3.0)
Month 12	N		29	28	69	71	98	99
	Gain ≥ 15 letters	n (%)	7 (24.1)	6 (21.4)	12 (17.4)	2 (2.8)	19 (19.4)	8 (8.1)
	Gain of 10 to 14 letters	n (%)	5 (17.2)	2 (7.1)	4 (5.8)	8 (11.3)	9 (9.2)	10 (10.1)
	Gain of 5 to 9 letters	n (%)	5 (17.2)	3 (10.7)	9 (13.0)	14 (19.7)	14 (14.3)	17 (17.2)
	Gain of 1 to 4 letters	n (%)	6 (20.7)	6 (21.4)	20 (29.0)	18 (25.4)	26 (26.5)	24 (24.2)
	Loss of 0 to 4 letters	n (%)	2 (6.9)	4 (14.3)	13 (18.8)	18 (25.4)	15 (15.3)	22 (22.2)
	Loss of 5 to 9 letters	n (%)	1 (3.4)	5 (17.9)	6 (8.7)	6 (8.5)	7 (7.1)	11 (11.1)
	Loss of 10 to 14 letters	n (%)	3 (10.3)	2 (7.1)	4 (5.8)	2 (2.8)	7 (7.1)	4 (4.0)
	Loss ≥ 15 letters	n (%)	0	0	1 (1.4)	3 (4.2)	1 (1.0)	3 (3.0)

*Progressive keratoconus subjects only

6.5.5.2.2. Observed Case Analysis

Table 16 summarizes categorical changes from baseline in BSCVA in the randomized eye using observed values for UVX-001 (keratoconus subjects), UVX-002, and the pooled studies.

UVX-001 (Progressive Keratoconus Subjects)

In UVX-001, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 71.4% (20/28) and 58.8% (10/17) in the CXL and control groups, respectively. At Month 12, the proportion of subjects in the CXL group who showed any improvement in BSCVA was 90.0% (18/20). The proportion of subjects with a ≥15-letter improvement in BSCVA was 17.9% in the CXL group and 23.5% in the control group at Month 6. At Month 12, the proportion of subjects in the CXL group with a ≥15-letter improvement in BSCVA was 25.0%.

UVX-002

In UVX-002, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 67.2% (43/64) and 50.0% (9/18) in the CXL and control groups, respectively. At Month 12, the proportion of subjects in the CXL group who showed any improvement in BSCVA was 68.3% (43/63). The proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group compared with the control group at Month 6 (15.6% vs. 5.6%). At Month 12, the proportion of subjects in the CXL group with a ≥15-letter improvement in BSCVA was 17.5%.

Pooled Studies

In the pooled studies, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 68.5% (63/92) and 54.3% (19/35) in the CXL and control groups, respectively. At Month 12, the proportion of subjects in the CXL group who showed any improvement in BSCVA was 73.5% (61/83). The proportion of subjects with a ≥15-letter improvement in BSCVA was 16.3% in the CXL group and 14.3% in the control group at Month 6. At Month 12, the proportion of subjects in the CXL group with a ≥15-letter improvement in BSCVA was 19.3%.

These studies showed that CXL subject experienced clinically significant improvements from baseline and greater improvements over control subjects in visual acuity.

Table 16: Categorical Changes from Baseline in Best Spectacle-Corrected Visual Acuity in the Randomized Eye (ITT Population, Observed Values): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002

			UVX-001*		UVX-002		Pooled Studies	
Visit	Category		CXL Group (N=29)	Control Group (N=29)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=102)	Control Group (N=103)
Month 1	N		29	27	67	68	96	95
	Gain ≥ 15 letters	n (%)	1 (3.4)	5 (18.5)	4 (6.0)	4 (5.9)	5 (5.2)	9 (9.5)
	Gain of 10 to 14 letters	n (%)	3 (10.3)	1 (3.7)	3 (4.5)	7 (10.3)	6 (6.3)	8 (8.4)
	Gain of 5 to 9 letters	n (%)	2 (6.9)	4 (14.8)	7 (10.4)	9 (13.2)	9 (9.4)	13 (13.7)
	Gain of 1 to 4 letters	n (%)	9 (31.0)	5 (18.5)	14 (20.9)	19 (27.9)	23 (24.0)	24 (25.3)
	Loss of 0 to 4 letters	n (%)	7 (24.1)	7 (25.9)	21 (31.3)	17 (25.0)	28 (29.2)	24 (25.3)
	Loss of 5 to 9 letters	n (%)	1 (3.4)	2 (7.4)	11 (16.4)	6 (8.8)	12 (12.5)	8 (8.4)
	Loss of 10 to 14 letters	n (%)	4 (13.8)	2 (7.4)	5 (7.5)	4 (5.9)	9 (9.4)	6 (6.3)
	Loss ≥ 15 letters	n (%)	2 (6.9)	1 (3.7)	2 (3.0)	2 (2.9)	4 (4.2)	3 (3.2)
Month 3	N		29	27	66	66	95	93
	Gain ≥ 15 letters	n (%)	6 (20.7)	5 (18.5)	9 (13.6)	2 (3.0)	15 (15.8)	7 (7.5)
	Gain of 10 to 14 letters	n (%)	4 (13.8)	3 (11.1)	6 (9.1)	7 (10.6)	10 (10.5)	10 (10.8)
	Gain of 5 to 9 letters	n (%)	7 (24.1)	3 (11.1)	13 (19.7)	10 (15.2)	20 (21.1)	13 (14.0)
	Gain of 1 to 4 letters	n (%)	7 (24.1)	6 (22.2)	14 (21.2)	19 (28.8)	21 (22.1)	25 (26.9)
	Loss of 0 to 4 letters	n (%)	2 (6.9)	5 (18.5)	13 (19.7)	19 (28.8)	15 (15.8)	24 (25.8)
	Loss of 5 to 9 letters	n (%)	2 (6.9)	4 (14.8)	7 (10.6)	3 (4.5)	9 (9.5)	7 (7.5)
	Loss of 10 to 14 letters	n (%)	0	1 (3.7)	3 (4.5)	2 (3.0)	3 (3.2)	3 (3.2)
	Loss ≥ 15 letters	n (%)	1 (3.4)	0	1 (1.5)	4 (6.1)	2 (2.1)	4 (4.3)

Table 16: Categorical Changes from Baseline in Best Spectacle-Corrected Visual Acuity in the Randomized Eye (ITT Population, Observed Values): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002 (Cont'd)

			UVX-001*		UVX-002		Pooled Studies	
Visit	Category		CXL Group (N=29)	Control Group (N=29)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=102)	Control Group (N=103)
Month 6	N		28	17	64	18	92	35
	Gain ≥ 15 letters	n (%)	5 (17.9)	4 (23.5)	10 (15.6)	1 (5.6)	15 (16.3)	5 (14.3)
	Gain of 10 to 14 letters	n (%)	4 (14.3)	2 (11.8)	6 (9.4)	1 (5.6)	10 (10.9)	3 (8.6)
	Gain of 5 to 9 letters	n (%)	7 (25.0)	2 (11.8)	14 (21.9)	4 (22.2)	21 (22.8)	6 (17.1)
	Gain of 1 to 4 letters	n (%)	4 (14.3)	2 (11.8)	13 (20.3)	3 (16.7)	17 (18.5)	5 (14.3)
	Loss of 0 to 4 letters	n (%)	4 (14.3)	3 (17.6)	14 (21.9)	4 (22.2)	18 (19.6)	7 (20.0)
	Loss of 5 to 9 letters	n (%)	1 (3.6)	3 (17.6)	5 (7.8)	3 (16.7)	6 (6.5)	6 (17.1)
	Loss of 10 to 14 letters	n (%)	3 (10.7)	1 (5.9)	0	1 (5.6)	3 (3.3)	2 (5.7)
	Loss ≥ 15 letters	n (%)	0	0	2 (3.1)	1 (5.6)	2 (2.2)	1 (2.9)
Month 12	N		20	0	63	2	83	2
	Gain ≥ 15 letters	n (%)	5 (25.0)	0	11 (17.5)	0	16 (19.3)	0
	Gain of 10 to 14 letters	n (%)	3 (15.0)	0	4 (6.3)	0	7 (8.4)	0
	Gain of 5 to 9 letters	n (%)	5 (25.0)	0	8 (12.7)	1 (50.0)	13 (15.7)	1 (50.0)
	Gain of 1 to 4 letters	n (%)	5 (25.0)	0	20 (31.7)	0	25 (30.1)	0
	Loss of 0 to 4 letters	n (%)	2 (10.0)	0	9 (14.3)	0	11 (13.3)	0
	Loss of 5 to 9 letters	n (%)	0	0	6 (9.5)	1 (50.0)	6 (7.2)	1 (50.0)
	Loss of 10 to 14 letters	n (%)	0	0	4 (6.3)	0	4 (4.8)	0
	Loss ≥ 15 letters	n (%)	0	0	1 (1.6)	0	1 (1.2)	0

*Progressive keratoconus subjects only

6.5.6. Efficacy in Progressive Keratoconus – Conclusions

CXL treatment provided statistically significant and clinically relevant improvements in K_{max} in subjects with progressive keratoconus. The primary efficacy endpoint (i.e., a difference of ≥1 D in mean change from baseline in K_{max} between the CXL and control groups at Month 12 using LOCF) was achieved in each study (UVX-001 and UVX-002) and in the pooled (UVX-001 + UVX-002) keratoconus population. The mean changes in K_{max} from baseline to Month 12 in the CXL group versus the control group, respectively, were –1.4 D vs. 0.5 D (p=0.0175) in UVX-001, –1.7 D vs. 1.2 D (p=0.0010) in UVX-002, and -1.6 D vs. 1.0 D (p<0.0001) in the pooled keratoconus population.

Analysis of the observed case K_{max} data provides strong evidence of the effectiveness of CXL in subjects with keratoconus. At Month 6, there was a demonstrated difference between treatment groups in favor of the CXL group. The mean changes in K_{max} from baseline to Month 6 in the CXL group versus the control group, respectively, were –1.0 D vs. 0.2 D (p=0.1517) in UVX-001, –1.3 D vs. 1.8 D (p=0.0151) in UVX-002, and -1.2 D vs. 1.1 D (p=0.0067) in the pooled keratoconus population. At Month 12, an absolute decrease from baseline in Kmax was seen in the CXL arm alone that far exceeded 1 D. In the CXL group, the absolute decreases from baseline to Month 12 in K_{max} were -1.6 D in UVX-001, -1.8 D in UVX-002, and -1.8 D in the pooled keratoconus population. These observed case data are profoundly meaningful and demonstrate CXL not only halts progression but also improves corneal curvature in the majority of subjects with progressive keratoconus.

CXL treatment was effective in stopping disease progression in the majority of the keratoconus study population with actual improvement seen in many subjects. The proportion of progressive keratoconus subjects in the CXL group with either stabilization or improvement in K_{max} over baseline increased over time, reaching over 70% (76% in UVX-001, 70% in UVX-002, and 72% pooled) at Month 12.

Further, meaningful improvements in BSCVA were observed in this patient population following treatment with CXL. Mean improvements from baseline in BSCVA were greater in the CXL group (5.6 letters) compared to the control group (2.0 letters) at Month 12 (p=0.0094) (LOCF) in the pooled analysis, and the proportion of subjects with a ≥15-letter (3 lines or greater) improvement in BSCVA was approximately 2-fold higher in the CXL group compared to the control group (Month 12, 19.4% vs. 8.1%). The proportion of subjects who showed any improvement in BSCVA at Month 12 was 69.4% in the CXL group and 59.6% in the control group.

The efficacy results of fellow eyes treated with CXL is similar to that seen in the randomized study eyes (Appendix 1).

6.6. Efficacy in Corneal Ectasia following Refractive Surgery – Randomized Study Eye

6.6.1. Analysis Populations

In UVX-001 and UVX-003, all subjects received the appropriate randomized treatment; therefore, the ITT and Safety populations were the same and all analyses were performed on the ITT/Safety population. The ITT population consisted of 179 primary eyes (91, CXL group; 88, control group).

6.6.2. Primary Endpoint - Mean Change from Baseline K_{max} in the Randomized Eye

6.6.2.1. Primary Analysis – LOCF Analysis

Table 17 presents mean changes from baseline K_{max} (LOCF) in randomized study eyes over time for UVX-001, UVX-003, and the pooled studies. The efficacy data were analyzed 3 ways: (1) the UVX-001 corneal ectasia data alone 2) the UVX-003 data alone and 3) the UVX-001 ectasia data pooled with the UVX-002 data.

In corneal ectasia patients, all three analyses met the primary endpoint of $\geq$ 1D difference in mean change in baseline Kmax between the cross-linked group and the control group at Month 12.

UVX-001 (Corneal Ectasia Subjects Only)

The difference between the CXL and control groups in mean change from baseline K_{max} progressively improved, in favor of CXL, from Month 3 through Month 12. The difference between treatment groups was slightly less than 1.0 D at Month 3 (0.9 D) and exceeded 1.0 D at Month 6 (1.6 D) and Month 12 (2.0 D). The difference between treatment groups in mean change from baseline K_{max} was statistically significant at Month 12 (p=0.0001).

UVX-003

The difference between the CXL and control groups in mean change from baseline K_{max} favored CXL from Month 3 through Month 12. The difference between treatment groups was less than 1.0 D at Month 3 (0.8 D) and reached 1.0 D at Month 6 and Month 12. The difference between treatment groups in mean change from baseline K_{max} was statistically significant (p=0.0080) at Month 12.

Pooled Studies

Figure 14 presents mean changes from baseline K_{max} (LOCF) in randomized study eyes over time for the UVX-001 corneal ectasia data pooled with the UVX-003 data.

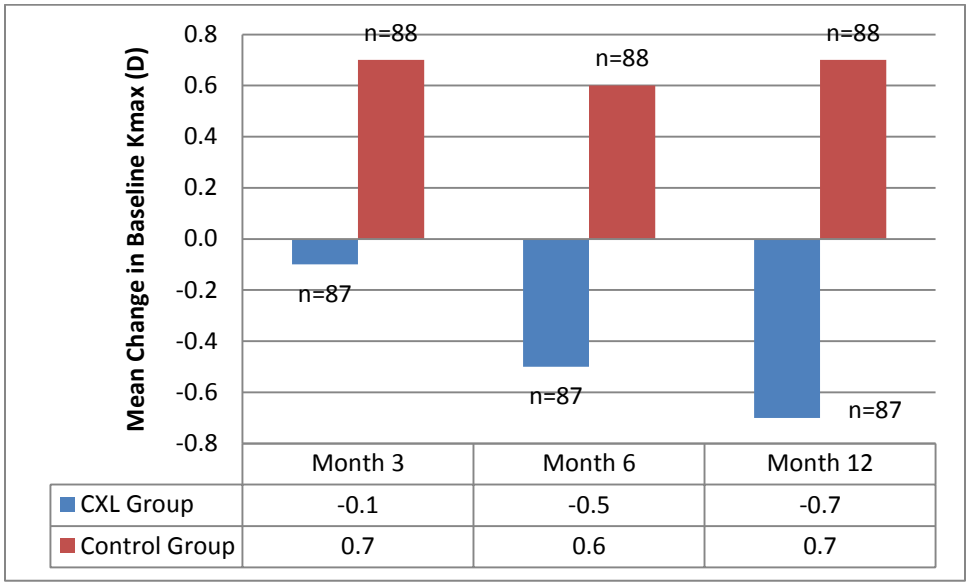
In corneal ectasia patients, the primary endpoint of $\geq$ 1D difference in mean change in baseline Kmax between the cross-linked group and the control group was met at months 6 and 12.

The difference between treatment groups in mean change from baseline K_{max} progressively improved, in favor of CXL, from Month 3 through Month 12. Clinically meaningful improvements in K_{max} were observed at Month 6 (–0.5 D vs. 0.6 D, difference of 1.1 D) and

Month 12 (–0.7 D vs. 0.7 D, difference of 1.4 D) in favor of CXL. The difference between treatment groups in mean change from baseline K_{max} was statistically significant at Month 6 (p=0.0001) and Month 12 (p<0.0001).

Given that 1 D is generally accepted as a meaningful difference, the aforementioned finding of treatment effects ≥1.0 D in favor of CXL is considered to be clinically significant.

Figure 14: Mean Changes from Baseline K_{max} (D) in the Randomized Study Eye of Corneal Ectasia Subjects (LOCF)



	Month 3	Month 6	Month 12
CXL Group	-0.1	-0.5	-0.7
Control Group	0.7	0.6	0.7

For patients, halting progression (no increase in curvature) at 6 or 12 months is clinically meaningful. The data demonstrates that cross-linking not only halted progression but also improved corneal curvature in many treated subjects. This outcome is especially meaningful. A change in corneal curvature makes it more feasible for patients to avoid wearing uncomfortable hard contact lenses to mechanically flatten their corneas.

Table 17: Corneal Ectasia: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF)

		UVX-001*			UVX-003			Pooled Studies		
Visit	**Statistic**	**CXL Group (N=24)**	**Control Group (N=25)**	**P-value[a]**	**CXL Group (N=67)[b]**	**Control Group (N=63)**	**P-value[a]**	**CXL Group (N=91)[b]**	**Control Group (N=88)**	**P-value[a]**
Baseline	N	24	25		63	63		87	88	
	Mean	56.3	55.0		55.1	54.7		55.4	54.8	
	SD	6.26	5.45		7.09	6.77		6.86	6.40	
Month 1	N	24	25		63	63		87	88	
	Mean Change from Baseline	1.1	0.8	0.6408	1.0	0.0	0.0005	1.0	0.3	0.0026
	SD	2.06	1.73		1.84	1.10		1.89	1.34	
Month 3	N	24	25		63	63		87	88	
	Mean Change from Baseline	0.1	1.0	0.0382	–0.2	0.6	0.0386	–0.1	0.7	0.0061
	SD	1.26	1.68		2.38	1.88		2.13	1.83	
Month 6	N	24	25		63	63		87	88	
	Mean Change from Baseline	–0.6	1.0	0.0010	–0.5	0.5	0.0084	–0.5	0.6	0.0001
	SD	1.61	1.69		1.95	2.28		1.85	2.14	
Month 12	N	24	25		63	63		87	88	
	Mean Change from Baseline	–1.0	1.0	0.0001	–0.5	0.5	0.0080	–0.7	0.7	<0.0001
	SD	1.68	1.69		2.21	2.26		2.08	2.11	

[a] P-value is based on the difference between CXL and Control using a 2-sided t-test. Per the SAP, while p-values are reported for all visits, the only one reported in this table that was used for statistical inference was the analysis of Month 12 (alpha=0.049 due to the unplanned analysis at Month 3).

[b] Four subjects in the CXL group of UVX-003 did not have data for the primary (study) eye at baseline.

*Corneal ectasia subjects only

6.6.2.2. Observed Case Analysis

K_{max} results were summarized using observed values at each visit through Month 12; however, the number of observations in the randomized study eye dropped after Month 3 in the control group when the study eye could receive CXL treatment. As a result, none of the subjects in the control group of UVX-001 and 2 subjects in the control group of UVX-003 had an observation for the randomized study eye at Month 12.

Table 18 presents mean changes from baseline K_{max} in randomized study eyes over time using observed values for UVX-001, UVX-003, and the pooled studies.

UVX-001 (Corneal Ectasia Subjects Only)

At baseline, the mean K_{max} was similar in the CXL (56.3 D) and control (55.0 D) groups. After CXL treatment, mean K_{max} observed values increased from baseline at Month 3 (0.1 D) and then decreased from baseline at Month 6 (–0.8 D) and Month 12 (–1.4 D). By comparison, in the control group, mean K_{max} increased from baseline at Month 3 (N=24, 0.9 D) and Month 6 (N=13, 1.6 D), indicative of a worsening in K_{max}.

The difference in mean changes from baseline K_{max} between the CXL and control groups was < 1.0 D at Month 3 (0.1 D vs. 0.9 D, p=0.0511) and exceeded 1.0 D at Month 6 (–0.8 D vs. 1.6 D, p=0.0002).

UVX-003

K_{max} at baseline was 55.1 D in the CXL group and 54.7 D in the control group. After CXL treatment, mean K_{max} observed values progressively decreased (i.e., improved) from baseline to Month 3 (–0.2 D), Month 6 (–0.5 D), and Month 12 (–0.6 D). By comparison, in the control group, mean K_{max} increased from baseline to every evaluation time point: Month 3 (N=61, 0.7 D), Month 6 (N=19, 0.1 D), and Month 12 (N=2, 0.4 D), indicative of a worsening in K_{max}.

The difference in mean changes from baseline K_{max} between the CXL and control groups was < 1.0 D at Month 3 (–0.2 D vs. 0.7 D, p=0.0397) and Month 6 (–0.5 D vs. 0.1 D, p=0.2901). Given that there were only 2 subjects in the control group with an observed value at Month 12, the difference between treatment groups at that time point is not meaningful.

Pooled

Figure 15 presents mean changes from baseline K_{max} in randomized study eyes over time using observed values for the UVX-001 corneal ectasia data pooled with the UVX-003 data.

