CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig1s000

CLINICAL REVIEW(S)

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 203324
Related IND	IND 77,882 IND 78,933
Applicant Name	Avedro, Inc.
Date of Submission **Date of Receipt**	September 16, 2013 September 16, 2013
Review Type:	Priority
Complete Response Letter:	March 14, 2014
Complete Resubmission:	September 29, 2014
PDUFA Goal Date:	March 29, 2015 (Sunday)
Proprietary Name / **Established (USAN) Name** **Proprietary Name /** **Established (USAN) Name**	Photrexa Viscous riboflavin 5'-phosphate in 20% dextran ophthalmic solution, 0.146% Photrexa riboflavin 5'-phosphate ophthalmic solution, 0.146%
Formulation **Use**	ophthalmic solution 1 drop topically on the eye every 2 minutes for 30 minutes during post epithelial debridement. When corneal thickness is ≥400 microns, continue topical instillation 1 drop onto the eye every 2 minutes during the 30 minute UVA irradiation (if corneal thickness is <400 microns, riboflavin without dextran is used to increase thickness)
Device component of combination Product	The KXL® System is a portable electronic medical device and serves as a UVA light source
Proposed Indication(s)	Treatment of progressive keratoconus and corneal ectasia following refractive surgery
Action for Application	*Complete Response (#2)*

Material Reviewed/Consulted during the current review cycle	**Names of discipline reviewers**
Medical Officer Review	William Boyd 3/24/2015
CDTL Review	Bill Boyd, Wiley Chambers 3/27/2015
CDRH Device Clinical Review	Maryam Mokhtarzadeh, 3/24/2015
CDRH EMC Review	Jeffrey Silberberg 3/24/2015, 3/27/2015
CDRH Electrical Safety Review	Sandy Weininger 1/9/2015
CDRH Software Review	Joseph Jorgens III 3/3/2014, 3/26/2015
CDRH Engineering Review	Dexiu Shi 3/26/2015
Statistical Review Team Leader Review	Dongliang Zhuang, Yan Wang 3/12/2015 Yan Wang, Dionne Price 3/15/2015
Pharmacology/Toxicology Review	No new studies
Clinical Pharmacology Review	No new studies
Product Quality Manufacturing Review	George Lunn, Dorota Matecka 3/5/2015
Methods Validation	See CMC review
Product Quality Microbiology	See CMC review
CDER/ OC/Facilities Inspection	See CMC review
CHDR/OC/DMQ/ASDB Device Inspection	Felicia Brayboy, Ronald Swann 1/15/2014
OSI/DGCPC	Janice Pohlman, Kassa Ayalew 3/27/2015
OSE/DMEPA Proprietary Name Review Name granted	Rachna Kapoor, Yelena Maslov, Lubna Merchant 1/13/2015 Todd Bridges (Karen Townsend) 1/14/2015
OSE/DMEPA Label Review	Rachna Kapoor, Yelena Maslov 3/9/2015 Yelena Maslov 3/17/2015
SEALD Review	Jessica Voqui, Elektra Papadopoulos 2/23/2015
OPDP/DPDP (formerly DDMAC)	CR – not reviewed during this cycle
Pediatric Review Committee	Orphan designation – PREA does not apply

CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
OC/DMQ/ASDB = Abdominal and Surgical Devices Branch, Division of Manufacturing and Quality, Office of Compliance
SEALD=Study Endpoint and Labeling Development

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1. Summary and Recommendations

Comment:
In the interest of brevity, this review focuses on information reviewed and considered during this review cycle to address deficiencies in the Complete Response letter of March 14, 2014. The Division Director Review dated March 14, 2014, should be consulted for an overview of findings and issued during the first review cycle.

NDA 203324 is submitted for approval of a combination product consisting of the drug constituent Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146% without dextran and the device constituent, KXL System, a UVA irradiation device. The applicant submitted controlled clinical trials for each of two proposed indications – progressive keratoconus and corneal ectasia following refractive surgery. The applicant has obtained orphan designation for each indication. The application was reviewed by CDER (drug component) and CDRH (device component), presented for discussion and advice at the combined Advisory Committee meeting and Device Panel meeting on February 24, 2015, and also presented at the March 20, 2015 CDER Regulatory Briefing, attended by CDRH and Office of Combination Products (OCP) staff.

The main issues raised at these meetings or in discussion are:

The device proposed for marketing has not been tested in any clinical studies submitted to the application. Concern about the absence of clinical studies with the to-be-marketed device has been voiced by CDRH, by member of the Advisory Committee/Device Panel, , and the Regulatory Briefing. In DTOP, sponsors developing eye products are generally advised that for approval, the to-be-marketed product should be used in at least one of the clinical trials in the application. For the reasons above, the applicant will be asked to submit at least one clinical trial with the to-be-marketed combination product.

- Such a trial may not be needed if a link that can be established between the clinical study device (UV-X) and the to-be-marketed device (KXL System), however, such a link has not been established to date.

- Given that the studies submitted in this application showed statistically significant improvement in Kmax at 6 months after the corneal collagen cross-linking procedure (see Section 7 Efficacy), it is conceivable that for the new study, 6-month clinical results could be submitted for approval (e.g., accelerated approval with the Kmax endpoint) and final study results could be submitted when complete Month 12 data are available..

- As presented in Section 2 Background, published literature on the natural history over 7-8 years suggests that progression of keratoconus is associated with reduction in visual function, and after treatment, reduction of Kmax is associated with improvement in refractive correction. Collecting information on these outcomes in the study of the to-be-marketed combination would be informative and potentially show an association between the corneal curvature change and clinical benefit. This view that clinical benefit should be

shown is not shared by all reviewers. Another view is that keratoconus is a structural change with the formation of a cone in the cornea, and stopping the formation of the cone is stopping the disease. A change in structure or function is one of the FD&C definitions of a drug. Whether or not required, demonstration of clinical benefit to the patient is of interest.