After CXL treatment, mean K_{max} observed values progressively decreased (showing improvement) from baseline at Month 3 (–0.1 D), Month 6 (–0.6 D), and Month 12 (–0.8 D). By comparison, in the control group, mean K_{max} increased (showing worsening) from baseline at Month 3 (N=85, 0.7 D) and Month 6 (N=32, 0.7 D), indicative of a worsening in K_{max}. The difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D at Month 6 (1.3 D, p=0.0021).

Observed case data supports treatment effect of cross-linking as well as the utilization of LOCF analysis. In post-refractive corneal ectasia subjects, there is a demonstrated treatment effect seen at both 6 and 12 months. Both studies met the endpoint of ≥1 D difference in the mean change in K_{max} in the CXL treated arm with observed case data. These observed case data demonstrate

cross-linking not only halts progression but also can improve corneal curvature in many subjects with corneal ectasia following refractive surgery.

Figure 15: Corneal Ectasia: Mean Changes from Baseline K_{max} in the Randomized Study Eye (Observed)

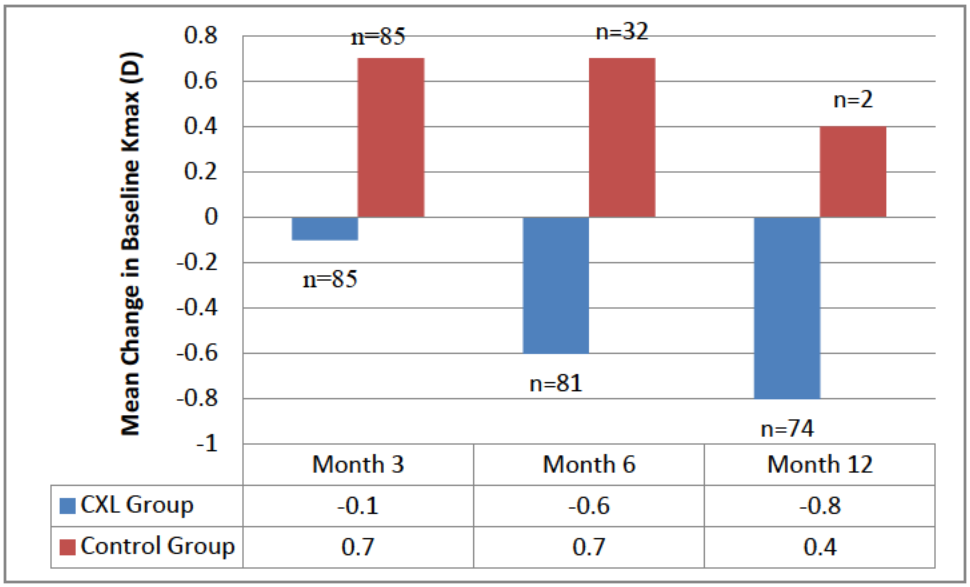


Table 18: Corneal Ectasia: Mean Changes from Baseline K_{max} in the Randomized Study Eye (Observed Values)

		UVX-001*			UVX-003			Pooled Studies		
Visit	**Statistic**	**CXL Group (N=24)**	**Control Group (N=25)**	**P-value[a]**	**CXL Group (N=67)[b]**	**Control Group (N=63)**	**P-value[a]**	**CXL Group (N=91)[b]**	**Control Group (N=88)**	**P-value[a]**
Baseline	N	24	25		63	63		87	88	
	Mean	56.3	55.0		55.1	54.7		55.4	54.8	
	SD	6.26	5.45		7.09	6.77		6.86	6.40	
Month 1	N	24	25		60	61		84	86	
	Mean Change from Baseline	1.1	0.8	0.6408	1.1	0.1	0.0005	1.1	0.3	0.0022
	SD	2.06	1.73		1.87	1.11		1.91	1.36	
Month 3	N	23	24		62	61		85	85	
	Mean Change from Baseline	0.1	0.9	0.0511	–0.2	0.7	0.0397	–0.1	0.7	0.0073
	SD	1.27	1.66		2.38	1.89		2.13	1.82	
Month 6	N	22	13		59	19		81	32	
	Mean Change from Baseline	–0.8	1.6	0.0002	–0.5	0.1	0.2901	–0.6	0.7	0.0021
	SD	1.42	2.03		1.78	2.60		1.69	2.47	
Month 12	N	20	0		54	2		74	2	
	Mean Change from Baseline	–1.4	----	----	–0.6	0.4	0.5571	–0.8	0.4	0.4388
	SD	1.47	----		2.32	1.84		2.15	1.84	

[a] P-value is based on the difference between CXL and Control using a 2-sided t-test. Per the SAP, while p-values are reported for all visits, the only one reported in this table that was used for statistical inference was the analysis of Month 12 (alpha=0.049 due to the unplanned analysis at Month 3).

[b] Four subjects in the CXL group of UVX-003 did not have data for the primary (study) eye at baseline.

*Corneal ectasia subjects only

6.6.2.3. Sensitivity Analyses Support Primary Efficacy Results

In support of the clinical efficacy results presented in NDA 203-324, Avedro conducted additional statistical analyses. The sensitivity analyses explored the bounds of the treatment effect at 1 year based on a variety of different assumptions which included mixed-effects regression models based on linear, log-linear, and nonparametric time trends. The analyses were robust, consistent and support the primary efficacy analyses (Appendix 6).

Among patients with corneal ectasia, the log-linear model provided the best fit of pooled results (BIC= 2650.55). After one year, there was a 1.65 D magnitude in treatment difference between the CXL and control groups (SE= 0.34, p<0.0001). An analysis of site-specific time trends showed that the overall variability was about 22%; though there was little variability at baseline and some variability in terms of rate of change, the estimated magnitude of treatment effect was consistent across all sites. In a between subjects analysis among the CXL group, a linear model was the best fit with a 2.43 D effect at 1 year (SE=0.58, p<0.0001). In a within subject analysis among control subjects who crossed over to receive treatment in the primary eye, a log-linear model was the best fit with an estimated 1.10 D within subject effect (SE=0.45, p=0.0159). Lastly, in a within subject analysis comparing control subjects for treated and untreated eyes, a linear model was the best fit with an estimated 2.63 D treatment effect (SE=1.30, p=0.044) at 1 year.

6.6.3. Distribution of Change from Baseline K_{max} in the Randomized Eye

6.6.3.1. LOCF

Table 19 presents the categorical distribution of change from baseline K_{max} (LOCF) in randomized CXL eyes for UVX-001, UVX-003, and the pooled studies.

UVX-001 (Corneal Ectasia Subjects Only)

The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 45.8% (11/24) at Month 3; 62.5% (15/24) at Month 6; and 70.8% (17/24) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} was 12.5% (3/24) at Month 3, 37.5% (9/24) at Month 6, and 41.7% (10/24) at Month 12.

UVX-003

The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 46.0% (29/63) at Month 3; 52.4% (33/63) at Month 6; and 58.7% (37/63) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} was 27.0% (17/63) at Month 3, 27.0% (17/63) at Month 6, and 28.6% (18/63) at Month 12.

The proportion of CXL subjects who showed no change or had any worsening in K_{max} progressively decreased over time, ranging from 53.9% at Month 3 to 41.3% at Month 12.

Pooled

In the pooled studies, the proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 46.0% (40/87) at Month 3; 55.2% (48/87) at Month 6; and 62.1% (54/87) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e.,

improvement) from baseline K_{max} was 23.0% (20/87) at Month 3, 29.9% (26/87) at Month 6, and 32.2% (28/87) at Month 12.

Figure 16 presents the categorical distribution of change from baseline K_{max} (LOCF) in randomized CXL eyes for the UVX-001 corneal ectasia data pooled with the UVX-003 data at Month 12. 62% of subjects who received cross-linking experienced stopping of progression (no change) or improvement by Month 12. In a patient population struggling with a progressive sight threatening disease, this result is profoundly meaningful.

Figure 16: Distribution of Change from Baseline K_{max} in Randomized CXL Eyes (ITT Population, LOCF) at 12 Months: Pooled UVX-001 and UVX-003

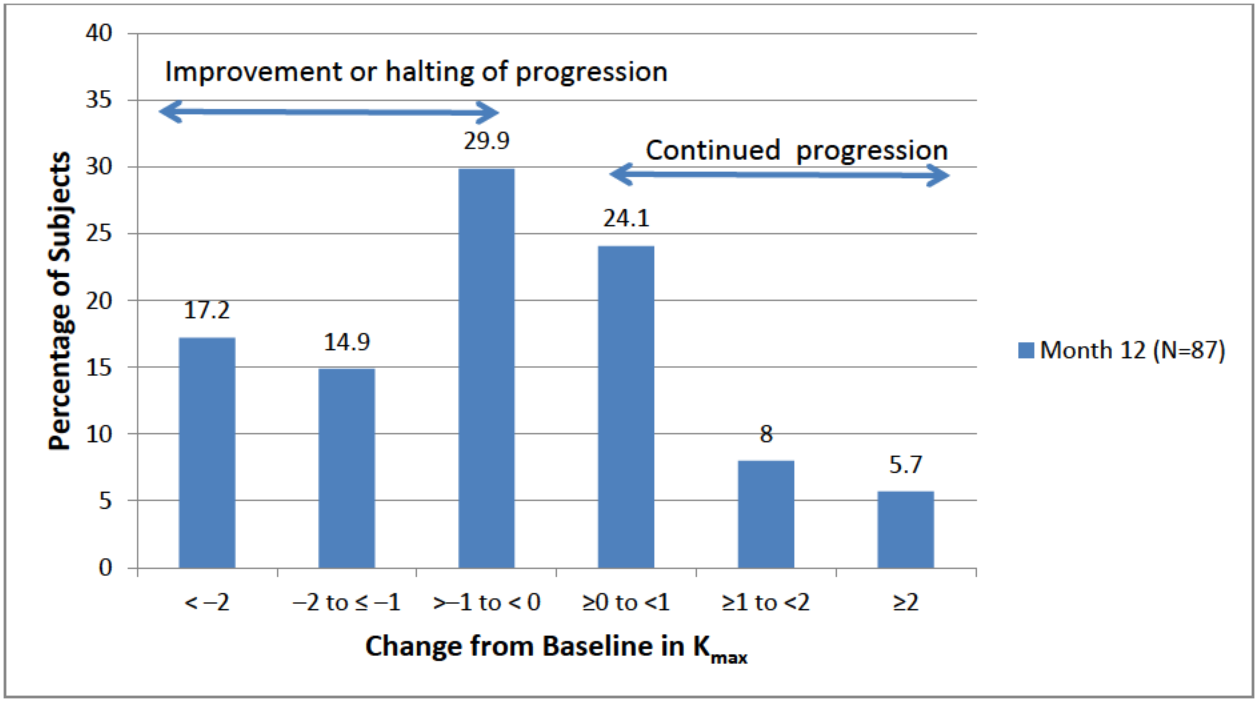


Table 19: Distribution of Change from Baseline in K_{max} in Randomized CXL Eyes (ITT Population, LOCF): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

	Change from Baseline in K_{max}											
	< –2		–2 to ≤ –1		>–1 to < 0		≥0 to <1		≥1 to <2		≥2	
Visit	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
UVX-001*												
Month 1 (N=24)	1	4.2	1	4.2	1	4.2	10	41.7	6	25.0	5	20.8
Month 3 (N=24)	1	4.2	2	8.3	8	33.3	7	29.2	4	16.7	2	8.3
Month 6 (N=24)	4	16.7	5	20.8	6	25.0	6	25.0	2	8.3	1	4.2
Month 12 (N=24)	7	29.2	3	12.5	7	29.2	5	20.8	1	4.2	1	4.2
UVX-003												
Month 1 (N=63)	3	4.8	2	3.2	12	19.0	16	25.4	14	22.2	16	25.4
Month 3 (N=63)	10	15.9	7	11.1	12	19.0	23	36.5	5	7.9	6	9.5
Month 6 (N=63)	8	12.7	9	14.3	16	25.4	23	36.5	4	6.3	3	4.8
Month 12 (N=63)	8	12.7	10	15.9	19	30.2	16	25.4	6	9.5	4	6.3
Pooled Studies												
Month 1 (N=87)	4	4.6	3	3.4	13	14.9	26	29.9	20	23.0	21	24.1
Month 3 (N=87)	11	12.6	9	10.3	20	23.0	30	34.5	9	10.3	8	9.2
Month 6 (N=87)	12	13.8	14	16.1	22	25.3	29	33.3	6	6.9	4	4.6
Month 12 (N=87)	15	17.2	13	14.9	26	29.9	21	24.1	7	8.0	5	5.7

*Corneal ectasia subjects only

6.6.3.2. Observed Case Analysis

Table 20 presents the categorical distribution of change from baseline K_{max} in randomized CXL eyes using observed case data for UVX-001, UVX-003, and the pooled studies.

UVX-001 (Corneal Ectasia Subjects Only)

The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 47.8% (11/23) at Month 3; 68.2% (15/22) at Month 6; and 80.0% (16/20) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} was 13.0% (3/23) at Month 3, 40.9% (9/22) at Month 6, and 50.0% (10/20) at Month 12.

Since K_{max} is expected to increase over time in subjects with corneal ectasia, stopping progression is considered to be a clinically meaningful outcome.

UVX-003

The proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 45.2% (28/62) at Month 3; 52.5% (31/59) at Month 6; and 59.3% (32/54) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} was 25.8% (16/62) at Month 3, 27.1% (16/59) at Month 6, and 27.8% (15/54) at Month 12.

Pooled

Figure 17 presents the categorical distribution of change from baseline K_{max} in randomized CXL eyes using observed case data for the UVX-001 corneal ectasia data pooled with the UVX-003 data at Month 12.

In the pooled studies, the proportion of CXL subjects who had any improvement in K_{max} progressively increased over time: 45.9% (39/85) at Month 3; 56.8% (46/81) at Month 6; and 64.9% (48/74) at Month 12. The proportion of CXL subjects with a ≥1 D decrease (i.e., improvement) from baseline K_{max} was 22.4% (19/85) at Month 3, 30.9% (25/81) at Month 6, and 33.8% (25/74) at Month 12.

The proportion of CXL subjects who showed no change or had any worsening in K_{max} progressively decreased over time, ranging from 54.1% at Month 3 to 35.1% at Month 12.

Figure 17: Distribution of Change from Baseline K_{max} in Randomized CXL Eyes (ITT Population, Observed) at 12 Months: Pooled UVX-001 and UVX-003

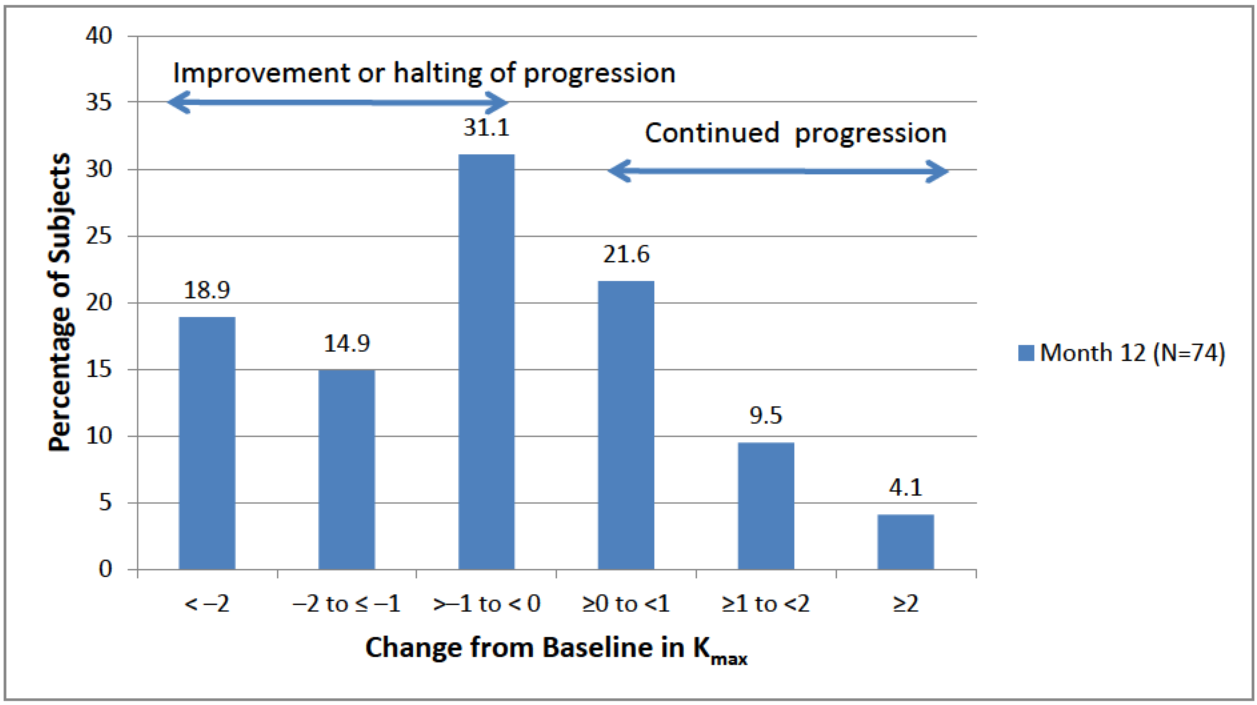


Table 20: Distribution of Change from Baseline in K_{max} in Randomized CXL Eyes (ITT Population, Observed Values): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

	Change from Baseline in K_{max}											
	< –2		–2 to ≤ –1		>–1 to < 0		≥0 to <1		≥1 to <2		≥2	
Visit	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
UVX-001*												
Month 1 (N=24)	1	4.2	1	4.2	1	4.2	10	41.7	6	25.0	5	20.8
Month 3 (N=23)	1	4.3	2	8.7	8	34.8	7	30.4	3	13.0	2	8.7
Month 6 (N=22)	4	18.2	5	22.7	6	27.3	5	22.7	2	9.1	0	0
Month 12 (N=20)	7	35.0	3	15.0	6	30.0	3	15.0	1	5.0	0	0
UVX-003												
Month 1 (N=60)	3	5.0	2	3.3	12	20.0	13	21.7	14	23.3	16	26.7
Month 3 (N=62)	9	14.5	7	11.3	12	19.4	23	37.1	5	8.1	6	9.7
Month 6 (N=59)	7	11.9	9	15.3	15	25.4	22	37.3	4	6.8	2	3.4
Month 12 (N=54)	7	13.0	8	14.8	17	31.5	13	24.1	6	11.1	3	5.6
Pooled Studies												
Month 1 (N=84)	4	4.8	3	3.6	13	15.5	23	27.4	20	23.8	21	25.0
Month 3 (N=85)	10	11.8	9	10.6	20	23.5	30	35.3	8	9.4	8	9.4
Month 6 (N=81)	11	13.6	14	17.3	21	25.9	27	33.3	6	7.4	2	2.5
Month 12 (N=74)	14	18.9	11	14.9	23	31.1	16	21.6	7	9.5	3	4.1

*Corneal ectasia subjects only

6.6.4. Mean Changes from Baseline K_{max} With and Without Dextran in the Riboflavin Solution

Subjects in the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed. Subjects then received riboflavin ophthalmic solution with dextran in the study eye for 30 minutes. If corneal thickness was < 400 microns in eyes in the CXL group after treatment with riboflavin ophthalmic solution with dextran, a second solution was instilled into the study eye: riboflavin without dextran.

Subjects in the sham treatment group had topical anesthetic administered to the study eye but did not have the corneal epithelium removed. Study eyes were treated with riboflavin ophthalmic solution as described above.

6.6.4.1. Observed Case Analysis

For subjects who received riboflavin with dextran, mean K_{max} at baseline was comparable between treatment groups in UVX-001 and UVX-003. After CXL treatment, mean K_{max} values increased from baseline to Month 3 and then decreased from baseline to Months 6 and 12 in each study. In comparison, in the control group, mean K_{max} increased from baseline at Months 1, 3, and 6, indicative of a worsening in K_{max}. The difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor of CXL, at Month 6 (difference of 2.5 D, p=0.0007) in UVX-001 only.

For subjects who received riboflavin with dextran followed by riboflavin without dextran, mean K_{max} at baseline was generally comparable between treatment groups in each study. After CXL treatment, mean K_{max} values decreased from baseline to Months 3, 6, and 12 in each study. In comparison, in the control group, mean K_{max} increased from baseline at Months 1, 3, and 6. In both studies, the difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor of CXL, at Month 3 (UVX-001: difference of 1.4 D, p=0.0515; UVX-003: difference of 1.2 D, p=0.0090). The difference also was ≥ 1.0 D at Month 6 in UVX-001 (difference of 2.2 D, p=0.0249).

Similar results were generally observed in the pooled studies (Table 21). For subjects who received riboflavin with dextran, mean K_{max} at baseline was 54.8 D in each treatment group. After CXL treatment, mean K_{max} values increased from baseline at Month 1 (1.1 D) and Month 3 (0.4 D), and then decreased from baseline at Month 6 (–0.5 D) and Month 12 (–0.8 D). In comparison, in the control group, mean K_{max} increased from baseline at Month 1 (N=86, 0.3 D), Month 3 (N=85, 0.7 D), and Month 6 (N=32, 0.7 D), indicative of a worsening in K_{max}. The difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor of CXL, at Month 6 (difference of 1.2 D, p=0.0185).

For subjects in the pooled studies who received riboflavin with dextran followed by riboflavin without dextran, mean K_{max} at baseline was 55.9 D in the CXL group and 54.8 D in the control group (Table 21). After CXL treatment, mean K_{max} values increased from baseline at Month 1 (1.0 D) and then progressively decreased from baseline at Month 3 (–0.5 D), Month 6 (–0.7 D), and Month 12 (–0.8 D). In comparison, in the control group, mean K_{max} increased from baseline at Month 1 (N=86, 0.3 D), Month 3 (N=85, 0.7 D), and Month 6 (N=32, 0.7 D). The difference in mean changes from baseline K_{max} between the CXL and control groups was ≥ 1.0 D, in favor

of CXL, at Month 3 (difference of 1.2 D, p=0.0010) and Month 6 (difference of 1.4 D, p=0.0078).

Table 21: Mean Changes from Baseline K_{max} in the Randomized Study Eye by Use of Riboflavin with and without Dextran (ITT Population, Observed Values): Pooled UVX-001 and UVX-003

		Riboflavin with Dextran			Riboflavin with Dextran Followed by Riboflavin Without Dextran		
Visit	**Statistic**	**CXL (N=38)**	**Control (N=88)**	**P-value[a]**	**CXL (N=53)[b]**	**Control (N=88)[c]**	**P-value**
Baseline	N	38	88		49	88	
	Mean	54.8	54.8		55.9	54.8	
	SD	6.15	6.40		7.39	6.40	
Month 1	N	38	86		46	86	
	Mean Change from Baseline	1.1	0.3	0.0100	1.0	0.3	0.0069
	SD	2.10	1.36		1.77	1.36	
Month 3	N	36	85		49	85	
	Mean Change from Baseline	0.4	0.7	0.3718	–0.5	0.7	0.0010
	SD	1.97	1.82		2.20	1.82	
Month 6	N	33	32		48	32	
	Mean Change from Baseline	–0.5	0.7	0.0185	–0.7	0.7	0.0078
	SD	1.28	2.47		1.93	2.47	
Month 12	N	32	2		42	2	
	Mean Change from Baseline	–0.8	0.4	0.4190	–0.8	0.4	0.4684
	SD	1.98	1.84		2.28	1.84	

[a] P-value is based on the difference between CXL and Control using a 2-sided t-test. Per the SAP, while p-values are reported for all visits, the only one reported in this table that was used for statistical inference was the analysis of Month 12 (alpha=0.049 due to the unplanned analysis at Month 3).
[b] Four subjects did not have a K_{max} measurement at baseline.
[c] Per protocol, none of the subjects in the control group received riboflavin with dextran followed by riboflavin without dextran in the primary (study) eye on Day 0. Therefore, the riboflavin with dextran only data were used for the control group in this analysis.

6.6.5. Improvements in Visual Acuity

These studies showed that CXL subject experienced greater improvements in visual acuity over control subjects.

6.6.5.1. Mean change from baseline BSCVA

6.6.5.1.1. LOCF Analysis

Table 22 summarizes mean changes from baseline in BSCVA in the randomized eye using LOCF for UVX-001, UVX-003, and the pooled studies.

UVX-001 (Corneal Ectasia Subjects) and UVX-003

In both studies, mean BSCVA was generally comparable between treatment groups at baseline. In UVX-001, the mean change from baseline ranged from -0.5 letters to 5.9 letters in the CXL group and from –0.9 to 0.2 letters in the control group; in UVX-003, values ranged from -1.9 letters to 5.0 letters in the CXL group and from –0.2 to 0.5 letters in the control group. In UVX-001, the mean change from baseline in BSCVA was 5.9 letters in the CXL group and –0.9 letters in the control group at Month 6 (p=0.0086); in UVX-003, these values were 3.4 letters in the CXL group and –0.2 letters in the control group (p=0.0300). In both studies, the difference between treatments in mean change from baseline in BSCVA at Month 12 was statistically significant (UVX-001: 5.0 letters vs. –0.9 letters, p=0.0184; UVX-003: 5.0 letters vs. –0.1 letters, p=0.0014).

Pooled

In the pooled studies, mean BSCVA was comparable between treatment groups at baseline. The mean change from baseline ranged from -1.6 letters to 5.0 letters in the CXL group and from –0.4 to 0.5 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 4.0 letters in the CXL group versus –0.4 letters in the control group (p=0.0014). At Month 12, the mean change from baseline in BSCVA was 5.0 letters and –0.3 letters in the CXL and control groups, respectively; this difference between treatments was statistically significant (p<0.0001).

Table 22: Best Spectacle-Corrected Visual Acuity (ETDRS Letters Read) in the Randomized Eye (ITT Population, LOCF): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

		UVX-001*		UVX-003		Pooled Studies	
Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=91)	Control Group (N=88)
Baseline	N	24	25	67	63	91	88
	Mean	37.7	34.5	36.7	39.5	37.0	38.1
	SD	11.31	13.28	13.66	11.90	13.03	12.44
Month 1	N	24	25	67	63	91	88
	Mean Change from Baseline	–0.5	0.1	–1.9	0.7	–1.6	0.5
	SD	9.44	6.74	9.87	9.52	9.73	8.79
Month 3	N	24		67	63	91	88
	Mean Change from Baseline	5.9	0.2	2.1	0.5	3.1	0.4
	SD	9.01	6.98	8.95	9.63	9.07	8.92
Month 6	N	24	25	67	63	91	88
	Mean Change from Baseline	5.9	–0.9	3.4	–0.2	4.0	–0.4
	SD	10.45	6.37	9.03	9.64	9.43	8.81
Month 12	N	24	25	67	63	91	88
	Mean Change from Baseline	5.0	–0.9	5.0	–0.1	5.0	–0.3
	SD	10.23	6.37	8.38	9.60	8.85	8.77

*Corneal ectasia subjects only

6.6.5.2. Observed Case Analysis

Table 23 summarizes mean changes from baseline in BSCVA in the randomized eye using observed values for UVX-001, UVX-003, and the pooled studies.

UVX-001 (Corneal Ectasia Subjects) and UVX-003

In UVX-001, the mean change from baseline in BSCVA ranged from -0.5 to 6.7 letters in the CXL group and from –1.8 to 0.2 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 6.7 letters in the CXL group and –1.8 letters in the control group (p=0.0124).

In UVX-003, the mean change from baseline in BSCVA ranged from -2.0 letters to 5.9 letters in the CXL group and from –1.5 to 0.8 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 3.8 letters in the CXL group and 0.6 letters in the control group (p=0.1854).

Pooled

In the pooled studies, mean BSCVA was comparable between treatment groups at baseline. The mean change from baseline in BSCVA ranged from -1.6 letters to 5.8 letters in the CXL group and from -1.5 to 0.6 letters in the control group. At Month 6, the mean change from baseline in BSCVA was 4.6 letters for the CXL group versus –0.4 letters in the control group (p=0.0101).

Table 23: Best Spectacle-Corrected Visual Acuity (ETDRS Letters Read) in the Randomized Eye (ITT Population, Observed Values): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

		UVX-001*		UVX-003		Pooled Studies	
Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=91)	Control Group (N=88)
Baseline	N	24	25	67	63	91	88
	Mean	37.7	34.5	36.7	39.5	37.0	38.1
	SD	11.31	13.28	13.66	11.90	13.03	12.44
Month 1	N	24	25	65	61	89	86
	Mean Change from Baseline	–0.5	0.1	–2.0	0.8	–1.6	0.6
	SD	9.44	6.74	10.02	9.64	9.84	8.86
Month 3	N	23	24	64	58	87	82
	Mean Change from Baseline	5.3	0.2	2.4	0.0	3.1	0.0
	SD	8.76	7.13	8.60	9.18	8.69	8.59
Month 6	N	22	13	61	18	83	31
	Mean Change from Baseline	6.7	–1.8	3.8	0.6	4.6	–0.4
	SD	10.25	6.93	9.16	8.20	9.48	7.66
Month 12	N	20	0	55	2	75	2
	Mean Change from Baseline	5.6	----	5.9	–1.5	5.8	–1.5
	SD	10.45	----	8.66	2.12	9.10	2.12

*Corneal ectasia subjects only

6.6.5.3. Categorical Changes from Baseline in BSCVA

6.6.5.3.1. LOCF Analysis

Table 24 summarizes categorical changes from baseline in BSCVA in the randomized eye using LOCF for UVX-001, UVX-003, and the pooled studies.

UVX-001 (Corneal Ectasia Subjects)

In UVX-001, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 73.9% (17/23) and 37.5% (9/24) in the CXL and control groups, respectively. At Month 12, these values were 69.6% and 37.5%, respectively. The proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group compared to the control group at Month 6 (30.4% vs. 4.2%) and Month 12 (21.7% vs. 4.2%).

UVX-003

In UVX-003, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 61.5% (40/65) and 45.2% (28/62) in the CXL and control groups, respectively. At Month 12, these values were 73.8% and 45.2%, respectively. The proportion of subjects with a ≥15-letter improvement in BSCVA was approximately 2-fold higher in the CXL group compared with the control group, both at Month 6 (10.8% vs. 4.8%) and Month 12 (9.2% vs. 4.8%).

In the pooled studies, the proportion of subjects who showed any improvement in BSCVA at Month 6 was 64.8% (57/88) and 43.0% (37/86) in the CXL and control groups, respectively. At Month 12, these values were 72.7% and 43.0%, respectively. The proportion of subjects with a ≥15-letter improvement in BSCVA was approximately 2-fold higher in the CXL group compared with the control group, both at Month 6 (15.9% vs. 4.7%) and Month 12 (12.5% vs. 4.7%).

Table 24: Categorical Changes from Baseline in Best Spectacle-Corrected Visual Acuity (ITT Population, LOCF): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

			UVX-001*		UVX-003		Pooled Studies	
Visit	**Category**		**CXL Group (N=24)**	**Control Group (N=25)**	**CXL Group (N=67)**	**Control Group (N=63)**	**CXL Group (N=91)**	**Control Group (N=88)**
Month 1	N		23	24	65	62	88	86
	Gain ≥ 15 letters	n (%)	1 (4.3)	1 (4.2)	2 (3.1)	4 (6.5)	3 (3.4)	5 (5.8)
	Gain of 10 to 14 letters	n (%)	2 (8.7)	1 (4.2)	6 (9.2)	1 (1.6)	8 (9.1)	2 (2.3)
	Gain of 5 to 9 letters	n (%)	5 (21.7)	3 (12.5)	8 (12.3)	7 (11.3)	13 (14.8)	10 (11.6)
	Gain of 1 to 4 letters	n (%)	1 (4.3)	5 (20.8)	8 (12.3)	16 (25.8)	9 (10.2)	21 (24.4)
	Loss of 0 to 4 letters	n (%)	5 (21.7)	7 (29.2)	20 (30.8)	23 (37.1)	25 (28.4)	30 (34.9)
	Loss of 5 to 9 letters	n (%)	5 (21.7)	5 (20.8)	6 (9.2)	7 (11.3)	11 (12.5)	12 (14.0)
	Loss of 10 to 14 letters	n (%)	2 (8.7)	2 (8.3)	7 (10.8)	1 (1.6)	9 (10.2)	3 (3.5)
	Loss ≥ 15 letters	n (%)	2 (8.7)	0	8 (12.3)	3 (4.8)	10 (11.4)	3 (3.5)
Month 3	N		23	24	65	62	88	86
	Gain ≥ 15 letters	n (%)	3 (13.0)	1 (4.2)	5 (7.7)	3 (4.8)	8 (9.1)	4 (4.7)
	Gain of 10 to 14 letters	n (%)	4 (17.4)	0	5 (7.7)	3 (4.8)	9 (10.2)	3 (3.5)
	Gain of 5 to 9 letters	n (%)	6 (26.1)	2 (8.3)	13 (20.0)	10 (16.1)	19 (21.6)	12 (14.0)
	Gain of 1 to 4 letters	n (%)	4 (17.4)	9 (37.5)	14 (21.5)	17 (27.4)	18 (20.5)	26 (30.2)
	Loss of 0 to 4 letters	n (%)	4 (17.4)	9 (37.5)	17 (26.2)	11 (17.7)	21 (23.9)	20 (23.3)
	Loss of 5 to 9 letters	n (%)	0	1 (4.2)	6 (9.2)	11 (17.7)	6 (6.8)	12 (14.0)
	Loss of 10 to 14 letters	n (%)	1 (4.3)	1 (4.2)	3 (4.6)	3 (4.8)	4 (4.5)	4 (4.7)
	Loss ≥ 15 letters	n (%)	1 (4.3)	1 (4.2)	2 (3.1)	4 (6.5)	3 (3.4)	5 (5.8)

Table 24: Categorical Changes from Baseline in Best Spectacle-Corrected Visual Acuity (ITT Population, LOCF): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003 (Continued)

			UVX-001*		UVX-003		Pooled Studies	
Visit	Category		CXL Group (N=24)	Control Group (N=25)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=91)	Control Group (N=88)
Month 6	N		23	24	65	62	88	86
	Gain ≥ 15 letters	n (%)	7 (30.4)	1 (4.2)	7 (10.8)	3 (4.8)	14 (15.9)	4 (4.7)
	Gain of 10 to 14 letters	n (%)	2 (8.7)	0	8 (12.3)	2 (3.2)	10 (11.4)	2 (2.3)
	Gain of 5 to 9 letters	n (%)	1 (4.3)	2 (8.3)	8 (12.3)	7 (11.3)	9 (10.2)	9 (10.5)
	Gain of 1 to 4 letters	n (%)	7 (30.4)	6 (25.0)	17 (26.2)	16 (25.8)	24 (27.3)	22 (25.6)
	Loss of 0 to 4 letters	n (%)	1 (4.3)	9 (37.5)	13 (20.0)	16 (25.8)	14 (15.9)	25 (29.1)
	Loss of 5 to 9 letters	n (%)	3 (13.0)	4 (16.7)	7 (10.8)	11 (17.7)	10 (11.4)	15 (17.4)
	Loss of 10 to 14 letters	n (%)	2 (8.7)	2 (8.3)	4 (6.2)	2 (3.2)	6 (6.8)	4 (4.7)
	Loss ≥ 15 letters	n (%)	0	0	1 (1.5)	5 (8.1)	1 (1.1)	5 (5.8)
Month 12	N		23	24	65	62	88	86
	Gain ≥ 15 letters	n (%)	5 (21.7)	1 (4.2)	6 (9.2)	3 (4.8)	11 (12.5)	4 (4.7)
	Gain of 10 to 14 letters	n (%)	3 (13.0)	0	11 (16.9)	2 (3.2)	14 (15.9)	2 (2.3)
	Gain of 5 to 9 letters	n (%)	3 (13.0)	2 (8.3)	15 (23.1)	7 (11.3)	18 (20.5)	9 (10.5)
	Gain of 1 to 4 letters	n (%)	5 (21.7)	6 (25.0)	16 (24.6)	16 (25.8)	21 (23.9)	22 (25.6)
	Loss of 0 to 4 letters	n (%)	2 (8.7)	9 (37.5)	11 (16.9)	17 (27.4)	13 (14.8)	26 (30.2)
	Loss of 5 to 9 letters	n (%)	3 (13.0)	4 (16.7)	4 (6.2)	10 (16.1)	7 (8.0)	14 (16.3)
	Loss of 10 to 14 letters	n (%)	1 (4.3)	2 (8.3)	0	2 (3.2)	1 (1.1)	4 (4.7)
	Loss ≥ 15 letters	n (%)	1 (4.3)	0	2 (3.1)	5 (8.1)	3 (3.4)	5 (5.8)

*Corneal ectasia subjects only

6.6.6. Efficacy in Corneal Ectasia Following Refractive Surgery – Conclusions

CXL treatment provided statistically significant and clinically meaningful improvements in K_{max} in subjects with corneal ectasia following refractive surgery. The data from the individual studies (UVX-001 and UVX-003) as well as the pooled corneal ectasia population (UVX-001 + UVX-003) met the primary efficacy endpoint (i.e., a difference of ≥1 D in mean change from baseline in K_{max} between the CXL and control groups at Month 12 LOCF). The mean changes in K_{max} from baseline to Month 12 in the CXL group versus the control group, respectively, were –1.0 D vs. 1.0 D (p=0.0001) in UVX-001, –0.5 D vs. 0.5 D (p=0.0080) in UVX-003, and -0.7 D vs. 0.7 D (p<0.0001) in the pooled corneal ectasia population.

Analysis of the observed case K_{max} data provides added support for the effectiveness of CXL in subjects with corneal ectasia. At Month 6, there was a demonstrated difference between treatment groups in favor of the CXL group. The mean changes in K_{max} from baseline to Month 6 in the CXL group versus the control group, respectively, were –0.8 D vs. 1.6 D (p=0.0002) in UVX-001, –0.5 D vs. 0.1 D (p=0.2901) in UVX-003, and -0.6 D vs. 0.7 D (p=0.0021) in the pooled corneal ectasia population. At Month 12, despite the lack of observed case data in the control arm, an absolute decrease from baseline of -1.4 D in K_{max} was seen in the CXL arm alone in Study UVX-001.

The effectiveness of the CXL treatment in subjects with corneal ectasia was also established when considering the proportion of subjects who had a decrease of 1 D or greater in K_{max} from baseline to Month 12. CXL was effective in stopping or reversing disease progression in over 60% of the corneal ectasia subjects. The proportion of corneal ectasia subjects in the CXL group with either stabilization or improvement in K_{max} over baseline increased over time, reaching approximately 60% (71% in UVX-001, 59% in UVX-003 and 62% pooled) at Month 12. This result is clinically meaningful for ectasia patients.

In addition to the improvements in K_{max}, meaningful improvements in BSCVA were observed in this patient population following treatment with CXL. Mean change from baseline in BSCVA showed an improvement in the CXL group (5.0 letters) compared to a slight worsening in the control group (-0.3 letters) at Month 12 (p<0.0001) (LOCF) in the pooled analysis, and the proportion of subjects with a ≥15-letter (3 lines or greater) improvement in BSCVA was more than 2-fold higher in the CXL group compared to the control group (Month 12, 12.5% vs. 4.7%). The proportion of subjects who showed any improvement in BSCVA at Month 12 was 72.7% in the CXL group and 43.0% in the control group.

The efficacy results of fellow eyes treated with CXL is similar to that seen in the randomized study eyes (Appendix 1).

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6.7. Safety of Corneal Cross-linking – Primary Study Eyes

6.7.1. Summary

The UVX Phase III studies provide a substantial body of safety evidence supporting approval of corneal collagen cross-linking in subjects with progressive keratoconus, or corneal ectasia following refractive surgery.

The safety evaluation in the primary study eyes of progressive keratoconus subjects was based on the safety population which included all subjects enrolled into the study summarized according to the treatment actually received. In UVX-002, 2 subjects, 1 per treatment group, inadvertently received the incorrect randomized study treatment on Day 0. The safety population consisted of 205 subjects (102, CXL group, 103, control group) and 205 eyes.

The safety evaluation in the primary study eyes of corneal ectasia subjects was based on the ITT/Safety population which consisted of 179 subjects (91, CXL group; 88, control group) and 179 primary study eyes.

For safety assessments, the results from UVX-002 were pooled with results for subjects with progressive keratoconus from UVX-001, and the results from UVX-003 were pooled with the results for subjects with corneal ectasia from UVX-001.

Study design called for CXL eyes to be followed for a period of 12 months. For both indications, the number of control eyes diminished between 3 and 12 months as eyes crossed-over for treatment.

The safety data of primary study eyes demonstrated that corneal collagen cross-linking was safe and well tolerated. Specifically:

- No subjects died or discontinued due to any AE
- From baseline to Month 3, the TEAEs in the CXL group were expected sequelae following corneal epithelial debridement
- TEAE's occurred in twice as many CXL subjects as compared to control due to the control group not being debrided. Findings are consistent with the expected time course of corneal healing.
- Most of the TEAEs were of mild or moderate intensity and resolved by Month 12
- CXL subjects did not experience a loss of visual acuity more frequently than control subjects.

6.7.2. Time Course of Adverse Events Reported in ≥2% of Subjects

6.7.2.1. Progressive Keratoconus

Table 25 summarizes TEAEs reported in ≥2% of the progressive keratoconus subjects in the CXL group.

The cumulative incidence of ocular TEAEs in the CXL group up to Month 3 was approximately twice that of the control group (84% vs. 38%). The increased numbers of TEAEs in the CXL

group were expected due to the corneal epithelial debridement performed in treatment group compared to no debridement in the control group. The most frequently reported ocular TEAEs were corneal opacity (haze)(57%), punctate keratitis (25%), corneal striae (24%) and corneal epithelium defect (23%), eye pain (17%), vision blurred (16%) and photophobia (11%).