- A further reason for a new clinical trial is due to the many flaws identified in the studies submitted to the application, including the lower-than planned enrollment of patients. Overall 193 patients were randomized to CXL treatment: 102 patients with progressive keratoconus and 91 patients with corneal ectasia following refractive surgery. Typically, DTOP has asked sponsors to submit data on 500 patients receiving the proposed regimen for marketing with the expectation that comparative safety data will be available for 300 patients.

- There are non-comparative data from a total of 293 progressive keratoconus eyes exposed to CXL (including CXL treated patients, sham patients treated with CXL after Month 3 and fellow eyes treated after Month 3), and 219 corneal ectasia eyes, the majority are uncontrolled data (See Section 8 Safety). If the size of the safety database were the only remaining issue with the application, one could consider approval with agreement to collect additional data post-marketing to better characterize the safety profile. But given that there are no data on the to-be-marketed device, conduct of a new study will provide additional safety information.

An alternative approach may be for Avedro to identify published studies with the KXL System and compare them with their studies to try to show a bridge to the current clinical studies. In that approach is chosen, it would be important to provide further details on the characteristics of the device to augment the published information. (See Appendix A for deficiencies and additional comments to the applicant)

In addition to remaining deficiencies with the KXL System, and need for comparative information between the UV-X device and the KXL System device, colleagues in CDRH have identified multiple concerns about the clinical trial design, conduct and analysis. Recommendations include exploratory analyses (by age, illumination diameter size, corneal thickness) and additional subset analyses of safety data, and a comprehensive literature search of corneal collagen cross-linking studies. It is not clear that any of these would yield an approval recommendation; however, because these analyses may be informative in the design of a new study, they will be shared with the applicant.

The following disciplines recommend approval following review of their portion of the application: CMC, Pharmacology/Toxicology, Clinical Pharmacology, and Statistics. In addition the Office of Compliance recommends that manufacturing facility inspections are acceptable and the Office of Scientific Inspections considers the clinical data submitted in the application acceptable for regulatory action.

Because there are no clinical studies using the to-be-marketed device and there are outstanding Device deficiencies, the application will be issued a Complete Response letter.

1.1 Deficiencies
See Appendix A.

1.2 Post-Marketing Studies:
Not applicable

1.3 Other Issues
None

2. Background

Approved Products
There are currently no medical treatments approved for keratoconus or corneal ectasia following refractive surgery. The Intacs corneal implant, surgically-implanted ring segments, is approved for the treatment of myopia and keratoconus.

Medical Condition
Keratoconus is a naturally occurring condition and corneal ectasia is a described complication following laser in-situ keratomileusis (LASIK), photorefractive keratectomy (PRK) and other refractive surgeries. The irregular anatomy of the cornea is a result of thinning and steeping/protrusion of the cornea and is associated with visual impairment and can include myopia, astigmatism, abnormal vision which may not be adequately managed with contacts and corrective spectacles. In advanced stages, patients may need a corneal transplant to restore visual acuity.

2.1 Regulatory History

The detailed regulatory history is documented in the CDTL review by Dr. Boyd.

IND 77,882 was originally submitted by Peschke Meditrade GmbH (Hüenenberg, Switzerland) on November 7, 2007, and Studies UVX-002 and UVX-003 were initiated. Study UVX-001 was conducted under IND 78,933 by Dr. R. Doyle Stulting.

Sponsorship was transferred to Avedro on May 7, 2010, and included all three studies. The final statistical analysis plans (SAP) were submitted after the studies had been completed and after one investigator, Dr. Hersh, published his results from studies UVX-002 and UVX-003. This raised questions about the appropriateness of changing in the primary endpoint from Month 3 to Month 12 in the SAP. These concerns are addressed in Section 7 Efficacy.

The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for these combination products under RFD070013.

Avedro, Inc. submitted a New Drug Application (NDA) 203324 on March 8, 2012 as a 505(b)(2) application that relies on nonclinical studies from the literature.
FDA issued a refuse to file (RTF) letter dated May 4, 2012 because the application was not sufficiently complete to permit a substantive review (21 CFR 314.101(d)): there were 7 deficiencies and 14 potential review issues for Avedro to address before resubmission.

NDA 203324 was resubmitted September 16, 2013 and granted priority review. The combination product was reviewed by CDER and CDRH. Multiple deficiencies were identified and the application was issued a Complete Response letter March 14, 2014 with the following deficiencies (numbering corresponds to CR letter):

- CMC deficiencies in methods validations, specifications, stability data (#1-#3)
- Manufacturing facility deficiencies, the Office of Compliance recommends withhold (#4)
- Device deficiencies including differences between the device used in clinical trials and the to-be-marketed device, need for software modification, validation activities, electromagnetic compatibility and consensus standards, labeling and instruction for use (#5-#12)
- Clinical/Statistical deficiencies include failure to meet primary endpoint, data errors, additional safety information, audit of data monitoring data are requested (#13-#14)
- Additional Comments including information on post-marketing experience, relationship of published article data by one of the investigators from the current studies in the NDA (#15-#17).

The applicant met with the FDA on August 6, 2014, to review the proposed responses to the deficiencies identified in the March 14, 2014, letter and submitted a Complete Response to the application on September 29, 2014. The application was assigned 6-month resubmission goal date. As summarized in this review, the applicant addressed all items but items #9 and #10.

The NDA was presented at the February 24, 2015, Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee and at the CDER Regulatory Briefing March 20, 2015 attended also by CDRH reviewers and management and Office of Combination Products (OCP). The committee vote was split (see Section 9) and at the Regulatory Briefing discussion included the clinical trial results and to-be-marketed device (See Section 9a).

2.2 Orphan Designation

As noted in the clinical review, the Office of Orphan Products Development granted orphan designation for both proposed indications: keratoconus and corneal ectasia following refractive surgery.