The majority of events were mild to moderate in intensity and resolved by Month 12. These findings are consistent with corneal debridement and the expected time course of corneal healing.

Low rates of AE's occurred at months 6, 9 and 12. Corneal opacity (haze) (4%) punctate keratitis (2%) and corneal scar (2%) were reported in subjects in the CXL group at Month 12.

6.7.2.2. Corneal Ectasia

Table 26 summarizes TEAEs reported in ≥2% of the corneal ectasia subjects in the CXL group.

The cumulative incidence of ocular TEAEs in the CXL group up to Month 3 was approximately twice that of the control group (90% vs. 38%). The increased numbers of TEAEs in the CXL group were expected due to the corneal epithelial debridement compared to no debridement in the control group. The most frequently reported ocular TEAEs were corneal opacity (haze)(68%), corneal epithelium defect (26%), eye pain (26%), punctate keratitis (20%), photophobia (19%), vision blurred (17%), dry eye (14%), and visual acuity reduced (11%).

The majority of events were mild to moderate in intensity and resolved by Month 12. These findings are consistent with corneal debridement and the expected time course of corneal healing.

Low rates of AE's occurred at months 6, 9 and 12. Visual acuity reduced (4%) and corneal scar (2%) did not resolve by the last study visit for subjects in the CXL group.

Table 25: Time Course of Adverse Events Reported by ≥2% of Subjects in Progressive Keratoconus Subjects (Safety Population)

	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group
MedDRA System Organ Class/ Preferred Term	**Baseline to Month 3**		**Month 6**		**Month 9**		**Month 12**	
Number (%) of Subjects Reporting Any AEs[a]	336:87 (85.3%)	75:44 (42.7%)	21:15 (14.7%)	11:9 (8.7%)	11:9 (8.8%)	1:1 (1.0%)	15:11 (10.8%)	0
Eye Disorders	304:86 (84.3%)	59:40 (38.8%)	13:10 (9.8%)	8:7 (6.8%)	9:8 (7.8%)	1:1 (1.0%)	12:9 (8.8%)	0
Corneal opacity	73:58 (56.9%)	4:4 (3.9%)	4:4 (3.9%)	1:1 (1.0%)	3:3 (2.9%)	0	4:4 (3.9%)	0
Punctate keratitis	28:25 (24.5%)	8:8 (7.8%)	--	--	2:2 (2.0%)	0	2:2 (2.0%)	0
Corneal striae	25:24 (23.5%)	12:12 (11.7%)	2:2 (2.0%)	0	--	--	--	--
Corneal epithelium defect	26:23 (22.5%)	1:1 (1.0%)	--	--	--	--	--	--
Eye pain	17:17 (16.7%)	3:3 (2.9%)	--	--	--	--	--	--
Vision blurred	19:16 (15.7%)	2:2 (1.9%)	--	--	--	--	--	--
Photophobia	11:11 (10.8%)	0	--	--	--	--	--	--
Conjunctival hyperaemia	10:10 (9.8%)	1:1 (1.0%)	--	--	--	--	--	--
Eye irritation	10:10 (9.8%)	1:1 (1.0%)	--	--	--	--	--	--
Visual acuity reduced	10:10 (9.8%)	11:9 (8.7%)	1:1 (1.0%)	3:3 (2.9%)	--	--	--	--
Eye oedema	7:7 (6.9%)	0	--	--	--	--	--	--
Dry eye	7:6 (5.9%)	2:2 (1.9%)	--	--	--	--	--	--
Eyelid oedema	5:5 (4.9%)	0	--	--	--	--	--	--
Foreign body sensation in eyes	5:5 (4.9%)	0	--	--	--	--	--	--
Lacrimation increased	5:5 (4.9%)	0	--	--	--	--	--	--
Anterior chamber flare	4:4 (3.9%)	0	--	--	--	--	--	--
Glare	4:4 (3.9%)	1:1 (1.0%)	--	--	--	--	--	--
Ocular hyperaemia	4:4 (3.9%)	1:1 (1.0%)	--	--	--	--	--	--
Corneal disorder	3:3 (2.9%)	1:1 (1.0%)	--	--	--	--	--	--
Corneal oedema	3:3 (2.9%)	0	--	--	--	--	--	--
Visual impairment	3:3 (2.9%)	2:2 (1.9%)	--	--	--	--	--	--

Table 25: Time Course of Adverse Events Reported by ≥2% of Subjects in Progressive Keratoconus Subjects (Safety Population) (Continued)

	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group
MedDRA System Organ Class/ Preferred Term	**Baseline to Month 3**		**Month 6**		**Month 9**		**Month 12**	
Anterior chamber cell	2:2 (2.0%)	0	--	--	--	--	--	--
Diplopia	2:2 (2.0%)	1:1 (1.0%)	--	--	--	--	--	--
Eye discharge	2:2 (2.0%)	1:1 (1.0%)	--	--	--	--	--	--
Eye Pruritus	2:2 (2.0%)	0	--	--	--	--	--	--
Vitreous detachment	2:2 (2.0%)	0	--	--	--	--	--	--
Corneal scar	9:7 (6.9%)	5:5 (4.9%)	4:3 (2.9%)	0	2:2 (2.0%)	0	2:2 (2.0%)	0
Eye complication associated with device	2:2 (2.0%)	0	--	--	--	--	--	--
Non-Ocular TEAEs				--	--	--	--	--
Headache	4:4 (3.9%)	0	--	--	--	--	--	--
Nasopharyngitis	2:2 (2.0%)	1:1 (1.0%)	--	--	--	--	--	--

Statistics displayed are number of events:number of subjects (percent of subjects at risk). At each level of summarization, subjects reporting more than 1 event are only counted once.
Note: Ocular events in the fellow eye are excluded

Table 26: Time Course of Adverse Events Reported by ≥2% of Subjects in Corneal Ectasia Subjects (Safety Population)

	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group
MedDRA System Organ Class/ Preferred Term	**Baseline to Month 3**		**Month 6**		**Month 9**		**Month 12**	
Number (%) of Subjects Reporting Any AEs[a]	328:82 (90.1%)	66:38 (43.2%)	29:20 (22.0%)	9:7 (8.0%)	11:8 (8.8%)	1:1 (1.1%)	15:11 (12.1%)	0
Eye Disorders	296:82 (90.1%)	53:33 (37.5%)	24:19 (20.9%)	9:7 (8.0%)	10:8 (8.8%)	1:1 (1.1%)	11:9 (9.9%)	0
Corneal opacity	74:62 (68.1%)	7:7 (8.0%)	8:7 (7.7%)	1:1 (1.1%)	3:3 (3.3%)	0	--	--
Corneal epithelium defect	31:24 (26.4%)	3:3 (3.4%)	--	--	--	--	--	--
Eye pain	29:24 (26.4%)	0	--	--	--	--	--	--
Punctate keratitis	18:18 (19.8%)	4:3 (3.4%)	--	--	2:2 (2.2%)	0	--	--
Photophobia	18:17 (18.7%)	0	--	--	--	--	--	--
Vision blurred	15:15 (16.5%)	4:4 (4.5%)	2:2 (2.2%)	1:1 (1.1%)	--	--	--	--
Dry eye	14:13 (14.3%)	4:4 (4.5%)	2:2 (2.2%)	0	--	--	--	--
Visual acuity reduced	10:10 (11.0%)	1:1 (1.1%)	5:5 (5.5%)	2:2 (2.3%)	--	--	4:4 (4.4%)	0
Lacrimation increased	9:9 (9.9%)	1:1 (1.1%)	--	--	--	--	--	--
Corneal striae	9:8 (8.8%)	6:6 (6.8%)	--	--	--	--	--	--
Eye irritation	8:8 (8.8%)	1:1 (1.1%)	--	--	--	--	--	--
Ocular discomfort	8:8 (8.8%)	0	--	--	--	--	--	--
Anterior chamber flare	5:5 (5.5%)	2:2 (2.3%)	--	--	--	--	--	--
Eyelid oedema	5:5 (5.5%)	1:1 (1.1%)	--	--	--	--	--	--
Foreign body sensation in eyes	5:5 (5.5%)	1:1 (1.1%)	--	--	--	--	--	--
Conjunctival hyperaemia	4:4 (4.4%)	3:3 (3.4%)	--	--	--	--	--	--
Visual impairment	4:4 (4.4%)	1:1 (1.1%)	--	--	--	--	--	--
Corneal disorder	3:3 (3.3%)	0	--	--	--	--	--	--
Corneal oedema	3:3 (3.3%)	0	--	--	--	--	--	--
Keratitis	3:3 (3.3%)	0	--	--	--	--	--	--
Meibomian gland dys.	4:3 (3.3%)	2:2 (2.3%)	--	--	--	--	--	--
Ocular hyperaemia	3:3 (3.3%)	1:1 (1.1%)	--	--	--	--	--	--

Table 26: Time Course of Adverse Events Reported by ≥2% of Subjects in Corneal Ectasia Subjects (Safety Population) (Continued)

	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Month 6**		**Month 9**		**Month 12**	
Corneal scar	3:3 (3.3%)	1:1 (1.1%)	--	--	--	--	2:2 (2.2%)	0
Anterior chamber cell	2:2 (2.2%)	1:1 (1.1%)	--	--	--	--	--	--
Asthenopia	2:2 (2.2%)	0	--	--	--	--	--	--
Glare	2:2 (2.2%)	0	--	--	--	--	--	--
Halo vision	2:2 (2.2%)	0	--	--	--	--	--	--
Corneal abrasion	2:2 (2.2%)	0	--	--	--	--	--	--
Non-ocular TEAEs								
Headache	7:7 (7.7%)	4:3 (3.4%)						
Dizziness	2:2 (2.2%)	0						

Statistics displayed are number of events:number of subjects (percent of subjects at risk). At each level of summarization, subjects reporting more than 1 event are only counted once.
Note: Ocular events in the fellow eye are excluded.

6.7.3. Serious Adverse Events

No subjects died or prematurely discontinued the study due to any AE.

Table 27 lists SAEs experienced by subjects with progressive keratoconus. Three subjects in the control group experienced an SAE. None were ocular related and all resolved. One subject treated with cross-linking experienced an ocular SAE which resolved. Subject 02206 (control group) was a 19-year-old Caucasian, non-Hispanic male who received sham treatment OS (14 July 2008) and subsequently received CXL treatment OU at the Month 6 follow-up visit (19 December 2008). He developed ulcerative keratitis (verbatim: corneal ulcer) (OS) with onset 3 days after receiving CXL treatment. The investigator considered this event to be non-serious and of moderate intensity. The ulcerative keratitis persisted. On 05 January 2009, the investigator considered this event to be of severe intensity and serious. The investigator applied a pressure patch and treated the condition with zymar, fortified vancomycin, Pred Forte, bacitracin, doxycycline, and Refresh. The ulcerative keratitis resolved on 27 May 2009. The investigator considered this TEAE to be not related to riboflavin or UVA light and definitely related to epithelial defect.

Table 28 contains SAE's experienced by subjects with corneal ectasia. Two SAE's were reported, of which, 1 subject experienced an ocular SAE. Subject 04308 (CXL group) was a 47-year-old Caucasian, non-Hispanic male who developed corneal epithelium defect (verbatim: epithelial growth OS) in the randomized eye on Day 35 that the Investigator considered to be of moderate intensity, not related to riboflavin or UVA light and related to epithelial defect. The LASIK flap was lifted to remove the epithelial growth. The outcome of this SAE was resolved on Day 43. No other SAEs were reported at any time during the study.

Table 27: Serious Adverse Events (Safety Population: Progressive Keratoconus)

Treatment Group	Subject	Start-End (day)	System Organ Class (Preferred Term)	Intensity	Relationship to: Riboflavin	Relationship to: UVA Light	Relationship to: Epithelium Defect	Outcome	Study Medication Permanently Discontinued	Event Site	Study Eye
Control	00211	26-26	Psychiatric disorders (Suicide attempt)	Severe	None	None	None	Resolved	No		OD
		72-72	Psychiatric disorders (Suicide attempt)	Severe	None	None	None	Resolved	No		OD
Cross-over to CXL	02206	3-159	Eye disorders (ulcerative keratitis)	Severe	None	None	Related	Resolved	No	OS	OS
Control	08201	138-141	Infections and infestations (Appendicitis)	Moderate	Unlikely	Unlikely	Unlikely	Resolved	No		
Control	10211	235-238	Injury, poisoning and procedural complications (Infectious cat bite)	Severe	None	None	None	Resolved	No		

Table 28: Serious Adverse Events (Safety Population: Corneal Ectasia)

Treatment Group	Subject	Start-End Day	System Organ Class Preferred Term	Intensity	Relationship to: Riboflavin	Relationship to: UVA Light	Relationship to: Epithelium Defect	Outcome	Study Medication Permanently Discontinued	Event Site	Study Eye
CXL	04308	35-43	Eye disorders (Corneal epithelium defect)	Moderate	None	None	Related	Resolved	NO	OS	OS
Control	03203	34-	Injury, poisoning and procedural complications (Head injury)	Severe	None	None	None	Resolved	NO		OS

6.7.4. Adverse Events Reported from Baseline to Month 3 Summarized by Intensity

6.7.4.1. Progressive Keratoconus

Ocular TEAEs with an incidence ≥2% in the CXL group from baseline to Month 3 are summarized by maximum intensity in Table 29. The majority of the adverse events reported were considered by the investigator to be mild or moderate in intensity.

In the CXL group, the proportion of subjects who experienced at least 1 mild or moderate TEAE was 70.6% (vs. 38.8%, control) and 12.7% (vs. 2.9%, control), respectively. Two (2.7%) subjects in the CXL group and no subjects in the control group had a severe TEAE. TEAEs of severe intensity were corneal epithelium defect and photophobia, each occurred in 1 (1.0%) subject in the CXL group.

6.7.4.2. Corneal Ectasia

Ocular TEAEs with an incidence ≥2% in the CXL group from baseline to Month 3 are summarized by maximum intensity in Table 30. The majority of the adverse events reported were considered by the investigator to be mild or moderate in intensity.

In the CXL group, the proportion of subjects who experienced at least 1 mild or moderate TEAE was 74.7% (vs. 39.8%, control) and 15.4% (vs. 2.3 %, control), respectively. TEAEs of severe intensity were reported for no subjects in the CXL group and for 1 (1.1%) subject in the control group. This subject attempted suicide on two separate occasions and each event was deemed severe.

Table 29: Summary of Ocular Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 by Maximum Intensity (Safety Population: Keratoconus)

MedDRA Preferred Term[a]	Maximum Intensity[b]	CXL Group (N=102)	Control Group (N=103)
Corneal opacity	Mild	57 (55.9%)	4 (3.9%)
	Moderate	1 (1.0%)	0
Punctate keratitis	Mild	24 (23.5%)	8 (7.8%)
	Moderate	1 (1.0%)	0
Corneal striae	Mild	24 (23.5%)	12 (11.7%)
Corneal epithelium defect	Mild	22 (21.6%)	1 (1.0%)
	Severe	1 (1.0%)	0
Eye pain	Mild	14 (13.7%)	2 (1.9%)
	Moderate	3 (2.9%)	1 (1.0%)
Vision blurred	Mild	15 (14.7%)	2 (1.9%)
	Moderate	1 (1.0%)	0
Photophobia	Mild	10 (9.8%)	0
	Severe	1 (1.0%)	0
Conjunctival hyperaemia	Mild	10 (9.8%)	1 (1.0%)
Eye irritation	Mild	9 (8.8%)	1 (1.0%)
	Moderate	1 (1.0%)	0
Visual acuity reduced	Mild	9 (8.8%)	7 (6.8%)
	Moderate	1 (1.0%)	2 (1.9%)
Eye oedema	Mild	7 (6.9%)	0
Corneal scar	Mild	7 (6.9%)	5 (4.9%)
Dry eye	Mild	6 (5.9%)	2 (1.9%)
Eyelid oedema	Mild	5 (4.9%)	0
Foreign body sensation in eyes	Mild	4 (3.9%)	0
	Moderate	1 (1.0%)	0
Lacrimation increased	Mild	4 (3.9%)	0
	Moderate	1 (1.0%)	0
Anterior chamber flare	Mild	3 (2.9%)	0
	Moderate	1 (1.0%)	0
Glare	Mild	4 (3.9%)	1 (1.0%)
Ocular hyperaemia	Mild	3 (2.9%)	1 (1.0%)
	Moderate	1 (1.0%)	0
Corneal disorder	Mild	3 (2.9%)	1 (1.0%)

Table 29: Summary of Ocular Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 by Maximum Intensity (Safety Population: Keratoconus) (Continued)

MedDRA Preferred Term	Maximum Intensity	CXL Group (N=102)	Control Group (N=103)
Corneal oedema	Mild	3 (2.9%)	0
Visual impairment	Mild	3 (2.9%)	2 (1.9%)
Anterior chamber cell	Mild	2 (2.0%)	0
Diplopia	Mild	2 (2.0%)	1 (1.0%)
Eye discharge	Mild	2 (2.0%)	1 (1.0%)
Eye pruritus	Mild	2 (2.0%)	0
Vitreous detachment	Mild	1 (1.0%)	0
	Moderate	1 (1.0%)	0
Eye complication associated with device	Mild	1 (1.0%)	0
	Moderate	1 (1.0%)	0

[a] An intensity category is not shown if there were no observations in the category for the specific preferred term.
Note: Ocular events in the fellow eye are excluded.

Table 30: Summary of Ocular Adverse Events Reported with Incidence ≥2% from Baseline to Month 3 by Maximum Intensity (Safety Population: Corneal Ectasia)

MedDRA Preferred Term	Maximum Intensity[a]	CXL Group (N=91)	Control Group (N=88)
Corneal opacity	Mild	61 (67.0%)	7 (8.0%)
	Moderate	1 (1.1%)	0
Corneal epithelium defect	Mild	20 (22.0%)	3 (3.4%)
	Moderate	4 (4.4%)	0
Eye pain	Mild	21 (23.1%)	0
	Moderate	3 (3.3%)	0
Punctate keratitis	Mild	16 (17.6%)	3 (3.4%)
	Moderate	2 (2.2%)	0
Photophobia	Mild	16 (17.6%)	0
	Moderate	1 (1.1%)	0
Vision blurred	Mild	15 (16.5%)	4 (4.5%)
Dry eye	Mild	13 (14.3%)	4 (4.5%)
Visual acuity reduced	Mild	10 (11.0%)	1 (1.1%)
Lacrimation increased	Mild	7 (7.7%)	1 (1.1%)
	Moderate	2 (2.2%)	0
Corneal striae	Mild	8 (8.8%)	6 (6.8%)
Eye irritation	Mild	7 (7.7%)	1 (1.1%)
	Moderate	1 (1.1%)	0
Ocular discomfort	Mild	8 (8.8%)	0
Anterior chamber flare	Mild	5 (5.5%)	2 (2.3%)
Eyelid oedema	Mild	4 (4.4%)	1 (1.1%)
	Moderate	1 (1.1%)	0
Foreign body sensation in eyes	Mild	3 (3.3%)	1 (1.1%)
	Moderate	2 (2.2%)	0
Conjunctival hyperaemia	Mild	4 (4.4%)	3 (3.4%)
Visual impairment	Mild	4 (4.4%)	1 (1.1%)

Table 30: Summary of Ocular Adverse Events Reported with Incidence ≥2% from Baseline to Month 3 by Maximum Intensity (Safety Population: Corneal Ectasia) (Continued)

MedDRA Preferred Term	Maximum Intensity	CXL Group (N=91)	Control Group (N=88)
Corneal disorder	Mild	3 (3.3%)	0
Corneal oedema	Mild	3 (3.3%)	0
Keratitis	Mild	2 (2.2%)	0
Meibomian gland dysfunction	Mild	2 (2.2%)	2 (2.3%)
	Moderate	1 (1.1%)	0
Ocular hyperaemia	Mild	3 (3.3%)	1 (1.1%)
Corneal scar	Mild	3 (3.3%)	1 (1.1%)
Anterior chamber cell	Mild	2 (2.2%)	1 (1.1%)
Asthenopia	Mild	2 (2.2%)	0
Glare	Mild	2 (2.2%)	0
Halo vision	Mild	2 (2.2%)	0
Corneal abrasion	Mild	1 (1.1%)	0
	Moderate	1 (1.1%)	0

[a] An intensity category is not shown if there were no observations in the category for the specific preferred term.
Note: Ocular events in the fellow eye are excluded.

6.7.5. Adverse Events Reported from Baseline to Month 3 Summarized by Outcome

6.7.5.1. Progressive Keratoconus

Table 31 summarizes ocular TEAEs reported in ≥2% of subjects in the CXL group from baseline to Month 3 by outcome. Of the 86 subjects in the CXL group with any eye disorder during the controlled phase of the study, most subjects (70/86, 81.4%) had resolution of the event by the last Month 3 (versus 92.5% [37/40] in the control group). Most of the specific events listed in Table 31 resolved by Month 3. Corneal opacity (haze) did not resolve by Month 3 for 3/58 (5.2%) subjects in the CXL group.

6.7.5.2. Corneal Ectasia

Table 32 summarizes ocular TEAEs reported in ≥2% of subjects in the CXL group from baseline to Month 3 by outcome. Of the 82 subjects in the CXL group with any eye disorder during the controlled phase of the study, most subjects (67/82, 81.7%) had resolution of the event by Month 3 (versus 84.8% [28/33] in the control group). Most of the specific events listed in Table 32 resolved by Month 3. Corneal opacity (haze) did not resolve by the last study visit in 6/62 (9.7%) subjects in the CXL.

Table 31: Outcome for Ocular Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Keratoconus)

MedDRA Preferred Term[a]	Outcome	CXL Group (N=102)	Control Group (N=103)
Number of subjects with any AE	Resolved	67 (65.7%)	40 (38.8%)
	Ongoing	20 (19.6%)	4 (3.9%)
Eye disorders	Resolved	70 (68.6%)	37 (35.9%)
	Ongoing	16 (15.7%)	3 (2.9%)
Corneal opacity	Resolved	55 (53.9%)	4 (3.9%)
	Ongoing	3 (2.9%)	0
Punctate keratitis	Resolved	25 (24.5%)	8 (7.8%)
Corneal striae	Resolved	19 (18.6%)	11 (10.7%)
	Ongoing	5 (4.9%)	1 (1.0%)
Corneal epithelium defect	Resolved	21 (20.6%)	1 (1.0%)
	Ongoing	2 (2.0%)	0
Eye pain	Resolved	17 (16.7%)	3 (2.9%)
Vision blurred	Resolved	15 (14.7%)	2 (1.9%)
	Ongoing	1 (1.0%)	0
Photophobia	Resolved	8 (7.8%)	0
	Ongoing	3 (2.9%)	0
Conjunctival hyperaemia	Resolved	10 (9.8%)	1 (1.0%)
	Ongoing	2 (2.0%)	0
Eye oedema	Resolved	7 (6.9%)	0
Eye irritation	Resolved	9 (8.8%)	0
	Ongoing	1 (1.0%)	1 (1.0%)
Visual acuity reduced	Resolved	8 (7.8%)	9 (8.7%)
Corneal scar	Resolved	4 (3.9%)	4 (3.9%)
	Ongoing	3 (2.9%)	1 (1.0%)
Dry eye	Resolved	6 (5.9%)	1 (1.0%)
	Ongoing	0	1 (1.0%)
Eyelid oedema	Resolved	5 (4.9%)	0
Foreign body sensation in eyes	Resolved	5 (4.9%)	0
Lacrimation increased	Resolved	5 (4.9%)	0
Anterior chamber flare	Resolved	4 (3.9%)	0

Table 31: Outcome for Ocular Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Keratoconus) (Continued)

MedDRA Preferred Term[a]	Outcome	CXL Group (N=102)	Control Group (N=103)
Glare	Resolved	3 (2.9%)	1 (1.0%)
	Ongoing	1 (1.0%)	0
Ocular hyperaemia	Resolved	4 (3.9%)	1 (1.0%)
Corneal disorder	Resolved	2 (2.0%)	1 (1.0%)
	Ongoing	1 (1.0%)	0
Corneal oedema	Resolved	2 (2.0%)	0
	Ongoing	1 (1.0%)	0
Visual impairment	Resolved	1 (1.0%)	1 (1.0%)
	Ongoing	2 (2.0%)	1 (1.0%)
Anterior chamber cell	Resolved	2 (2.0%)	0
Diplopia	Resolved	0	1 (1.0%)
	Ongoing	2 (2.0%)	0
Eye discharge	Resolved	2 (2.0%)	1 (1.0%)
Eye pruritus	Resolved	2 (2.0%)	0
Vitreous detachment	Resolved	1 (1.0%)	0
	Ongoing	1 (1.0%)	0
Eye complication associated with device	Resolved	2 (2.0%)	0

[a] An outcome category is not shown if there were no observations in the category for the specific preferred term.
Note: Ocular events in the fellow eye are excluded.

Table 32: Outcome for Ocular Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Corneal Ectasia)

MedDRA Preferred Term[a]	Outcome	CXL Group (N=91)	Control Group (N=88)
All TEAEs	Resolved	65 (71.4%)	33 (37.5%)
	Ongoing	17 (18.7%)	5 (5.7%)
Eye disorders	Resolved	67 (73.6%)	28 (31.8%)
	Ongoing	15 (16.5%)	5 (5.7%)
Corneal opacity	Resolved	56 (61.5%)	7 (8.0%)
	Ongoing	6 (6.6%)	0
Corneal epithelium defect	Resolved	23 (25.3%)	3 (3.4%)
	Ongoing	1 (1.1%)	0
Eye pain	Resolved	23 (25.3%)	0
	Ongoing	1 (1.1%)	0
Punctate keratitis	Resolved	18 (19.8%)	3 (3.4%)
Photophobia	Resolved	17 (18.7%)	0
Vision blurred	Resolved	13 (14.3%)	4 (4.5%)
	Ongoing	2 (2.2%)	0
Dry eye	Resolved	12 (13.2%)	3 (3.4%)
	Ongoing	1 (1.1%)	1 (1.1%)
Visual acuity reduced	Resolved	9 (9.9%)	0
	Ongoing	1 (1.1%)	1 (1.1%)
Lacrimation increased	Resolved	8 (8.8%)	1 (1.1%)
	Ongoing	1 (1.1%)	0
Corneal striae	Resolved	6 (6.6%)	5 (5.7%)
	Ongoing	2 (2.2%)	1 (1.1%)
Eye irritation	Resolved	8 (8.8%)	1 (1.1%)
Ocular discomfort	Resolved	8 (8.8%)	0
Anterior chamber flare	Resolved	5 (5.5%)	2 (2.3%)
Eyelid oedema	Resolved	5 (5.5%)	1 (1.1%)

Table 32: Outcome for Ocular Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Corneal Ectasia) (Continued)

MedDRA Preferred Term	Outcome	CXL Group (N=91)	Control Group (N=88)
Foreign body sensation in eyes	Resolved	5 (5.5%)	1 (1.1%)
Conjunctival hyperaemia	Resolved	4 (4.4%)	3 (3.4%)
Visual impairment	Resolved	3 (3.3%)	1 (1.1%)
	Ongoing	1 (1.1%)	0
Corneal disorder	Resolved	3 (3.3%)	0
Corneal oedema	Resolved	3 (3.3%)	0
Keratitis	Resolved	3 (3.3%)	0
Meibomian gland dysfunction	Resolved	3 (3.3%)	1 (1.1%)
	Ongoing	0	1 (1.1%)
Ocular hyperaemia	Resolved	3 (3.3%)	1 (1.1%)
Corneal scar	Resolved	1 (1.1%)	1 (1.1%)
	Ongoing	2 (2.2%)	0
Anterior chamber cell	Resolved	2 (2.2%)	1 (1.1%)
Asthenopia	Resolved	2 (2.2%)	0
Glare	Resolved	2 (2.2%)	0
Halo vision	Resolved	2 (2.2%)	0
Corneal abrasion	Resolved	2 (2.2%)	0

Note: Ocular events in the fellow eye are excluded.

6.7.6. Adverse Events Reported from Baseline to Month 3 Considered by the Investigator to be Related to Study Treatment

6.7.6.1. Progressive Keratoconus

Treatment-related TEAEs were reported for 83 (81.4%) subjects in the CXL group and 11 (10.7%) subjects in the control group.

In the CXL group, the most frequent treatment-related TEAEs were corneal opacity (haze), corneal epithelium defect, and punctate keratitis. In the control group, punctate keratitis was the only TEAE considered to be treatment-related in ≥2% of subjects.

These TEAE's were expected based upon the epithelial debridement procedure and the corneal remodeling process.

6.7.6.2. Corneal Ectasia

Treatment-related TEAEs were reported for 79 (86.8%) subjects in the CXL group and 8 (9.1%) subjects in the control group.

In the CXL group, the most frequent treatment-related TEAEs were corneal opacity (haze), eye pain and corneal epithelium defect. In the control group, corneal opacity (haze) and punctate keratitis were the only TEAEs considered to be treatment-related in ≥2% of subjects

These TEAE's were expected based upon the epithelial debridement procedure and the corneal remodeling process

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6.7.7. Loss of Visual Acuity

A transient reduction in BSCVA is an expected and well documented effect of corneal debridement (Hersh 1998; Sia 2012). This was observed in the UVX studies, whereby the proportion of progressive keratoconus and corneal ectasia subjects with a BSCVA loss ≥15 letters was higher in the CXL group than in the control group at Month 1. However, the proportion of subjects with a BSCVA loss ≥15 letters was generally low and comparable between treatment groups at subsequent visits, reaching no more than 4.2% in the CXL group for either indication (based on observed case values). This finding is consistent with the expected time course of healing post-debridement.

For both indications, the majority of cases of reduced visual acuity resolved by the last study visit, all but 1 event was mild or moderate in intensity. A corneal ectasia subject had severe reduced visual acuity after receiving CXL in the control study eye. The event developed with concurrent severe corneal infiltrates and moderate corneal epithelium defect. The reduced visual acuity resolved approximately 4.5 months after onset. In the opinion of the investigator, the reduced visual acuity, corneal infiltrates, and corneal epithelial defect were related to debridement.

For each indication, no clinically relevant differences were observed between studies for loss of visual acuity in CXL-treated subjects.

6.7.8. Endothelial Cell Count Data

Table 33 and Table 34 summarize endothelial cell counts using observed values for the Safety population for progressive keratoconus and corneal ectasia subjects, respectively.

For both indications, mean endothelial cell counts (cells/mm^2) were comparable between treatment groups at baseline. Mean changes from baseline in endothelial cell density at Month 3 (the first planned time point) were not clinically relevant: keratoconus (–64 cells/mm^2, CXL; 23.6 cells/mm^2, control) and corneal ectasia (–44 cells/mm^2, CXL; –53 cells/mm^2, control). Mean changes in cell counts at Month 12 (the second planned time point) were 18.4 cells/mm^2 and –108 cells/mm^2 in the CXL group for keratoconus and corneal ectasia, respectively; observed case values were not evaluable in the control group at this time point. The observed changes are not clinically meaningful and indicate that cross-linking as performed in this study has no demonstrable effect on the corneal endothelium.

Table 33: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed (Safety Population: Progressive Keratoconus)

				Change from Baseline			
Visit	**Statistic**	**CXL Group (N=102)**	**Control Group (N=103)**	**CXL Group (N=102)**	**% Change**	**Control Group (N=103)**	**% Change**
Baseline	n	95	94				
	Mean	2590	2575				
Month 3	n	86	91	82		86	
	Mean	2513	2598	-64	-2.5%	23.6	0.9%
Month 12	n	80	1	76		1	
	Mean	2624	2996	18.4	0.7%	330	--

Table 34: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed (Safety Population: Corneal Ectasia)

				Change from Baseline			
Visit	**Statistic**	**CXL Group (N=91)**	**Control Group (N=88)**	**CXL Group (N=91)**	**% Change**	**Control Group (N=88)**	**% Change**
Baseline	n	87	81				
	Mean	2487	2584				
Month 3	n	77	77	76		71	
	Mean	2419	2547	-44	-1.8%	-53	-2.1%
Month 12	n	69	2	67		2	
	Mean	2359	2283	-108	-4.3%	-343	--

6.7.9. Safety Conclusions

The safety evaluation of CXL using riboflavin ophthalmic solutions and UVA light was based on a total of 512 eyes treated with CXL (293 progressive keratoconus; 219 corneal ectasia) in the three Phase III studies (UVX-001, UVX-002, and UVX-003). Most CXL treated eyes were followed for a period of 12 months post CXL treatment (progressive keratoconus eyes 243/293, 82.9%; corneal ectasia eyes 177/219, 80.8%). Given the large number of eyes treated and length of safety follow-up, the three studies provide a substantial body of evidence of the safety of CXL treatment in these orphan indications.

None of the subjects died, experienced an SAE related to riboflavin or UVA light, or discontinued prematurely due to a TEAE. Seven SAEs were reported in six subjects, none of which were considered by the investigator to be related to the riboflavin ophthalmic solution or the UVA light. Two of the SAEs were ocular: one SAE of ulcerative keratitis in a progressive keratoconus subject, and one SAE of corneal epithelium defect in a corneal ectasia subject. Both SAEs were considered related to corneal debridement.

Most of the treatment emergent adverse events (TEAEs) were ocular in nature and developed in the short term (within the first 3 months of treatment). There was a higher incidence of ocular TEAEs in the CXL groups compared to the control groups within each indication. In the safety analysis of randomized study eyes, a total of 84.3% of subjects in the CXL group compared to 38.8% in the control group experienced an ocular TEAE within the first 3 months of treatment in the pooled keratoconus population. Similarly, in the corneal ectasia pooled population, 90.1% of subjects in the CXL group compared with 37.5% in the control group experienced an ocular TEAE within the first 3 months after treatment. However, the most common ocular TEAEs observed in the CXL groups were expected sequelae following corneal debridement. In progressive keratoconus subjects, the most common ocular TEAEs observed in the CXL group (≥10%) from baseline to Month 3 were corneal opacity (haze) (56.9%), punctate keratitis (24.5%), corneal striae (23.5%), corneal epithelium defect (22.5%), eye pain (16.7%), vision blurred (15.7%) and photophobia (10.8%). In corneal ectasia subjects, the most common ocular TEAEs observed in the CXL group (≥10%) from baseline to Month 3 were corneal opacity (haze) (68.1%), corneal epithelium defect (26.4%), eye pain (26.4%), punctate keratitis (19.8%), photophobia (18.7%), vision blurred (16.5%), dry eye (14.3%) and visual acuity reduced (11.0%).

Most TEAEs were of mild or moderate intensity, and resolution of the most frequent TEAEs was consistent with the expected time course for epithelial healing and corneal remodeling.

Transient reductions in BSCVA were seen in some patients in the CXL group specifically; the proportion of progressive keratoconus and corneal ectasia subjects with a BSCVA loss ≥15 letters was higher in the CXL group than in the control group at Month 1. However, the proportion of subjects with a BSCVA loss ≥15 letters was generally low and comparable between treatment groups at subsequent visits, reaching no more than 4.2% in the CXL group for either indication (based on observed case values). A transient reduction in BSCVA is an expected and well documented effect of corneal debridement (Hersh 1998; Sia 2012).

Additionally, transient corneal opacity similar to haze has been described and documented as a known effect of crosslinking and the subsequent remodeling (Mazzotta 2008). In the UVX studies, the most common TEAE was corneal opacity; all cases of corneal opacity were reported as haze and most all were mild in intensity and resolved.

There were no differences in change from baseline in endothelial cell counts between the CXL and control groups indicating that CXL therapy did not result in endothelial cell damage.

The safety profile of the randomized (primary) study eyes in the CXL group is comparable to that of all CXL treated eyes (including secondary CXL eyes)(Appendix 2). Evaluation of this large body of safety data did not reveal any unexpected findings or concerns. Overall, CXL performed as a one-time procedure was safe and well tolerated in subjects with progressive keratoconus or corneal ectasia following refractive surgery.

7. POST-APPROVAL STUDY PLANS

Avedro plans to conduct a post-approval safety study entitled "A Phase IV, Prospective, Observational Study of the Long-term Safety and Efficacy of Riboflavin Ophthalmic Solution/KXL System for Corneal Collagen Cross-Linking in Eyes with Progressive Keratoconus or Corneal Ectasia."

Study eyes will be followed for up to 3 years post cross-linking procedure. The study synopsis was submitted to FDA.

8. BENEFIT-RISK AND CONCLUSIONS

Riboflavin ophthalmic solution/KXL® System (CXL) has a positive benefit-to-risk profile for the treatment of subjects with progressive keratoconus or corneal ectasia following refractive surgery.

Progressive keratoconus and corneal ectasia following refractive surgery are orphan indications for which there is currently no FDA-approved therapeutic treatment available to treat the underlying disease.

Results from the 3 randomized and well-controlled studies in the Phase III clinical development program provide substantial evidence of safety and efficacy and a positive benefit to risk profile of riboflavin ophthalmic solution/KXL® System for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.

In these trials, CXL provided clinically meaningful and statistically significant improvements in corneal curvature, as measured by K_{max}, in subjects with these conditions. All three studies met the primary efficacy endpoint of a ≥1 D difference in the mean change in K_{max} between the CXL group and the control group at 12 months. CXL therapy was effective in reversing or stopping disease progression, as evidenced by a clinically relevant improvement in K_{max} over time. Stopping progression in these orphan patient populations is an important clinical benefit. CXL treatment not only stopped progression but also reversed disease progression in some subjects. Clinically meaningful improvements over baseline were observed in visual acuity within 12 months of CXL therapy, indicating that CXL not only corrects corneal curvature but improves visual function.

Results of the 3 randomized and well-controlled clinical trials also showed that CXL was safe and well tolerated over the 12-month study period. As expected, there were no deaths associated with the treatment. The most common events associated with CXL in these studies (e.g., corneal opacity [haze], punctate keratitis, corneal epithelium defect, eye pain, and blurred vision) are expected sequelae following debridement of the cornea or associated with the corneal remodeling process. Most were mild or moderate in intensity and resolved over time.

Currently available treatments for ketatoconus and corneal ectasia do not address the underlying problem of compromised corneal biomechanical integrity or prevent the progression of the disease, but rather offer temporary visual rehabilitation in the form of rigid contact lenses and intracorneal ring segments, or require penetrating keratoplasty. As a surgical procedure, corneal transplantation can significantly impact the patient's quality of life, with risk of rejection, lost time from work, and a lengthy vision rehabilitation period.

Patients in the US suffering from keratoconus and corneal ectasia would benefit from another treatment option that bridges the gap in between hard contacts and transplantation. If approved, CXL will be the first drug-device combination product in the US for the treatment of patients with progressive keratoconus or corneal ectasia following refractive surgery.

CXL is the only therapeutic treatment option which slows or prevents disease progression. As such, CXL has the potential to fill a significant unmet medical need for patients suffering from these progressive conditions which may lead to loss of visual function. CXL should be an option for the treatment of subjects with progressive keratoconus or corneal ectasia following refractive

surgery to increase corneal stability, mitigate disease progression, prevent vision loss, and decrease or delay the potential need for corneal transplantation.

CXL is approved for use in over 60 countries around the world and is a standard of care for treating keratoconus and corneal ectasia OUS. In the absence of an FDA approved therapy in the US, the procedure is being performed with devices that are not approved for cross-linking and compounded drug product that is not manufactured according to Good Manufacturing Practices (cGMP's).

The totality of the safety and efficacy data from Avedro's well-controlled studies provides substantial evidence of safety and efficacy for a product with orphan drug designation intended for one-time administration in affected eyes. The positive benefit to risk ratio of CXL greatly favors approval of CXL for the treatment of progressive keratoconus and corneal ectasia.

In conclusion, CXL is safe and effective as demonstrated in three well controlled studies in patients suffering from progressive keratoconus and corneal ectasia following refractive surgery. These two indications are orphan indications for which there is no FDA-approved therapeutic treatment available. Patients in the US who suffer from these progressive corneal disorders would benefit from another treatment option that bridges the gap in between hard contacts and transplantation. CXL could redefine the standard of care for these patients in the US.

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APPENDIX 1. EFFICACY IN ALL CXL-TREATED EYES

This section summarizes mean changes from baseline K_{max} (LOCF) in all CXL-treated eyes, including cross-overs from the control group and the untreated eye in the CXL group.

In each study, eligible subjects were randomized into 1 of 2 treatment groups: the CXL group and the control group. At Month 3 or later, subjects whose eye(s) had not developed any contraindications for performing the CXL treatment were given the option of having CXL performed on their untreated fellow eye (from CXL group) and untreated control eye and untreated fellow eye (from control group).

A total of 293 progressive keratoconus eyes (102 primary CXL eyes and 191 fellow or cross-over eyes) were included in the analysis of all CXL-treated eyes (Table 35).

A total of 219 corneal ectasia eyes (91 primary CXL eyes and 128 fellow or cross-over eyes) were included in the analysis of all CXL-treated eyes (Table 36).

Table 35: Treatments Administered: Progressive Keratoconus Subjects

	Primary (Study Eye)		Secondary Eyes			
Randomization:	**CXL**	**Control**	**Fellow Eye CXL**	**None**	**Control Eye CXL**	**Total**
Subjects Randomized to CXL	102	---	56	46	---	---
Subjects Randomized to Control	---	103	41	9	94	---
Total CXL	102	---	97	---	94	293

Table 36: Treatments Administered: Corneal Ectasia Subjects

	Primary (Study Eye)		Secondary Eyes			
Randomization:	**CXL**	**Control**	**Fellow Eye CXL**	**None**	**Control Eye CXL**	**Total**
Subjects Randomized to CXL	91	---	26	65	---	---
Subjects Randomized to Control	---	88	22	8	80	---
Total CXL	91	---	48	---	80	219

Efficacy in All CXL-Treated Eyes: Progressive Keratoconus

LOCF Analysis

Table 37 summarizes mean changes from baseline K_{max} (LOCF) in all CXL-treated eyes for progressive keratoconus subjects in UVX-001 (74 eyes), UVX-002 (219 eyes), and the pooled studies (293 eyes), including cross-overs from the control group and the untreated eye in the CXL group.