2.3 Normal cornea and the Natural History of Keratoconus

In the publication by McMahon[1] of the CLEK Study described below, the following summary of the maturation of the normal cornea and transition to keratoconus findings is provided.

> The normal cornea flattens from birth through the first decade. Asbell found that for infants younger than age 6 months, the average corneal curvature was 47.59 D, flattening

[1] Timothy T. McMahon, OD,* Timothy B. Edrington, OD, MS,† Loretta Szczotka-Flynn, OD, MS,‡ Harald E. Olafsson, OD,§ Larry J. Davis, OD,|| Kenneth B. Schechtman, PhD,¶ and the CLEK Study Group. Longitudinal Changes in Corneal Curvature in Keratoconus *Cornea* 2006;25:296Y305)

> to 45.37 D at age 18 to 24 months and stabilizing at approximately age 4.5 years at 42.69 D. In keratoconus, corneal curvature readings are consistently steeper than the unaffected population. Ninety-five percent of CLEK Study patients had steep keratometric values of $\geq$ 45 D at baseline. Additionally, in normal patients, corneal curvature readings have been documented to be fairly similar between eyes. In keratoconus, however, Zadnik et al found clinically and statistically different values comparing the better eye to the worse eye.
>
> As keratoconus progresses, corneal curvature typically steepens. Once the diagnosis of keratoconus is made, patients and clinicians often ask how much the condition is expected to progress during the coming years. Progression of the disease as defined by steeper corneal curvature readings commonly requires modification of the contact lens fit or referral for penetrating keratoplasty if an acceptable contact lens fit can no longer be achieved.

The following information on the natural history of keratoconus is excerpted from the CDTL Review:

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study was a long-term evaluation of the natural history of keratoconus involving 1209 patients during an 8 year period. Corneal curvature is the clinical variable most commonly used to monitor change in disease severity in keratoconus. The progression of disease is reported as defined by changes in corneal curvature measured directly, via keratometry, and indirectly, by using rigid contact lenses of varying base curves to achieve apical clearance (First Definite Apical Clearance Lens, i.e. FDACL).

The slope of the change with time in the FDACL or the flatter keratometric Reading (Flat K) was calculated. The 1032 patients evaluated exhibited a slow but clear increase in corneal curvature. The slope of the change in FDACL (0.18 ± 0.60 D/y) and Flat K (0.20 ± 0.80 D) during 8 years translates into expected 8-year increases of 1.44 D in FDACL and 1.60 D in Flat K. Increases of >3.00 D in either eye had an 8-year incidence of 25% for FDACL and 24% for Flat K.

The noninflammatory, asymmetric, bilateral, progressive corneal ectasia and thinning seen in keratoconus may result in irregular astigmatism and corneal scarring, both of which reduce the best-corrected visual acuity (BCVA) of the patient. Seven (7) years of follow-up data were obtained from 953 CLEK subjects who did not have penetrating keratoplasty in either eye at baseline and who provided enough data to compute the slope of the change over time in high- or low-contrast best-corrected visual acuity (BCVA), and the proportion of patients with a decrease of 10 letters or more in at least one eye in 7 years.

Independent predictors of reduced high- and low-contrast BCVA included better baseline acuity, steeper first definite apical clearance lens (FDACL), and fundus abnormalities. Each diopter of steeper baseline FDACL predicted an increased deterioration of 0.49 high- and 0.63 low-contrast letters correct. High- and low contrast visual acuity decreases of 10 or more letters correct occurred in 19% and 31% of subjects, respectively.

Comment: The natural history publications report that over the course of 7-8 years, patients with keratoconus on average have an increase in Kmax (up to an increase of >3.00 D in approximately 25%) and a decrease in visual acuity (loss of 10 letters of more in 19%-31%, depending on contrast).

2.4 Corneal Collagen Crosslinking (CXL) Procedures

The following text in Arial font is excerpted from the CDRH review, Systematic Literature Review on Corneal Collagen Crosslinking (CXL) Procedures for the Treatment of Keratoconus and Secondary Ectasia. The complete report, including the literature search strategy is included as Attachment 4 in the CDRH Clinical Review. These excepts focus on the result of the review of the 6 references listed in the report.

References

1. Wollensak, G. et al. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. American Journal of Ophthalmology. 2003;135:620-627.
2. Renesto Ada C., et al., Impression cytologic analysis after corneal collagen cross-linking using riboflavin and ultraviolet-A light in the treatment of keratoconus. Cornea 2010;29:1139–1144
3. O'Brart, D., et al., A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. Br J Ophthalmol 2011; 95:1519-1524.
4. Henriquez, MA. et al., Riboflavin/ultravioletA corneal collagen cross-linking for the treatment of keratoconus: Visual Outcomes and Scheimpflug Analysis. Cornea 2011; 30:281–286.
5. Wittig-Silva, C., et al., A Randomized, controlled trial of corneal collagen cross linking in progressive keratoconus. Ophthalmology 2014; 121:812-821.
6. Sorkin, N. and D. Varssano. Corneal collagen crosslinking: A systematic review. Ophthalmologica. 2014; 232:10-27.

Summary of Efficacy

Efficacy of the CXL procedure in these studies [see references] was defined as improvements in visual acuity, keratometry readings, and spherical equivalent values measured by uncorrected visual acuity (UCVA), best corrected spherical visual acuity (BSCVA), minimal (K-min), maximum (K-max) and average (K-ave) keratometry values and refractive changes. Cell/tissue regeneration was rarely reported but for convenience, also grouped into this category.

Keratometry

Wittig-Silva et al.[5] reported that the non-treated eyes experienced a K-max increase by a mean of 1.20+0.28 diopters (D), 1.70+0.36 D, and 1.75+0.38 D at 12, 24, and 36 months, respectively (P<0.001). In treated eyes, K-max flattened by 0.72+0.15 D, 0.96+0.16 D, and 1.03+0.19 D at 12, 24, and 36 months, respectively (P<0.001).