In UVX-001, a mean increase from baseline in K_{max} was observed at Month 3 (0.2 D), followed by a mean decrease from baseline in K_{max} at Month 6 (–0.6 D) and Month 12 (–0.8 D). In UVX-002, a mean decrease from baseline in K_{max} was observed at Month 3 (–0.6 D), Month 6 (-1.1 D), and Month 12 (–1.6 D).

Similar results were generally observed in the pooled studies. The mean baseline K_{max} for all CXL-treated eyes was slightly less (59.4 D) than in the randomized study eyes (60.9 D). In all CXL-treated eyes, a mean decrease from baseline in K_{max} was observed at Month 3 (–0.4 D), Month 6 (–1.0 D) and Month 12 (–1.4 D).

Observed

Table 38 summarizes mean changes from baseline K_{max} (observed values) in all CXL-treated eyes for UVX-001 (74 eyes), UVX-002 (219 eyes), and the pooled studies (293 eyes).

In both UVX-001 and UVX-002, mean K_{max} in all CXL-treated eyes at baseline was slightly less than that observed in randomized CXL study eyes. In UVX-001, mean increases from baseline were observed in all CXL-treated eyes at Month 3 (0.2 D), followed by a mean decrease from baseline in K_{max} at Month 6 (–0.7 D) and Month 12 (–1.5 D). In UVX-002, a mean decrease from baseline was observed at Month 3 (–0.6 D), Month 6 (–1.0 D), and Month 12 (–1.6 D).

Similar results were generally observed in the pooled studies. The mean baseline K_{max} for all CXL-treated eyes was slightly less (59.4 D, Table 38) than in the randomized study eyes (60.9 D). In all CXL-treated eyes, a mean decrease from baseline was observed in K_{max} at Month 3 (-0.4 D), Month 6 (–0.9 D) and Month 12 (–1.6 D).

Table 37: Mean Changes from Baseline K_{max} in All CXL-Treated Eyes (Safety Population, LOCF): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002

		UVX-001	UVX-002	Pooled Studies
Visit	**Statistic**	**All CXL-Treated Eyes (N=74)**	**All CXL-Treated Eyes (N=219)**	**All CXL-Treated Eyes (N=293)**
Baseline	N	74	219	293
	Mean	59.7	59.3	59.4
	SD	8.74	10.37	9.97
Month 1	N	74	219	293
	Mean Change from Baseline	1.3	0.8	1.0
	SD	2.16	4.22	3.80
Month 3	N	74	219	293
	Mean Change from Baseline	0.2	–0.6	–0.4
	SD	2.64	4.56	4.17
Month 6	N	74	219	293
	Mean Change from Baseline	–0.6	–1.1	–1.0
	SD	2.95	4.71	4.34
Month 12	N	74	219	293
	Mean Change from Baseline	–0.8	–1.6	–1.4
	SD	3.10	4.79	4.43

Table 38: Mean Changes from Baseline K_{max} in All CXL-Treated Eyes (Safety Population, Observed Values): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002

		UVX-001	UVX-002	Pooled Studies
Visit	**Statistic**	**All CXL-Treated Eyes (N=74)**	**All CXL-Treated Eyes (N=219)**	**All CXL-Treated Eyes (N=293)**
Baseline	N	74	219	293
	Mean	59.7	59.3	59.4
	SD	8.74	10.37	9.97
Month 1	N	72	210	282
	Mean Change from Baseline	1.3	0.9	1.0
	SD	2.18	4.30	3.87
Month 3	N	71	205	276
	Mean Change from Baseline	0.2	–0.6	–0.4
	SD	2.69	4.62	4.22
Month 6	N	67	201	268
	Mean Change from Baseline	–0.7	–1.0	–0.9
	SD	3.05	3.57	3.44
Month 12	N	49	194	243
	Mean Change from Baseline	–1.5	–1.6	–1.6
	SD	2.75	4.85	4.50

Efficacy in All CXL-Treated Eyes: Corneal Ectasia

LOCF Analysis

Table 39 summarizes mean changes from baseline K_{max} (LOCF) in all CXL-treated eyes for UVX-001 (57 eyes), UVX-003 (162 eyes), and the pooled studies (219 eyes), including cross-overs from the control group and the untreated eye in the CXL group.

In both UVX-001 and UVX-003, mean K_{max} in all CXL-treated eyes at baseline was slightly less than that observed in randomized CXL study eyes. In UVX-001, mean increases from baseline were observed in all CXL-treated eyes at Month 3 (0.4 D), followed by mean decreases at Month 6 (–0.4 D) and Month 12 (–0.6 D). In UVX-003, a mean decreases from baseline k_{max} was observed at Month 3 (–0.1 D), Month 6 (–0.4 D), and Month 12 (-0.5 D).

Similar results were generally observed in the pooled studies. The mean baseline K_{max} for all CXL-treated eyes was slightly less (54.3 D) than in the randomized study eyes (55.4 D). In all CXL-treated eyes, a mean increase from baseline in K_{max} was observed at Month 3 (0.1 D), followed by a mean decrease from baseline in K_{max} at Month 6 (-0.4 D) and Month 12 (-0.5 D).

Observed Case Analysis

Table 40 summarizes mean changes from baseline K_{max} (observed values) in all CXL-treated eyes for UVX-001 (57 eyes), UVX-003 (162 eyes), and the pooled studies (219 eyes).

In both UVX-001 and UVX-003, mean K_{max} in all CXL-treated eyes at baseline was slightly less than that observed in randomized CXL study eyes. In UVX-001, mean increases from baseline were observed in all CXL-treated eyes at Month 3 (0.4 D), followed by a mean decrease from baseline in K_{max} at Month 6 (–0.5 D) and Month 12 (–0.9 D). In UVX-003, a mean decrease from baseline was observed at Month 3 (–0.1 D), Month 6 (–0.5 D), and Month 12 (–0.5 D).

Similar results were generally observed in the pooled studies. The mean baseline K_{max} for all CXL-treated eyes was slightly less (54.3 D) than in the randomized study eyes (55.4 D). In all CXL-treated eyes, there was no change in mean baseline K_{max} at Month 3 (0.0 D), and a mean decrease from baseline K_{max} at Month 6 (–0.5 D) and Month 12 (–0.6 D).

Table 39: Mean Changes from Baseline K_{max} in All CXL-Treated Eyes (ITT Population, LOCF): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

		UVX-001	UVX-003	Pooled Studies
Visit	**Statistic**	**All CXL-Treated Eyes (N=57)**	**All CXL-Treated Eyes (N=162)[a]**	**All CXL-Treated Eyes (N=219)[a]**
Baseline	N	57	158	215
	Mean	55.0	54.1	54.3
	SD	6.22	6.71	6.58
Month 1	N	57	158	215
	Mean Change from Baseline	1.4	1.1	1.2
	SD	2.78	2.08	2.28
Month 3	N	57	158	215
	Mean Change from Baseline	0.4	–0.1	0.1
	SD	2.08	2.17	2.15
Month 6	N	57	158	215
	Mean Change from Baseline	–0.4	–0.4	–0.4
	SD	2.11	2.03	2.05
Month 12	N	57	158	215
	Mean Change from Baseline	–0.6	–0.5	–0.5
	SD	2.37	2.12	2.18

[a] Four subjects did not have a K_{max} measurement at baseline.

Table 40: Mean Changes from Baseline K_{max} in All CXL-Treated Eyes (ITT Population, Observed Values): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003

		UVX-001	UVX-003	Pooled Studies
Visit	**Statistic**	**All CXL-Treated Eyes (N=57)**	**All CXL-Treated Eyes (N=162)[a]**	**All CXL-Treated Eyes (N=219)[a]**
Baseline	N	57	158	215
	Mean	55.0	54.1	54.3
	SD	6.22	6.71	6.58
Month 1	N	56	152	208
	Mean Change from Baseline	1.4	1.1	1.2
	SD	2.80	2.10	2.31
Month 3	N	54	149	203
	Mean Change from Baseline	0.4	–0.1	0.0
	SD	2.13	2.19	2.18
Month 6	N	54	140	194
	Mean Change from Baseline	–0.5	–0.5	–0.5
	SD	2.11	1.81	1.89
Month 12	N	43	132	175
	Mean Change from Baseline	–0.9	–0.5	–0.6
	SD	2.14	2.24	2.22

[a] Four subjects did not have a Kmax measurement at baseline.

APPENDIX 2. SAFETY IN ALL CXL-TREATED EYES

This section summarizes safety results in all CXL-treated eyes. In each study, eligible subjects were randomized into 1 of 2 treatment groups: the CXL group and the control group. At Month 3 or later, subjects whose eye(s) had not developed any contraindications for performing the CXL treatment were given the option of having CXL performed on their untreated fellow eye (from CXL group) and untreated control eye and untreated fellow eye (from control group).

A total of 293 progressive keratoconus eyes (102 primary CXL eyes and 191 fellow or cross-over eyes) were included in the analysis of all CXL-treated eyes (Table 41).

A total of 219 corneal ectasia eyes (91 primary CXL eyes and 128 fellow or cross-over eyes) were included in the analysis of all CXL-treated eyes (Table 42).

Table 41: Treatments Administered: Progressive Keratoconus Subjects

	Primary (Study Eye)		Secondary Eyes			
Randomization:	**CXL**	**Control**	**Fellow Eye CXL**	**None**	**Control Eye CXL**	**Total**
Subjects Randomized to CXL	102	---	56	46	---	---
Subjects Randomized to Control	---	103	41	9	94	---
Total CXL	102	---	97	---	94	293

Table 42: Treatments Administered: Corneal Ectasia Subjects

	Primary (Study Eye)		Secondary Eyes			
Randomization:	**CXL**	**Control**	**Fellow Eye CXL**	**None**	**Control Eye CXL**	**Total**
Subjects Randomized to CXL	91	---	26	65	---	---
Subjects Randomized to Control	---	88	22	8	80	---
Total CXL	91	---	48	---	80	219

Summary of Ocular Adverse Events with Incidence ≥ 2% in Any CXL Eye at Any Time

Table 43 and Table 44 summarize TEAEs with incidence ≥2% at any time during follow-up in any eye receiving CXL in subjects with progressive keratoconus and corneal ectasia, respectively. The results for the CXL group from baseline to Month 3 are provided for perspective. In both populations, the results for any CXL eye were consistent with the results during the controlled phase. The proportion of CXL eyes with

a TEAE (at any time) was generally comparable to the incidence of TEAEs from baseline to Month 3 (controlled phase).

Table 43: Summary of Ocular Adverse Events with Incidence ≥ 2% in Any CXL Eye at Any Time During Follow-up (Safety Population: Progressive Keratoconus)

MedDRA Preferred Term	CXL Group (N=102)	Any CXL Eye (N=293)
Number (%) of CXL Eyes Reporting Any AEs	87 (85.3%)	249 (85.0%)
Corneal opacity	58 (56.9%)	178 (60.8%)
Corneal striae	24 (23.5%)	70 (23.9%)
Corneal epithelium defect	23 (22.5%)	69 (23.5%)
Punctate keratitis	25 (24.5%)	62 (21.2%)
Eye pain	17 (16.7%)	58 (19.8%)
Visual acuity reduced	10 (9.8%)	48 (16.4%)
Vision blurred	16 (15.7%)	42 (14.3%)
Photophobia	11 (10.8%)	28 (9.6%)
Conjunctival hyperaemia	10 (9.8%)	19 (6.5%)
Dry eye	6 (5.9%)	18 (6.1%)
Eye irritation	10 (9.8%)	18 (6.1%)
Lacrimation increased	5 (4.9%)	18 (6.1%)
Eyelid oedema	5 (4.9%)	10 (3.4%)
Foreign body sensation in eyes	5 (4.9%)	10 (3.4%)
Anterior chamber flare	4 (3.9%)	9 (3.1%)
Eye oedema	7 (6.9%)	9 (3.1%)
Corneal thinning	1 (1.0%)	8 (2.7%)
Eye pruritus	2 (2.0%)	8 (2.7%)
Glare	4 (3.9%)	8 (2.7%)
Ocular discomfort	0	8 (2.7%)
Corneal disorder	3 (2.9%)	7 (2.4%)
Ocular hyperaemia	4 (3.9%)	6 (2.0%)
Visual impairment	3 (2.9%)	6 (2.0%)
Corneal scar	7 (6.9%)	22 (7.5%)

Table 44: Summary of Ocular Adverse Events with Incidence ≥ 2% in Any CXL Eye at Any Time During Follow-up (Safety Population: Corneal Ectasia)

MedDRA Preferred Term	CXL Group (N=91)	Any CXL Eye (N=219)
Number (%) of CXL Eyes Reporting Any AEs	82 (90.1%)	191 (87.2%)
Corneal opacity	62 (68.1%)	148 (67.6%)
Corneal epithelium defect	24 (26.4%)	53 (24.2%)
Punctate keratitis	18 (19.8%)	51 (23.3%)
Eye pain	24 (26.4%)	43 (19.6%)
Photophobia	17 (18.7%)	42 (19.2%)
Visual acuity reduced	10 (11.0%)	37 (16.9%)
Vision blurred	15(16.5%)	36 (16.4%)
Corneal striae	8 (8.8%)	27 (12.3%)
Dry eye	13 (14.3%)	27 (12.3%)
Lacrimation increased	9 (9.9%)	20 (9.1%)
Ocular discomfort	8 (8.8%)	19 (8.7%)
Conjunctival hyperaemia	4 (4.4%)	16 (7.3%)
Foreign body sensation in eyes	5 (5.5%)	15 (6.8%)
Eye irritation	8 (8.8%)	15 (6.8%)
Meibomian gland dysfunction	3 (3.3%)	12 (5.5%)
Eyelid oedema	5 (5.5%)	11 (5.0%)
Visual impairment	4 (4.4%)	11 (5.0%)
Corneal scar	3 (3.3%)	9 (4.1%)
Anterior chamber flare	5 (5.5%)	9 (4.1%)
Ocular hyperaemia	3 (3.3%)	8 (3.7%)
Blepharitis	0	7 (3.2%)
Corneal disorder	3 (3.3%)	7 (3.2%)
Corneal oedema	3 (3.3%)	6 (2.7%)
Keratitis	3 (3.3%)	5 (2.3%)
Halo vision	2 (2.2%)	5 (2.3%)

Treatment Emergent Adverse Events of Severe Intensity in Any CXL Eye

Progressive Keratoconus

During the entire follow-up period, 8 TEAEs of severe intensity were reported; 6 after CXL (CXL in the primary eye, sham CXL, fellow eye CXL) treatment and 2 after control treatment. Five of the 8 severe TEAEs were ocular in nature. The relationship to riboflavin and UVA light was none or unlikely for all events, and 6/8 resolved during the study.

Table 45 lists all TEAEs of severe intensity and the treatment of the subject prior to the occurrence.

Corneal Ectasia

During the entire follow-up period, 7 TEAEs of severe intensity were reported, 5 following the CXL treatment (CXL in the primary eye, sham CXL, fellow eye CXL) and 2 following sham treatment. Four of the 7 severe TEAEs were ocular in nature. The relationship to riboflavin and UVA light was none or unlikely for all events. All resolved during the study.

Table 46 lists all TEAEs of severe intensity and the treatment of the subject prior to the occurrence.

Table 45: Subjects with TEAEs of Severe Intensity at Any Time During the Study (Safety Population: Keratoconus)

						Relationship to:				
Randomized Treatment	**Subject**	**Age**	**Race**	**Gender**	**Preferred Term / Reported Term**	**Riboflavin**	**UVA Light**	**Epithelium Defect**	**Outcome**	**SAE**
Sham	00211	20	White	Female	Suicide attempt / attempted suicide #1	None	None	None	Resolved	Yes
					Suicide attempt / attempted suicide #2	None	None	None	Resolved	Yes
Sham CXL	02206	19	White	Male	Ulcerative keratitis / Corneal ulcer	None	None	Definite	Resolved	Yes
CXL	02210	23	Indian/South Asian	Female	Photophobia / light sensitivity OU	Unlikely	Unlikely	Unlikely	Ongoing	No
Fellow CXL					Eye irritation / burning dry eyes OU	None	None	None	Ongoing	No
CXL	04210	16	Black	Male	Corneal epithelium defect / persistent epithelial defect	None	None	Definite	Resolved	No
Sham CXL	10211	52	White	Female	Eye pain / pain (OD)	None	None	Probably	Resolved	No
Sham CXL					Animal bite / infectious cat bite to right hand (hospitalized)	None	None	None	Resolved	Yes

Table 46: Subjects with TEAEs of Severe Intensity at Any Time During the Study (Safety Population: Corneal Ectasia)

						Relationship to:				
Treatment	**Subject**	**Age**	**Race**	**Gender**	**Preferred Term / Reported Term**	**Riboflavin**	**UVA Light**	**Epithelium Defect**	**Outcome**	**SAE**
Sham CXL	02305	40	Black	Female	Headache / headaches	None	None	None	Resolved	No
Fellow CXL	02309	29	Black	Male	Headache / pain left temple	Unlikely	Unlikely	Unlikely	Resolved	No
Fellow CXL					Eye pain / eye pain OS	None	None	Definitely	Resolved	No
Sham CXL	02311	36	White	Male	Corneal infiltrates / corneal infiltrate (OD)	Unlikely	Unlikely	Definitely	Resolved	No
Sham CXL					Visual acuity reduced / decrease visual acuity to count fingers 4’ OD	None	None	None	Resolved	No
Sham	03203	49	White	Male	Head injury / head trauma	None	None	None	Resolved	Yes
Sham	03233	45	White	Male	Iridocele / wound revision (iris prolapse to wound) right eye	None	None	None	Resolved	No

Treatment Emergent Adverse Events in Any CXL Eye Summarized by Outcome at Month 12

Progressive Keratoconus

Table 47 summarizes ocular events occurring at any time during the study that were reported for ≥2% CXL eyes by outcome at the last study visit. For many of the preferred terms, all events had resolved by the last study visit. The percentage of events that resolved (resolved events/total number of events) by the last study visit was 97.6% for vision blurred, 92.8% for corneal epithelium defect, 90.3% for punctate keratitis, and 82.8% for corneal opacity (haze). For most of the other preferred terms, at least 70% of the events resolved by the final study visit.

Corneal Ectasia

Table 48 summarizes ocular events occurring at any time during the study that were reported for ≥2% CXL eyes by outcome at the last study visit. For many of the preferred terms, all events had resolved by the last study visit. The percentage of events that resolved (resolved events/total number of events) by the last study visit was 90.0% for punctate keratitis, 88.9% for vision blurred, 88.7% for corneal epithelium defect, and 79.7% for corneal opacity (haze). For most of the other preferred terms, at least 80% of events resolved by the last study visit.

Table 47: Summary of Ocular Adverse Events in Any CXL Eye Reported for ≥2% of Eyes Summarized by Outcome (Safety Population: Keratoconus)

MedDRA Preferred Term[a]	Outcome	Any CXL Eyes (N=293)
All TEAEs		249 (85.0%)
Eye disorders	Resolved	165 (56.3%)
	Ongoing	83 (28.3%)
Corneal opacity	Resolved	147 (50.2%)
	Ongoing	31 (10.6%)
Corneal striae	Resolved	52 (17.7%)
	Ongoing	18 (6.1%)
Corneal epithelium defect	Resolved	64 (21.8%)
	Ongoing	5 (1.7%)
Punctate keratitis	Resolved	56 (19.1%)
	Ongoing	6 (2.0%)
Eye pain	Resolved	58 (19.8%)
Visual acuity reduced	Resolved	33 (11.3%)
	Ongoing	15 (5.1%)
Vision blurred	Resolved	41 (14.0%)
	Ongoing	1 (0.3%)
Photophobia	Resolved	22 (7.5%)
	Ongoing	6 (2.0%)
Conjunctival hyperaemia	Resolved	18 (6.1%)
	Ongoing	1 (0.3%)
Dry eye	Resolved	15 (5.1%)
	Ongoing	3 (1.0%)
Eye irritation	Resolved	14 (4.8%)
	Ongoing	4 (1.4%)
Lacrimation increased	Resolved	18 (6.1%)
Eyelid oedema	Resolved	10 (3.4%)
Foreign body sensation in eyes	Resolved	10 (3.4%)
Anterior chamber flare	Resolved	9 (3.1%)
Eye oedema	Resolved	9 (3.1%)
Corneal thinning	Resolved	6 (2.0%)

	Ongoing	2 (0.7%)

Table 47: Summary of Ocular Adverse Events in Any CXL Eye Reported for ≥2% of Eyes Summarized by Outcome (Safety Population: Keratoconus) (Continued)

MedDRA Preferred Term[a]	Outcome	Any CXL Eyes (N=293)
Eye pruritus	Resolved	8 (2.7%)
Glare	Resolved	4 (1.4%)
	Ongoing	4 (1.4%)
Ocular discomfort	Resolved	8 (2.7%)
Corneal disorder	Resolved	5 (1.7%)
	Ongoing	2 (0.7%)
Corneal scar	Resolved	10 (3.4%)
	Ongoing	12 (4.1%)
Ocular hyperaemia	Resolved	6 (2.0%)
Visual impairment	Resolved	3 (1.0%)
	Ongoing	3 (1.0%)

Table 48: Summary of Ocular Adverse Events in Any CXL Eye Reported for ≥2% of Eyes Summarized by Outcome (Safety Population: Corneal Ectasia)

MedDRA Preferred Term[a]	Outcome	CXL Group (N=219)
All TEAEs		191 (87.2%)
Eye disorders	Resolved	118 (53.9%)
	Ongoing	72 (32.9%)
Corneal opacity	Resolved	118 (53.9%)
	Ongoing	30 (13.7%)
Corneal epithelium defect	Resolved	47 (21.5%)
	Ongoing	6 (2.7%)
Punctate keratitis	Resolved	45 (20.5%)
	Ongoing	5 (2.3%)
Eye pain	Resolved	42 (19.2%)
	Ongoing	1 (0.5%)
Photophobia	Resolved	39 (17.8%)
	Ongoing	3 (1.4%)
Visual acuity reduced	Resolved	22 (10.0%)
	Ongoing	15 (6.8%)
Vision blurred	Resolved	32 (14.6%)
	Ongoing	4 (1.8%)
Corneal striae	Resolved	22 (10.0%)
	Ongoing	5 (2.3%)
Dry eye	Resolved	20 (9.1%)
	Ongoing	7 (3.2%)
Lacrimation increased	Resolved	19 (8.7%)
	Ongoing	1 (0.5%)
Ocular discomfort	Resolved	19 (8.7%)
Conjunctival hyperaemia	Resolved	14 (6.4%)
	Ongoing	2 (0.9%)
Eye irritation	Resolved	15 (6.8%)
Foreign body sensation in eyes	Resolved	15 (6.8%)

Table 48: Summary of Ocular Adverse Events in Any CXL Eye Reported for ≥2% of Eyes Summarized by Outcome (Safety Population: Corneal Ectasia) (Continued)

MedDRA Preferred Term[a]	Outcome	CXL Group (N=219)
Meibomian gland dysfunction	Resolved	11 (5.0%)
	Ongoing	1 (0.5%)
Eyelid oedema	Resolved	10 (4.6%)
	Ongoing	1 (0.5%)
Visual impairment	Resolved	9 (4.1%)
	Ongoing	2 (0.9%)
Anterior chamber flare	Resolved	9 (4.1%)
Corneal Scar	Resolved	6 (2.7%)
	Ongoing	3 (1.4%)
Ocular hyperaemia	Resolved	7 (3.2%)
	Ongoing	1 (0.5%)
Blepharitis	Resolved	4 (1.8%)
	Ongoing	3 (1.4%)
Corneal disorder	Resolved	6 (2.7%)
	Ongoing	1 (0.5%)
Corneal oedema	Resolved	6 (2.7%)
Halo vision	Resolved	5 (2.3%)
Keratitis	Resolved	5 (2.3%)

APPENDIX 3. EQUIVALENCE ASSESSMENT OF THE UVX AND AVEDRO KXL DEVICE

Parameter	IROC UV-X (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL (device to be marketed)	Equivalence Assessment
Device Description	Portable electronic device used to delivered a dose of UV-A light to a targeted treatment area for illuminating the cornea after application of riboflavin ophthalmic solution	Portable electronic device which delivers ultraviolet light in a circular pattern onto the cornea after application of riboflavin ophthalmic solution	Both devices are portable electronic devices which deliver UV-A light to cornea after application of riboflavin ophthalmic solution. Differences in the device description do not impact the safety or effectiveness of the treatment performed with the devices.
Components	UV LED light source, UV light detector, UV detector sensor probe and adapter, wall power supply with DC cord, transportation case, safety goggles, mechanical stand and instruction manual	Optics head with LED UV source, KXL console with user interface, wireless remote control, RFID activation card, articulating arm, battery, AC power cord, and instruction manual	The two systems have different components but both include an LED UV source. The housings and user interfaces differ. The KXL System includes an internal calibration system while the UV-X System uses an external UV light detector for calibration. Both systems have power cords while the KXL System can also be operated on an internal battery. The KXL System includes a wireless remote control and RFID activation card while the UV-X System can only be controlled with knobs on the system. Differences in the components do not impact the safety or effectiveness of the treatment performed with the devices.
Mounting	Table-top Stand	Independent movable (wheeled) console	The UV-X must be assembled by the user using bars and clamps while the KXL System is a standalone system which is fully assembled prior to use. The KXL System is more user friendly in that it does not require assembly by the user, however, this difference does not impact the safety or effectiveness of the treatment performed with the devices.

Differences between the IROC UVX and Avedro KXL Device (Cont'd)

Parameter	IROC UV-X (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL (device to be marketed)	Equivalence Assessment
Patient Position	Sitting or Supine	Supine Only	The UV-X system allows UV delivery for treatment in a sitting or supine position while the KXL System is used only in the supine position. However, the UVX-001, UVX-002 and UVX-003 clinical protocols all specified treatments were performed in the supine position. Therefore, this difference has no impact on the safety or effectiveness of the devices.
Patient Contact	Non-contacting	Non-contacting	Same
Power Monitoring	Stand-alone commercial power meter, used at start-up.	Continuous, on-board monitoring using two independent dedicated UV photodiodes	The UV-X system requires the user to strap the power meter sensor to the treatment head to obtain a power reading prior to treatment. In the KXL System, power monitoring is integrated in the system, is automated and continuous. The automated, continuous power monitoring provided in the KXL System is more user friendly and does not require the user to manually check calibration prior to treatment. However, as both devices have calibration methods available, the differences in methodology should not impact the safety or effectiveness of the devices.
UV Light Emission	Initiated via a manual switch	Initiated via touch-screen menus and a valid RFID card must be detected to allow UV treatments	Different methodologies are used for initiating UV light treatment; however, this has no impact on the treatment performed or the safety or effectiveness of the devices.
UV Source	LED Illumination Source	LED Illumination Source	Same
UV Irradiance	3.0 ± 0.3 mW/cm^2	3.0 ± 0.3 mW/cm^2	Same
UV Exposure Time	30 minutes	30 minutes	Same
UV Wavelength	365 nm (nominal)	365 nm (nominal)	Same
UV Emission	Continuous	Continuous	Same

Differences between the IROC UVX and Avedro KXL Device (Cont'd)

Parameter	IROC UV-X (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL (device to be marketed)	Equivalence Assessment
Available UV Beam (Ø)	7.5 mm 9.5 mm 11.5 mm	9.0 mm	The UV-X system had three available beam diameters while the KXL System only includes the medium setting; however, the vast majority of subjects in the clinical studies were treated with the medium setting of the UV-X system. Therefore, this difference does not affect the safety or effectiveness of the treatment with the devices.
UV Focal Alignment	User observes the riboflavin fluorescence to gauge beam shape to determine proper alignment.	Two visible aiming lasers provide direct alignment confirmation in x, y, and z directions.	The KXL System alignment system should be easier for users to correctly align the system compared to the more subjective process with the UV-X system, however, this difference should not impact the safety or effectiveness of the treatment delivered with the devices.
UV Focal Plane (working distance – instrument exit to patient corneal apex)	50 mm nominal	150 mm nominal	The working distances differ between the two systems; however, both systems have methods for the user to determine the correct focal plane for treatment and therefore, there should be no impact on the safety or effectiveness of the treatment performed with the devices.
Software	Controlled by internal microprocessor which controls the electrical current used to drive the UV-LEDs	Controlled by software which is responsible for handling the user interface, UV delivery, alignment lasers, and wireless remote.	Both systems' UV output is software controlled and both systems include software that was verified and validated before use. Therefore, the differences in software should not impact the safety or effectiveness of the treatment delivered with the devices.

Differences between the IROC UVX and Avedro KXL Device (Cont'd)

Parameter	IROC UV-X (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL (device to be marketed)	Equivalence Assessment
Operating	+10C - +40C 30-75% RH, non-condensing 700-1060 mbar	+10C - +40C 30-75% RH, non-condensing 700-1060 mbar	Same
Device Dimensions	32x5x5 cm	60x60x150 cm, maximum extended position.	The dimensions of the two systems differ. The differences in the exact size and shape of the two systems does not impact the safety or effectiveness of the treatments delivered with the two devices.
Device Weight	<10 kg	45 kg	The weights of the two systems differ. The differences in the weights of the two systems does not impact the safety or effectiveness of the treatments delivered with the two devices.
Power Supply	External, commercial, DC supply Input: 100-240VAC; 1A max; 50/60 Hz Output: 9VDC, 1.7A	Internal. 100-240VAC; 2A max; 50/60 Hz	The power supplies differ, however, this difference should not impact the safety or effectiveness of the treatment delivered with the devices.
EMI/EMC per IEC 60601-1-2 FCC Part 15	Class B	Class B, 3rd Ed.	Same
Safety Classification	Class II Equipment Type B Applied Part	Class II Equipment (IEC60601-1, 3rd Ed.) Type B Applied Part	Same
Electrical IEC 60601-1	Class 1 (external power)	Class 1 Internal Battery Operation	Same
Laser IEC 60825-1	N/A	Class 1 (aiming lasers)	The UV-X system did not include aiming lasers so that system did not comply with IEC 60825-1. However, compliance with the safety standard should ensure no impact on the safety or effectiveness of the KXL System.
Lamps IEC 62471	Risk Group 1	Risk Group 1	Same

APPENDIX 4. CLASS 2 RESUBMISSION LETTER FOR NDA 203324

Reference ID: 3

APPENDIX 5. ADDITIONAL SENSITIVITY ANALYSES SUPPORT PRIMARY EFFICACY RESULTS (PROGRESSIVE KERATOCONUS)

Mixed-Effects Regression Models

In the following we provide a series of sensitivity analyses to explore the bounds of the treatment effect at 1 year based on a variety of different assumptions which include mixed-effects regression models based on linear, log-linear, and nonparametric time trends.

The estimation of the treated versus control difference at 12 months can be represented by using generalized mixed-effects regression models (Hedeker 2006). These are models that have been endorsed by both FDA statisticians (Siddiqui 2009) and industry statisticians (Mallinckrodt 2001) alike.

The overall pooled results of the linear mixed-effects models which model the nesting of repeated measurements within subjects and subjects within sites (Study UVX-001 treated as the 10th UVX-002 site) is presented in Table 49. Both the intercept and slope were allowed to vary at both individual and site levels. Results showed clear statistical (p=0.0004) and clinical superiority of treatment over control conditions (4.03 D difference at one year) using all available data for each subject.

The overall pooled results of log-linear time trends model allowed the time trends to flatten over time, providing a more conservative and better fit to the expected curvilinearity of the observed temporal pattern. The Bayesian information criterion (BIC) indicate that these models fit marginally better than the simple linear models (i.e. BIC is slightly smaller). Again, both statistical (<0.0001) and clinical significance was achieved; however the magnitude of the difference at 1 year is smaller (2.68 D) based on the curvilinearity of the estimated time trends.

Table 49: Mixed-Effects Regression Models

Regression Model	**Linear**	**Log-Linear**
Estimated CXL vs. Control effect at 1 year	4.03 D	2.68D
SE	1.15	0.64
p value	0.0004	<0.0001
BIC	3772.14	3770.60

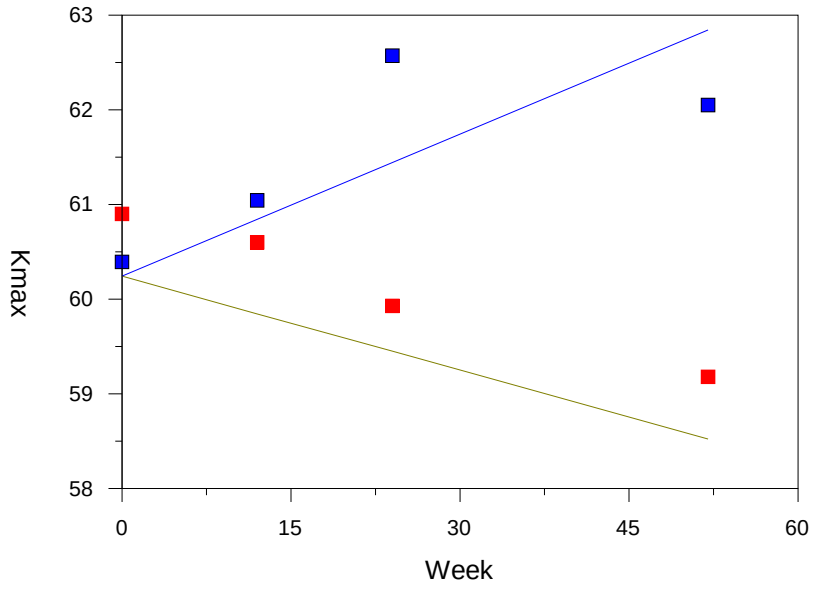
Nonparametric Time Trends

These models are nonparametric in the sense that time is treated as a factor with 4 levels (baseline, 3, 6 and 12 months). At 1 year the estimated treatment effects are intermediate between the linear and log-linear models but the standard error is inflated because there are so few control subjects. At 6 months both clinical and statistical significance is achieved. Note that the nonparametric model does not fit as well as either the linear or log-linear models.

- 12 weeks 1.15D (0.57) p=0.04
- 26 weeks 2.49D (0.73) p=0.0005
- 52 weeks 2.84D (2.38) p=0.23
- BIC = 3776.93

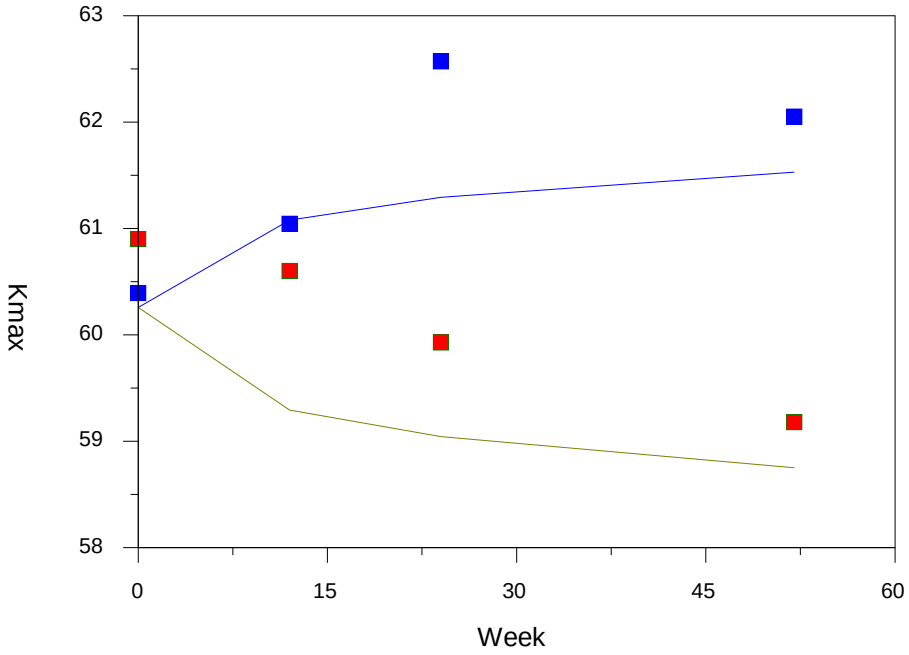
The following graph displays the observed estimated means for the linear time trend model for progressive keratoconus from the mixed-effects models (Figure 18), red squares treated, blue squares control). The squares represent the observed treatment means based on the subjects still in the study at each measurement occasion.

Figure 18: Linear Time Trends - Progressive Keratoconus



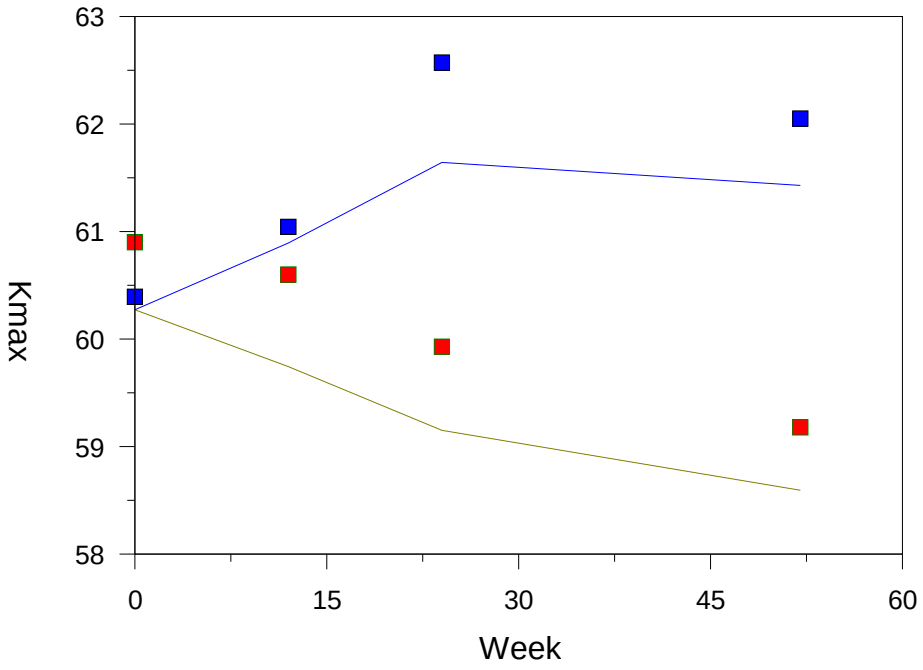
The following graph presents the estimated time-trends for the log-linear model for progressive keratoconus (Figure 19). The curvature in the time trends after 3 months is consistent with treatment effect in the CXL group and worsening in the control group (red squares treated, blue squares control).

Figure 19: Log-Linear Time Trends – Progressive Keratoconus



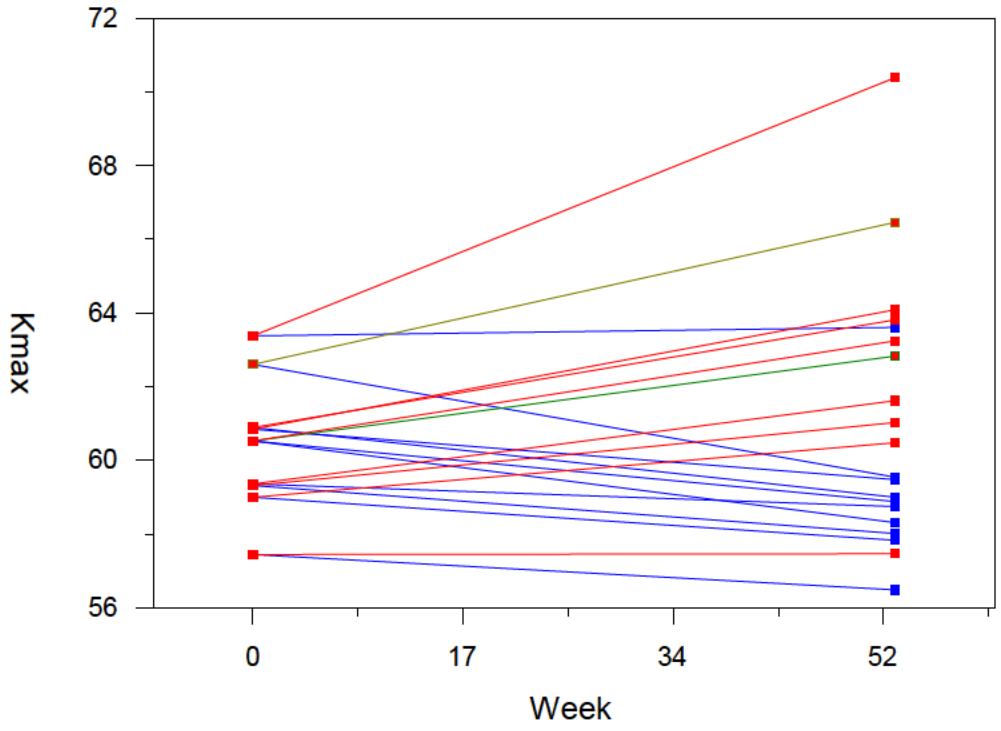
The following graph displays the estimated trend line for progressive keratoconus patients based on the nonparametric (discrete time) model (Figure 20), red squares treated, blue squares control). Note the similarity to the log-linear model.

Figure 20: Discrete Time Model – Progressive Keratoconus



The empirical Bayes estimates of the estimated time trends for each of the study sites for progressive keratoconus are provided below (Figure 21). Note that there is considerable variability at baseline and in terms of the rate of change (red lines treated, blue lines control) but the estimated treatment effect is consistent across all sites.

Figure 21: Estimated Site-Specific Time Trends – Progressive Keratoconus



Site Heterogeneity

In this linear model for progressive keratoconus, we allowed the treatment by time interaction to vary across sites. The overall variability is only 16% which is consistent with the previous graphical depictions. The lower 95% confidence limit for the site effect remains clinically significant at slightly less than 3 D.