O'Brart et al.[3] reported an improvement in average Orbscan simulated keratometry values by -0.62 D after 18 months in the treatment group (P<0.001), whereas the control group had a non-significant progression of +0.14 D (P = 0.3).

Henriquez et al. [4] confirmed a significant reduction in the mean K-max of 2.66D (P = 0.04) and K-min of 1.61 D (P = 0.03) not until 12 months postoperatively in 10 CXL treated eyes, but the control group showed mainly the opposite (9 out of 10 eyes increase in the K-max, and 4 of those had an increase greater than 1 D).

Visual Acuity

Wittig-Silva et al.[5] found the mean change in UCVA in the control group was +0.10+0.04 logMAR (P=0.034) at 36 months. In the treatment group, both UCVA (-0.15+0.06 logMAR; P=0.009) and BSCVA (-0.09+0.03 logMAR; P = 0.006) improved at 36 months.

O'Brart et al.[3] found there were improvements in BSCVA in both groups (treatment group: +0.12, control group: +0.13, P=0. 98), perhaps due to the "repeated visual function tests the patients went through".

Henriquez et al.[4] reported an UCVA of 0.46 logarithm of the minimum angle of resolution at 12 months postoperatively as compared to 1.18 logarithm preoperatively (P<0.001) for patients that underwent the CXL procedure.
The article reports that the study demonstrated improved refractive outcomes for patients undergoing riboflavin/UV-A cross-linking for keratoconus.

Refraction Change
Wittig-Silva et al.[5] reported a manifest cylinder increased only significant in the control group by 1.17+0.49 D (P = 0.020) at 36 months.

O'Brart et al.[3] reported a variety of refraction related measurements such as astigmatism, Keraton Scout-simulated astigmatism, cone apex power, RMS, coma and pentafoil decreased in treated eyes and increased/remained unchanged in untreated eyes, with significant differences between the means of postoperative changes from baseline.

Henriquez et al.[4] reported a 2.25 D reduction in the mean spherical equivalent (P = 0.01) in the treatment group.

Assessment of Efficacy and Critique
These articles support the efficacy of the CXL procedure for keratoconus based on flattening the corneal curvature measured by keratometry data, improvement in visual functioning measured by UCVA or BSCVA. The information is less consistent in the refractive status change in that one article by O'Brart et al.[3] reported improvement in BSCVA in both treated and non-treated eyes, and in another larger study (Wittig-Silva et al), obscure data obtained about the refractive change , perhaps contributed to baseline mean corneal curvature (Kmax) appearing steeper by 1.65 D in the treatment group compared with the control group (P=0.052). Further bias in the findings may have been induced through the12 patients that crossed-over after six months when disease progressed more than expected and data collection had to be terminated at that point in Wittig-Silva et al. Information on the efficacy of the CXL procedure for the treatment of secondary ectasia was not available.

Conclusion
Based on this systematic literature review, there are sufficient data to support the efficacy of the CXL procedures because of the favorable results achieved from the outcomes of major interest such as keratometry and visual function data. The reviewed studies did not reveal any new major safety concerns for the CXL procedure. The findings of this systematic literature review are supported by a recent review on corneal collagen crosslinking that reported that the procedure is relatively safe and effective for the treatment of Keratoconus.[6] However, there was insufficient information available to determine the efficacy of the CXL procedures for the treatment of secondary ectasia.

Comment: This CDRH review finds a reduction in Kmax in all CXL studies selected for review while stabilization or improvement in visual acuity and refractive change does not appear to be consistently achieved. Further literature review to understand the association will be requested.

3. CMC/Product Quality Microbiology

See complete CMC review by Drs. Lunn and Matecka.

3.1 Product Quality - Riboflavin

Two formulations of the drug are reviewed:
Photrexa Viscous™ (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% is a yellow sterile buffered viscous solution containing 1.46 mg/mL riboflavin 5'-phosphate and 20% dextran 500. The pH of the solution is approximately 7.1 and the osmolality is 301-339 mOsm/kg. Each 1 mL of solution contains 1.53 mg of riboflavin 5'-phosphate sodium (equivalent to 1.20 mg riboflavin). Riboflavin 5'-phosphate sodium USP is a mixture of the sodium salts of riboflavin, riboflavin monophosphates, and riboflavin diphosphates. The inactive ingredients are dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, and water for injection.

Photrexa™ (riboflavin 5'-phosphate ophthalmic solution) 0.146% is a yellow sterile buffered solution containing 1.46 mg/mL riboflavin 5'-phosphate. The pH of the solution is approximately 7.1 and the osmolality is 157-177 mOsm/kg. Each 1 mL of solution contains 1.53 mg of riboflavin 5'-phosphate sodium (equivalent to 1.20 mg riboflavin). Riboflavin 5'-phosphate sodium USP is a mixture of the sodium salts of riboflavin, riboflavin monophosphates, and riboflavin diphosphates. The inactive ingredients are dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, and water for injection.

The composition is summarized in the table below.

Component	**Function**	**Photrexa Viscous**		**Photrexa**	
		Amount	mg/mL	Amount	mg/mL
Riboflavin*	Active	(b) (4)	1.200**	(b) (4)	1.200**
Dextran 500					
Sodium chloride, USP					
Sodium phosphate, monobasic, USP					
Sodium phosphate, dibasic, USP					
Sterile water for injection, USP					
Total					

*Present as riboflavin 5'-phosphate sodium
**Equivalent to 1.46 mg/mL riboflavin phosphates
Source: CMC review dated 3/5/3015

Riboflavin is light sensitive therefore precautions are taken during manufacturing and packaging to protect it from light (p 28).

Dr. Lunn notes that it is reassuring (b) (4) (p 22).

Overall, the CMC revise concludes the NDA is recommended for approval from the CMC perspective. Deficiencies #1-#3 have been resolved, thus CMC issues concerning the drug

substance and the drug product have been satisfactorily addressed. An overall recommendation of Acceptable has been made by the Office of Compliance, resolving deficiency #4 (p 8).

3.2 Device – UVA light source

See **Section 11.5** for review findings/deficiencies related to the KXL Device.

3.3 Product Quality Microbiology

The CMC review notes Dr. Denise Miller's Product Quality Microbiology review recommends approval. The composition, manufacturing process, and specifications for the riboflavin phosphates ophthalmic solutions are appropriate and the expiration dating period of 18 months is supported by adequate data. The container-closure system is appropriate. (p 10)

3.4 Biopharmaceutics – BA/BE Waiver

The applicant requests a categorical exclusion from the requirement to perform an environmental assessment under 21 CFR 25.31. Dr. Lunn notes this request is accepted. (p 7)

Comment: CMC is recommending approval of Photrexa Viscous and Photrexa, and the Office of Compliance has issued a recommendation for Acceptable for manufacturing facilities. See Section 11.5 regarding the Device Constituent, and 11.2 regarding the acceptable Device inspection.

4. Nonclinical Pharmacology/Toxicology

There is no new information provided during this review cycle. Please refer to the original Pharmacology/Toxicology review and the Division Director review dated March 14, 2014, for a summary of the nonclinical studies.

Comment: The Pharmacology/Toxicology (P/T) reviewers in DTOP recommend approval pending discussion of labeling.

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology studies were submitted. Please refer to the original Clinical Pharmacology review a Division Director review dated March 14, 2014, for a summary of clinical pharmacology information.

Comment: The Clinical Pharmacology Reviewers recommend approval pending discussion of labeling.

6. Clinical Microbiology/Immunology

Not Applicable

7. Clinical/Statistical-Efficacy

There were no new studies submitted in the Complete Response on September 29, 2014, however, the applicant adequately addressed Clinical/Statistical deficiencies #13-#14, and additional analyses of the studies were performed by the Statistical Reviewers. The following is a brief summary of new key study findings and issues. Please refer to the Division Director review dated March 14, 2014, for a summary of the study design. For additional details, see clinical reviews by Drs. Boyd and Chambers, and statistical reviews by Drs. Zhuang, Wang and Price.

Corneal Collagen Cross-Linking Procedure
This is summarized in the Division Director Review dated March 14, 2014, and clinical reviews.

Clinical Trials
The design of the three clinical trials is summarized in the clinical reviews and the March 14, 2014 review, and includes the inclusion and exclusion criteria in Studies UVX-001, UVX-002 and UVX-003, three similarly designed trials.

Corneal ectasia patients had refractory surgery
As shown in the table below, the majority of patients had laser-assisted in-situ keratomileusis [LASIK] and a few patients had photorefractive keratectomy [PRK]

	CXL n=91	Control n=88
LASIK only	83	83
LASIK and PRK	4	4
PRK only	4	1

Keratoconus was defined as progressive disease if 1 or more of the following changes were met 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.

Comment: During review of the application questions were raised about similarities/differences between 'progressive keratoconus' and 'keratoconus,' specifically whether these were different populations, whether treatment effects could be extrapolated to all patients, as well as implication for labeling and orphan exclusivity, depending on the wording of the indication.

(b) (4)

During the February 24, 2015 Advisory Committee meeting, the committee members challenged the criterion of myopic shift of ≥ 0.50 D on subjective manifest refraction as evidence of "progression." Approximately 20% of the patients in the studies were

enrolled based on this criterion. Thus, the majority of patients enrolled met the remaining criteria for progression, and it was noted that all patients met the inclusion criteria for keratoconus, such as Fleischer ring, Vogt striae, corneal thinning, corneal scarring, or scissoring of the retinoscopic reflex (UVX-001 only).

Change in the Analysis of the Primary Endpoint

There was extensive discussion during the review by CDER and CDRH regarding the change of the primary endpoint because it was changed after the studies were completed and an investigator, Dr. Hersh, published his results from studies UVX-002 and UVX-003. According to the applicant, Avedro, the change in the time-point of the primary efficacy analysis from Month 3 to Month 12 occurred after the UVX cross-linking studies were acquired by Avedro from the original sponsor, Peschke Meditrade and before database lock. Avedro made this decision based on review of publications reporting that following CXL procedure, the effect on the flattening of the cornea may not be evident for 6 to 12 months after the procedure. The applicant also noted that many studies in the literature used 12 months or a longer timeframe for the efficacy evaluation.

Comment: The CDER clinical reviewers recommended the Month 12 time point to the original sponsors when the clinical trials were being designed. The sponsor declined to revise the timing of the primary protocol endpoint at that time because of the provision that patients in the control (sham) arm could receive CXL treatment after Month 3. However, the original sponsor agreed to collect additional data up to Month 12. Consistent with the explanation provided by Avedro, based on published literature, it appears that in the setting of corneal collagen cross-linking, the stabilization of the cornea and reduction in the Kmax continues for one year or longer after treatment. Although there has been extensive criticism of the change of the endpoint from Month 3 to Month 12, it should be noted that the corneal ectasia following refractive surgery studies showed statistically significant results in both study UVX-001 and UVX-003 at both the Month 3 and Month 12 time point. The keratoconus studies failed to reach statistical significance at Month 3.

This issue of the change in the primary endpoint analysis was examined by the Statistical reviewers in detail, and the information presented at the March 20, 2015, Regulatory Briefing.

As discussed during the Regulatory Briefing, the change in an endpoint raises concerns of multiplicity and whether such analyses could be used to choose the Month 12 outcome without proper adjustment. However, it was observed that in the case of these studies, all analyses, with the exception of the Month 3 results in the progressive keratoconus studies (shown in red font) were statistically significant (shown in blue font). And, the significant results were seen at the pre specified Month 3 in the corneal ectasia studies and all other time points in all four studies, supporting the interpretation that the treatment effect was real.