Empirical Bayes Estimates and Response to Treatment

Using the empirical Bayes estimates, we can estimate the expected change at 1 year for each subject based on their available data. This estimate was then used to compute the proportion of subjects with a 1D or greater improvement from baseline. For progressive keratoconus, 61% of the subjects achieved this clinically meaningful result whereas only 2% of the controls did. Note that this is a change of 1D or more, not a treated versus control difference of 1D; therefore this is an even more stringent criterion.

Between Subjects Analysis

Table 50 presents the results of a sensitivity analysis comparing the fit of linear, log-linear and nonparametric models based on different random-effects for the CXL group. The random-effects structures include random intercepts at both subject and study levels [int(2,3)], random intercepts at subject and sites and random trend across subjects [int+slope(2)] and random intercepts and slopes at subject and site levels [int+slope(2,3)]. The best fitting models are denoted by an asterisk. All models achieve statistical and clinical significance with the exception of the 52 week discrete time model which has an inflated standard error because there are so few control subjects available at that point in time. Based on this analysis, our best estimate of the 1-year effect for progressive keratoconus is 2.68 D.

Table 50: Sensitivity Analysis based on Different Random-Effects – CXL Group (Progressive Keratoconus)

	Random Effects	BIC	52 Weeks		
			Δ	SE	P
Linear	Int(2,3)	3768.71	-4.19	1.11	0.0002
	Int + slope(2)	3767.81	-4.17	1.10	0.0002
	Int + slope(2,3)	3772.14	-4.03	1.15	0.0004
Log linear	Int(2,3)	3770.88	-2.73	0.65	< .0001
	Int + slope(2)*	3765.98	-2.68	0.64	< .0001
	Int + slope(2,3)	3770.60	-2.68	0.64	< .0001
Discrete	52 weeks	3776.93	-2.84	2.38	0.23
	26 weeks		-2.49	0.72	0.0005

*Best fitting model

Within Subject Analysis – Primary Eye

Table 51 presents the results of a sensitivity analysis comparing the fit of linear, log-linear and nonparametric models based on different random-effects for control subjects who crossed-over to receive treatment in the primary eye. The treatment effect here is completely within-subject. The estimated within-subject effect for progressive keratoconus is 3.87D.

Table 51: Sensitivity Analysis based on Different Random-Effects (Control Group)

	Random Effects	**BIC**	**52 Weeks**		
			Δ	**SE**	**P**
Linear	Int(2,3)*	3360.18	-3.87	1.23	0.0016
	Int + slope(2)	3362.46	-3.87	1.22	0.0015
	Int + slope(2,3)	3371.46	-4.00	1.22	0.0011
Log linear	Int(2,3)	3363.28	-2.48	0.73	0.007
	Int + slope(2)	3368.24	-2.48	0.74	0.008
	Int + slope(2,3)	3378.81	-2.50	0.75	0.008
Discrete	52 weeks	3369.00	-2.35	3.36	0.4800
	26 weeks		-1.88	0.78	0.0160

*Best fitting model

Within Subject Analysis – Fellow Eye

Table 52 presents the results of a sensitivity analysis comparing the fit of linear, log-linear and nonparametric models based on different random-effects structures for comparison of control subjects for treated (fellow) and untreated (primary) control subject eyes. The data for the primary eye was before cross-over and data from the treated fellow eye followed treatment for the primary eye after the patient crossed over. The estimated treatment effect at 1 year was 5.81 D. Again, the same pattern of statistical and clinical significance was observed as in the two previous tables.

Table 52: Sensitivity Analysis based on Different Random-Effects – Comparison of Control Subjects for Treated (Fellow) and Untreated (Primary) Eyes

	Random Effects	**BIC**	**52 Weeks**		
			Δ	**SE**	**P**
Linear	Int(2,3)*	2594.99	-5.81	2.02	0.0041
	Int + slope(2)	2600.54	-5.79	2.10	0.0057
	Int + slope(2,3)	2605.54	-5.90	2.11	0.0051
Log linear	Int(2,3)	2597.15	-2.91	1.23	0.018
	Int + slope(2)	2601.62	-2.91	1.31	0.026
	Int + slope(2,3)	2606.31	-2.91	1.31	0.026
Discrete	52 weeks	2603.63	-3.79	5.42	0.48
	26 weeks		-3.28	1.40	0.019

*Best fitting model

APPENDIX 6. ADDITIONAL SENSITIVITY ANALYSES SUPPORT PRIMARY EFFICACY RESULTS (CORNEAL ECTASIA)

Mixed-Effects Regression Models

In the following we provide a series of sensitivity analyses to explore the bounds of the treatment effect at 1 year based on a variety of different assumptions which include mixed-effects regression models based on linear, log-linear, and nonparametric time trends.

The estimation of the treated versus control difference at 12 months can be represented by using generalized mixed-effects regression models (Hedeker 2006). These models have been provide endorsed by both FDA statisticians (Siddiqui 2009) and industry statisticians (Mallinckrodt 2001) alike.

The overall pooled results of linear mixed-effects models which model the nesting of repeated measurements within subjects and subjects within sites (Study UVX-001 treated as the 10th UVX-003 site) is presented in Table 53. Both the intercept and slope were allowed to vary at both individual and site levels. Results showed clear statistical (p=0.0001) and clinical superiority of treatment over control conditions (2.45 D difference at one year) using all available data for each subject.

The overall pooled results of log-linear time trends model allowed the time trends to flatten over time, providing a more conservative and better fit to the expected curvilinearity of the observed temporal pattern. The Bayesian information criterion (BIC) indicate that these models fit marginally better than the simple linear models (i.e. BIC is slightly smaller). Again, both statistical (<0.0001) and clinical significance was achieved; however the magnitude of the difference at 1 year is smaller (1.65 D) based on the curvilinearity of the estimated time trends.

Table 53: Mixed-Effects Regression Models

Regression Model	**Linear**	**Log-Linear**
Estimated CXL vs. Control effect at 1 year	2.45 D	1.65D
SE	0.62	0.34
p value	0.0001	<0.0001
BIC	2650.85	2650.55

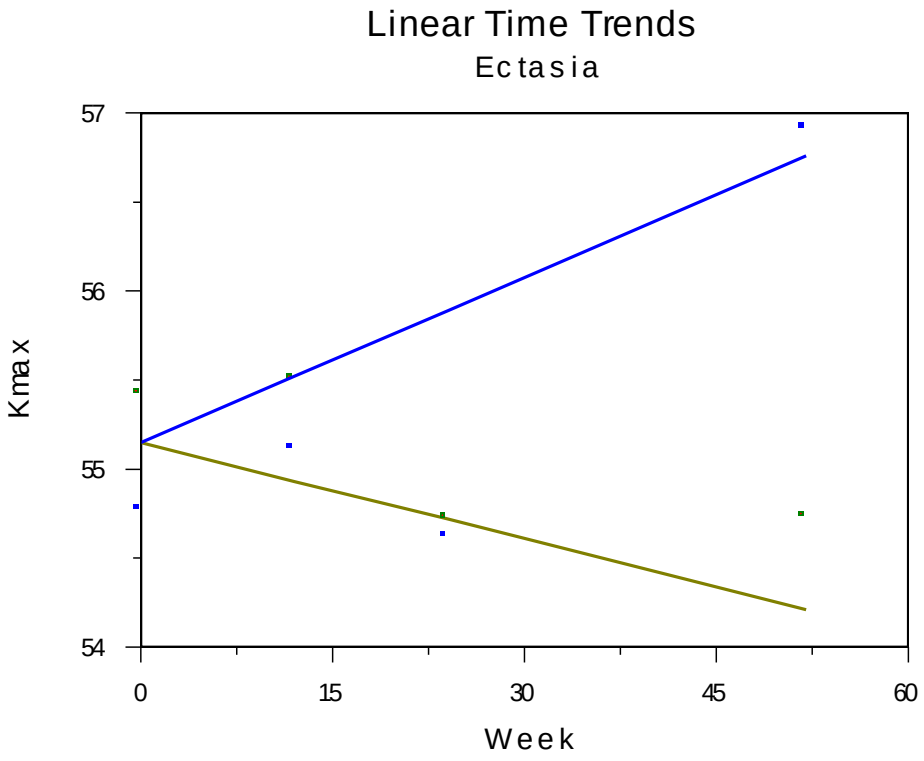
Nonparametric Time Trends

These models are nonparametric in the sense that time is treated as a factor with 4 levels (baseline, 3, 6 and 12 months). At 1 year the estimated treatment effects are intermediate between the linear and log-linear models but the standard error is inflated because there are so few control subjects. At 6 months both clinical and statistical significance is achieved. Note that the nonparametric model does not fit as well as either the linear or log-linear models.

- 12 weeks 0.77D (0.29) p=0.008
- 26 weeks 1.19D (0.37) p=0.001
- 52 weeks 1.92D (1.13) p=0.09
- BIC = 2654.70

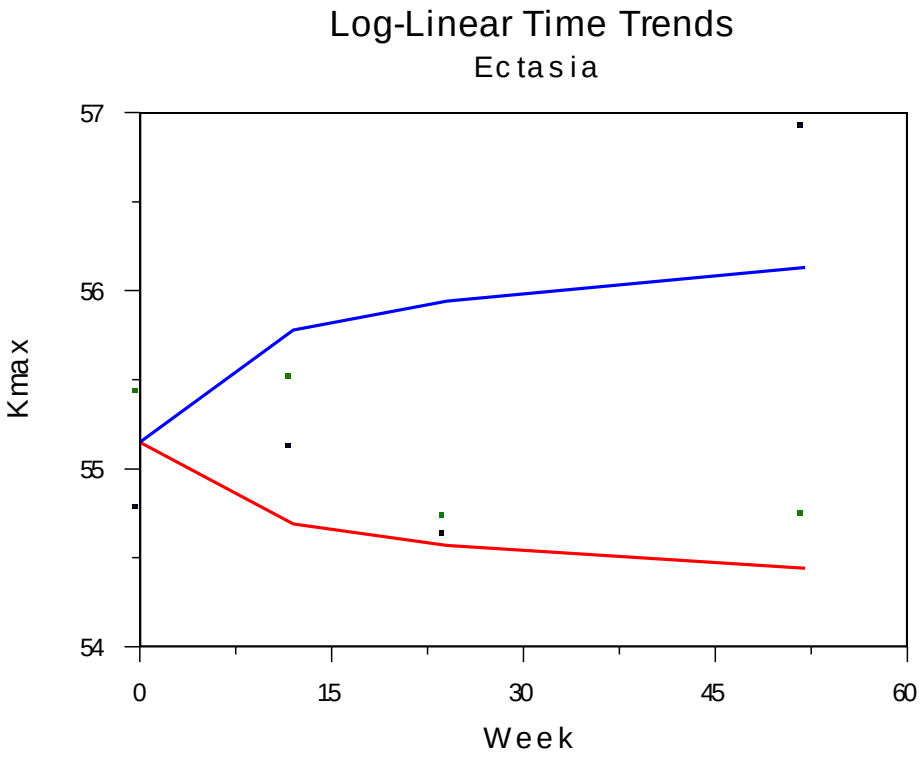
The following graph displays the observed estimated means for the linear time trend model for Ectasia from the mixed-effects models (Figure 22), red squares treated, blue squares control). The squares represent the observed treatment means based on the subjects still in the study at each measurement occasion.

Figure 22: Linear Time Trends – Ectasia



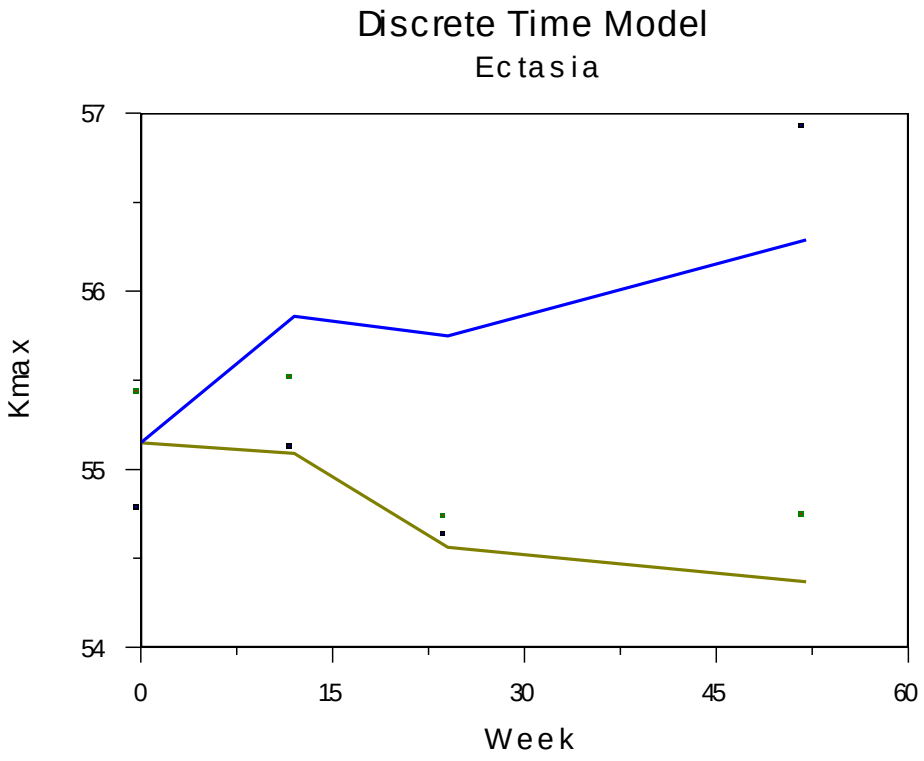
The following graph presents the estimated time-trends for the log-linear model for Ectasia (Figure 23). The curvature in the time trends after 3 months is consistent with treatment effect in the CXL group and worsening in the control group (red squares treated, blue squares control).

Figure 23: Log-Linear Time Trends - Ectasia



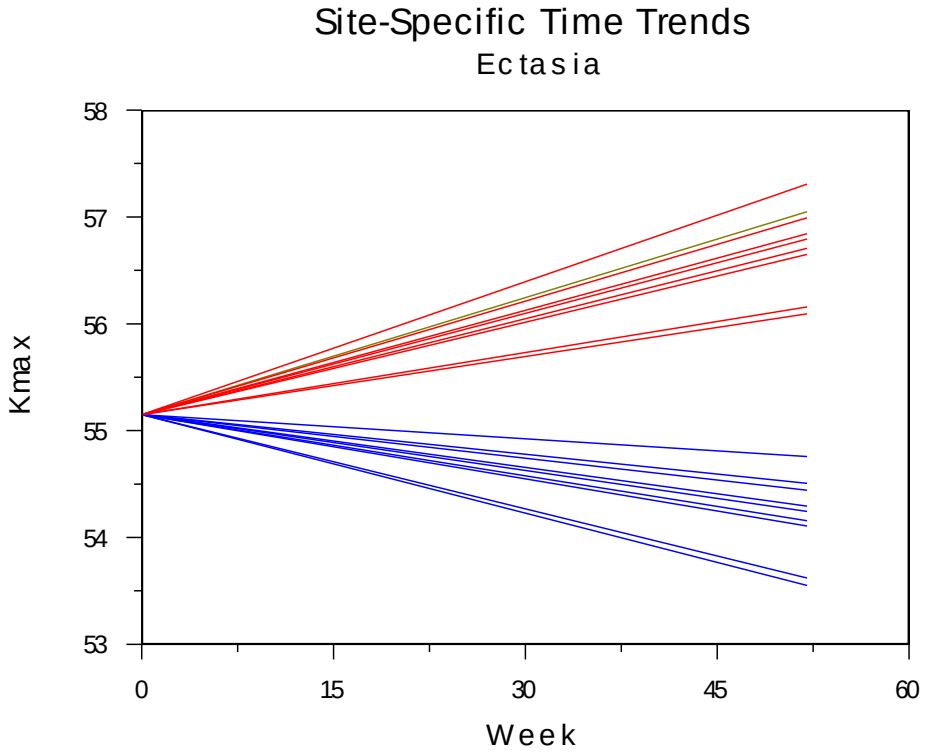
The following graph displays the estimated trend line for Ectasia patients based on the nonparametric (discrete time) model (Figure 24), red squares treated, blue squares control).

Figure 24: Discrete Time Model - Ectasia



The empirical Bayes estimates of the estimated time trends for each of the study sites for Ectasia are provided below (Figure 25). Note that there is very little if any variability at baseline, but there was some variability in the rate of change (red lines treated, blue lines control) but the estimated treatment effect is clear and consistent across all sites.

Figure 25: Estimated Site-Specific Time Trends - Ectasia



Site Heterogeneity

In this linear model for Ectasia, we allowed the treatment by time interaction to vary across sites. The overall variability is only 22% which is consistent with the previous graphical depictions. The lower 95% confidence limit for the site effect remains clinically significant at 1.56 D.

Empirical Bayes Estimates and Response to Treatment

Using the empirical Bayes estimates, we can estimate the expected change at 1 year for each subject based on their available data. This estimate was then used to compute the proportion of subjects with a 1D or greater improvement from baseline. For Ectasia, 18% of the subjects achieved this clinically meaningful result whereas none of the controls did. Note that this is a change of 1D or more, not a treated versus control difference of 1D; therefore this is an even more stringent criterion.

Between Subjects Analysis

Table 54 presents the results of a sensitivity analysis comparing the fit of linear, log-linear and nonparametric models based on different random-effects for the CXL group. The random-effects structures include random intercepts at both subject and study levels [int(2,3)], random intercepts at subject and sites and random trend across subjects [int+slope(2)] and random intercepts and slopes at subject and site levels [int+slope(2,3)]. The best fitting models are denoted by an asterisk. All models achieve statistical and clinical significance with the exception of the 52 week discrete time model which has an inflated standard error because there are so few control subjects available at that point in time. Based on this analysis, our best estimate of the 1-year effect for Ectasia is 2.43 D.

Table 54: Sensitivity Analysis based on Different Random-Effects – CXL Group (Ectasia)

	Random Effects	**BIC**	**52 Weeks**		
			Δ	**SE**	**P**
Linear	Int(2,3)*	2643.22	-2.43	0.58	< 0.0001
	Int + slope(2)	2647.06	-2.42	0.58	< 0.0001
	Int + slope(2,3)	2650.85	-2.45	0.62	0.0001
Log linear	Int(2,3)	2643.74	-1.66	0.34	< 0.0001
	Int + slope(2)	2645.92	-1.65	0.34	< 0.0001
	Int + slope(2,3)	2650.55	-1.65	0.34	< 0.0001
Discrete	52 weeks	2645.70	-1.92	1.13	0.090
	26 weeks		-1.19	0.37	0.0015

*Best fitting model

Within Subject Analysis – Primary Eye

Table 55 presents the results of a sensitivity analysis comparing the fit of linear, log-linear and nonparametric models based on different random-effects for control subjects who crossed-over to receive treatment in the primary eye. The treatment effect here is completely within-subject. The estimated within-subject effect for Ectasia is 1.10D.

Table 55: Sensitivity Analysis based on Different Random-Effects (Control Group)

	Random Effects	**BIC**	**52 Weeks**		
			Δ	**SE**	**P**
Linear	Int(2,3)	2382.01	-1.69	0.77	0.0287
	Int + slope(2)	2386.65	-1.70	0.78	0.0300
	Int + slope(2,3)	2391.29	-1.70	0.78	0.0303
Log linear	Int(2,3)	2381.79	-1.10	0.47	0.0194
	Int + slope(2)*	2381.02	-1.10	0.45	0.0159
	Int + slope(2,3)	2385.27	-1.08	0.46	0.0178
Discrete	52 weeks	2384.80	-0.92	1.49	0.5368
	26 weeks		-0.55	0.50	0.2706

*Best fitting model

Within Subject Analysis – Fellow Eye

Table 56 presents the results of a sensitivity analysis comparing the fit of linear, log-linear and nonparametric models based on different random-effects structures for comparison of control subjects for treated (fellow) and untreated (primary) control subject eyes. The data for the primary eye was before cross-over and data from the treated fellow eye followed treatment for the primary eye after the patient crossed over. The estimated treatment effect at 1 year was 2.63 D. Again, the same pattern of statistical and clinical significance was observed as in the two previous tables.

Table 56: Sensitivity Analysis based on Different Random-Effects – Comparison of Control Subjects for Treated (Fellow) and Untreated (Primary) Eyes

	Random Effects	**BIC**	**52 Weeks**		
			Δ	**SE**	**P**
Linear	Int(2,3)*	1641.53	-2.63	1.30	0.044
	Int + slope(2)	1642.54	-2.70	1.33	0.043
	Int + slope(2,3)	1647.18	-2.71	1.33	0.042
Log linear	Int(2,3)	1639.45	-2.34	0.91	0.010
	Int + slope(2)	1643.53	-2.35	0.92	0.011
	Int + slope(2,3)	1648.06	-2.35	0.92	0.010
Discrete	52 weeks	1647.75	-2.50	2.29	0.27
	26 weeks		-1.92	1.00	0.056

*Best fitting model