Study	CXL Mean (SD)	Sham Mean (SD)	Difference (95%)	P-value
UVX-001 Progressive Keratoconus (LOCF) Mean change from Baseline in Kmax				
Month 3	-0.3 (2.7)	0.1 (2.6)	-0.5 (-1.9, 0.9)	0.5085
Month 6	-0.9 (2.6)	0.5 (3.0)	-1.4 (-2.9, 0.1)	0.0674
Month 12	-1.4 (2.8)	0.5 (3.0)	-1.9 (-3.4, -0.3)	0.0175
UVX-002 Progressive Keratoconus (LOCF) Mean change from Baseline in Kmax				
Month 3	-0.6 (4.4)	0.7 (5.6)	-1.3 (-3.0, 0.3)	0.1142
Month 6	-1.1 (5.1)	1.2 (5.7)	-2.2 (-4.0, -0.5)	0.0010
Month 12	-1.7 (4.7)	1.2 (5.7)	-2.9 (-4.6, -1.2)	0.0010

Source: statistical presentation, CDER Regulatory Briefing March 20, 2015

Study	CXL Mean (SD)	Sham Mean (SD)	Difference (95%)	P-value
UVX-001 Corneal Ectasia (LOCF) Mean change from Baseline in Kmax				
Month 3	0.1 (1.3)	1.0 (1.7)	-0.9 (-1.8, -0.1)	0.0382
Month 6	-0.6 (1.6)	1.0 (1.7)	-1.7 (-2.6, -0.7)	0.0010
Month 12	-1.0 (1.7)	1.0 (1.7)	-2.0 (-3.0, -1.1)	0.0001
UVX-003 Corneal Ectasia (LOCF) Mean change from Baseline in Kmax				
Month 3	-0.2 (2.4)	0.6 (1.9)	-0.8 (-1.6, 0.0)	0.0386
Month 6	-0.5 (2.0)	0.5 (2.3)	-1.0 (-1.8, -0.3)	0.0084
Month 12	-0.5 (2.2)	0.5 (2.3)	-1.1 (-1.9, -0.3)	0.0080

Source: statistical presentation, CDER Regulatory Briefing March 20, 2015

In addition to the analyses of Mean change from Baseline in Kmax, a responder analysis of patients with at least a 1 diopter difference in Kmax from baseline was also done, and illustrates that numerically more patients had a 1 diopter reduction in Kmax. While not adjusted for multiplicity, it is supportive of the SAP-specified endpoint. (Source: Statistical Team Leader Review)

Proportion (%) of Subjects with a Reduction of at Least 1.0 Diopter in Kmax from Baseline in the Study Eye (ITT Population; LOCF)

Study	CXL	Sham	Difference (95% CI)	P-value (Chi-square)
UVX_001 (Keratoconus)	**N=29**	**N=29**		
Month 1	1 (3%)	11 (38%)	-35 (-53, -16)	0.0012
Month 3	13 (45%)	8 (28%)	17 (-7, 42)	0.1719
Month 6	15 (52%)	9 (31%)	21 (-4, 46)	0.1097
Month 12	15 (52%)	9 (31%)	21 (-4, 46)	0.1097
UVX_002 (Keratoconus)	**N=73**	**N=74**		
Month 1	9 (12%)	15 (20%)	-8 (-20, 4)	0.1927
Month 3	22 (30%)	15 (20%)	10 (-4, 24)	0.1681
Month 6	32 (44%)	14 (19%)	25 (11, 39)	0.0011
Month 12	37 (51%)	13 (18%)	33 (19, 48)	<.0001
UVX_001 (Corneal Ectasia)	**N=24**	**N=25**		
Month 1	2 (8%)	1 (4%)	4 (-9, 18)	0.5271
Month 3	3 (13%)	1 (4%)	9 (-7, 24)	0.2773
Month 6	9 (38%)	1 (4%)	34 (13, 54)	0.0036
Month 12	10 (42%)	1 (4%)	38 (17, 59)	0.0016
UVX_003 (Corneal Ectasia)	**N=63**	**N=63**		
Month 1	5 (8%)	13 (21%)	-13 (-25, -1)	0.0417
Month 3	17 (27%)	6 (10%)	18 (4, 31)	0.0112
Month 6	17 (27%)	8 (13%)	14 (1, 28)	0.0444
Month 12	18 (29%)	7 (11%)	18 (4, 31)	0.0140

Last observation carried forward method (LOCF) was used to impute missing data resulting from subject withdrawal or intermittent missed visit, as well as to impute data for sham subjects who received CXL during the study. For sham subjects who received CXL after randomization day, their last observed Kmax value prior to receiving CXL was carried forward in the analysis for later time points.

Source: secondary reviewer's analysis. In Study UVX-003, four subjects with missing baseline Kmax values were excluded from the analysis. In Study UVX-001, at Month 1, an erroneous Kmax value for sham subject (b) (6) was replaced by the baseline value (Table 7). In Study UVX-002, at Month 1, an erroneous Kmax value for sham subject (b) (6) was replaced by the baseline value; at Month 3, a potentially erroneous Kmax value for sham subject (b) (6) was replaced by the value at Month 1 (Table 7).

Comments: I concur with the conclusions reached by the statistical reviewers:

- *Statistically significant treatment difference was observed in the applicant's analyses at Months 3, 6 and 12 in the corneal ectasia studies*
- *Statistically significant treatment difference at Month 12, and numerically favorable treatment differences at Months 3 and 6 were observed in the applicant's analyses in keratoconus studies*

- *Continued improvement in Kmax over time was observed in CXL-treated subjects in all studies*
- *More CXL-treated subjects experienced a reduction of 1.0 diopter in Kmax from baseline at Months 3,6 and 12 compared to sham-treated subjects in all studies*

Use of Last Observation Carried Forward (LOCF)

As noted in the Statistical review (p 7):

The study design allowed sham subjects to receive CXL treatment at Month 3 or later. For sham subjects who received CXL treatment, their Kmax values after receiving CXL treatment were treated as missing and were imputed using the Kmax values at an earlier visit prior to CXL treatment. As seen in the table below, essentially all control (sham) patients received CXL treatment by Month 12, therefore it was important to assess whether use of the LOCF method was valid.

Number of sham study eyes that received CXL treatment or withdrew from the study by Month 12			
Progressive Keratoconus		**Corneal Ectasia**	
UVX-001 (N=29)	**UVX-002 (N=74)**	**UVX-001 (N=25)**	**UVX-003 (N=63)**
29 (100%)	72 (97%)	25 (100%)	61 (97%)

The applicant considered that this approach was valid for imputation because of the progressive nature of keratoconus. Moreover, the applicant stated that there were no data to demonstrate that keratoconus subjects experienced spontaneous remission or improved. The applicant provided publications to support the position that keratoconus is either stable or progressive.

The natural history of keratoconus evaluated in Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study summarized in Section 2 supports the assertion that keratoconus is a progressive disease. The study enrolled 1209 eligible patients at 16 participating clinics across the United States between May 1995 and June 1996. At the time of enrollment, patients were aged 12 years or older; and exhibited an irregular cornea, as determined by distortion of keratometric mires and/or scissoring of the retinoscopic reflex; and demonstrated at least one biomicroscopic sign of keratoconus, including Vogt's striae, Fleicher's ring of 2 mm or more of arc, or corneal scarring. Patients were examined annually for 8 years. Similar findings of increased Kmax and reduced visual acuity were reported in other studies (Jordan 2012, Caporossi 2010, and Vinciguerra 2009). (Statistical review p 9)

Comment: I agree that the evidence from the natural history study of keratoconus summarized in Section 2 of this document indicates keratoconus progresses or stabilizes over time; there is no clear evidence that the condition spontaneously improves. Therefore, the use of the Month 3 control data or Month 6 control data used in the LOCF analysis for the Month 12 control outcomes is acceptable, although the data are best described as comparing Month 12 CXL data to Month 3/6 control (sham) data.

The statistical and clinical reviewers conclude that the statistical and clinical issues in the Complete Response letter have been adequately addressed. However, none of these studies used the to-be-marketed device, there are outstanding deficiencies regarding the device, and the information to bridge the clinical trial device and to-be-marketed device is not considered sufficient. Therefore, a new clinical study with the KXL-System will be requested.

8. Safety

There are no new studies submitted, and additional analyses look at the number of randomized eyes in the studies as well as the total number of eyes (CXL treatment arm, control (sham) arm treated with CXL after Month 3, and fellow eyes in any patient treated with CXL after Month 3 in the study). Please also refer to the Division Director review dated March 14, 2014. For additional information, see original and current clinical reviews by Drs. Boyd and Chambers, and original statistical review by Drs. Zhuang, Wang and Price.

The CXL procedure involves removal of the corneal epithelial layer, which is expected to result in reduction of vision due to the injury to the epithelium. The reduction in visual function and other adverse reactions generally resolve with the healing of the endothelium. The table below shows the adverse events reported in the controlled portion of the study (first and second column) by indication, as well as overall adverse events in all eye treated with CXL (CXL study eye, control/sham study eye, fellow eye in either randomized group, third column) by indication.

Table 1: Most Common (≥2%) Ocular Adverse Events in Any CXL-Treated Eye in the Pooled Keratoconus and Corneal Ectasia Studies (Safety Population)

	Pooled Keratoconus Studies			Pooled Corneal Ectasia Studies		
Preferred Term	**CXL Group (N=102)[1]**	**Control Group (N=103)[1]**	**Any CXL Eye (N=293)[2]**	**CXL Group (N=91)[1]**	**Control Group (N=88)[1]**	**Any CXL Eye (N=219)[2]**
Anterior chamber cell	2 (2.0)	0	5 (1.7)	2 (2.2)	1 (1.1)	3 (1.4)
Anterior chamber flare	4 (3.9)	0	9 (3.1)	5 (5.5)	2 (2.3)	9 (4.1)
Asthenopia	1 (1.0)	1 (1.0)	1 (0.3)	2 (2.2)	0	3 (1.4)
Blepharitis	0	0	4 (1.4)	0	1 (1.1)	7 (3.2)
Conjunctival hyperaemia	10 (9.8)	1 (1.0)	19 (6.5)	4 (4.4)	3 (3.4)	16 (7.3)
Corneal abrasion	1 (1.0)	0	2 (0.7)	2 (2.2)	0	4 (1.8)
Corneal disorder	3 (2.9)	1 (1.0)	7 (2.4)	3 (3.3)	0	7 (3.2)
Corneal epithelium defect	23 (22.5)	1 (1.0)	69 (23.5)	24 (26.4)	3 (3.4)	53 (24.2)
Corneal oedema	3 (2.9)	0	3 (1.0)	3 (3.3)	0	6 (2.7)
Corneal opacity[3]	58 (56.9)	4 (3.9)	178 (60.8)	62 (68.1)	7 (8.0)	148 (67.6)
Corneal scar	7 (6.9)	5 (4.9)	22 (7.5)	3 (3.3)	1 (1.1)	9 (4.1)
Corneal striae	24 (23.5)	12 (11.7)	70 (23.9)	8 (8.8)	6 (6.8)	27 (12.3)
Corneal thinning	1 (1.0)	2 (1.9)	8 (2.7)	0	0	1 (0.5)
Diplopia	2 (2.0)	1 (1.0)	4 (1.4)	1 (1.1)	0	3 (1.4)
Dry eye	6 (5.9)	2 (1.9)	18 (6.1)	13 (14.3)	4 (4.5)	27 (12.3)
Eye complication associated with device	2 (2.0)	0	2 (0.7)	1 (1.1)	0	1 (0.5)

	Pooled Keratoconus Studies			Pooled Corneal Ectasia Studies		
Preferred Term	**CXL Group (N=102)[1]**	**Control Group (N=103)[1]**	**Any CXL Eye (N=293)[2]**	**CXL Group (N=91)[1]**	**Control Group (N=88)[1]**	**Any CXL Eye (N=219)[2]**
Eye discharge	2 (2.0)	1 (1.0)	4 (1.4)	0	0	1 (0.5)
Eye irritation	10 (9.8)	1 (1.0)	18 (6.1)	8 (8.8)	1 (1.1)	15 (6.8)
Eye oedema	7 (6.9)	0	9 (3.1)	0	0	2 (0.9)
Eye pain	17 (16.7)	3 (2.9)	58 (19.8)	24 (26.4)	0	43 (19.6)
Eye pruritus	2 (2.0)	0	8 (2.7)	0	0	2 (0.9)
Eyelid oedema	5 (4.9)	0	10 (3.4)	5 (5.5)	1 (1.1)	11 (5.0)
Foreign body sensation in eyes	5 (4.9)	0	10 (3.4)	5 (5.5)	1 (1.1)	15 (6.8)
Glare	4 (3.9)	1 (1.0)	8 (2.7)	2 (2.2)	0	3 (1.4)
Halo vision	1 (1.0)	0	1 (0.3)	2 (2.2)	0	5 (2.3)
Keratitis	1 (1.0)	0	3 (1.0)	3 (3.3)	0	5 (2.3)
Lacrimation increased	5 (4.9)	0	18 (6.1)	9 (9.9)	1 (1.1)	20 (9.1)
Meibomian gland dysfunction	1 (1.0)	1 (1.0)	5 (1.7)	3 (3.3)	2 (2.3)	12 (5.5)
Ocular discomfort	0	0	8 (2.7)	8 (8.8)	0	19 (8.7)
Ocular hyperaemia	4 (3.9)	1 (1.0)	6 (2.0)	3 (3.3)	1 (1.1)	8 (3.7)
Photophobia	11 (10.8)	0	28 (9.6)	17 (18.7)	0	42 (19.2)
Punctate keratitis	25 (24.5)	8 (7.8)	62 (21.2)	18 (19.8)	3 (3.4)	51 (23.3)
Vision blurred	16 (15.7)	2 (1.9)	42 (14.3)	15 (16.5)	4 (4.5)	36 (16.4)
Visual acuity reduced	10 (9.8)	9 (8.7)	48 (16.4)	10 (11.0)	1 (1.1)	37 (16.9)
Visual impairment	3 (2.9)	2 (1.9)	6 (2.0)	4 (4.4)	1 (1.1)	11 (5.0)
Vitreous detachment	2 (2.0)	0	2 (0.7)	0	0	0

1) Results are presented as the number (%) of subjects with an event from baseline to Month 3.
2) Results are presented as the number (%) of CXL-treated eye
3) Almost all cases of corneal opacity were reported as haze.

Comment: The Division typically requests comparative safety data from at least 300 patients for an indication to support approval of eye products; in these studies about 200 patients were randomized to CXL treatment. Given that an additional study (or studies) using the to-be marketed device is being requested, this will increase the available comparative safety data.

Endothelial Cell Counts

In the analysis of the endothelial cell counts (ECC), there were some non-physiologic values and/or increase in ECC at subsequent visits. Avedro examined the data from the three studies and identified several patients who had very low baseline values compared to ECC at later visits, but these were verified against the source documentation. For the new study with the KXL System, Avedro is asked to include procedures to identify non-physiologic ECC values at the study visit, allowing it to be repeated. One error where a missing baseline value was imputed as zero has been corrected.

Refractive Status and Vision Profile Questionnaire (RSVP)
CDRH expressed concern that the Patient Reported Outcome (PRO) RSVP Questionnaire administered during the Phase 3 studies was not analyzed and results provided in the application. Therefore a SEALD Study Endpoints Team consult request was sent by the Division of Transplant and Ophthalmology Products (DTOP). The Division requested that the Study Endpoints Team review and comment on the quality and validity of the questionnaire, fitness for purpose, and interpretation of the results. The consult provided the following recommendations:

> The sponsor has not provided any information or documentation of critical elements needed for our review. For example, we do not have information on the conceptual framework, scoring algorithm or development history of the instrument. Therefore, we are unable to determine whether the RSVP is a well-defined and reliable assessment in the targeted patient population and a consult review cannot be completed.
>
> We also note that the sponsor decided not to summarize the data for the RSVP results based on the following statement (Clinical Study Report for UVX-001): "The rationale for this decision was that the randomized eye in the case of subjects assigned to the sham group could later have received the CXL treatment; in addition, the fellow eye could also have been treated later. These circumstances would have made interpreting the results inappropriate as the questionnaire doesn't allow for analysis by eye."
>
> The SEALD Study Endpoints Team does not generally review exploratory assessments. Given that the RSVP was used for exploratory/descriptive purposes, and the sponsor does not seek labeling claims, a SEALD consult review is not needed and we will close out this consult request with this email.

Comment: The Division agrees with the Study Endpoint recommendations.

9. Advisory Committee Meeting

The application was presented at the February 24, 2015, Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee.

After presentations by Avedro, CDER and CDRH, the committee discussed the applications and fundamentally expressed concern about the quality of the studies, and the lack of information on the device.

During the open public hearing (OPH), 14 position papers were read. Some of these supported the approval of the application. Others expressed concern that if/when the progressive keratoconus and corneal ectasia indications were approved the Agency clearly state that the product is not to be used in LASIK surgery, referring to a publically-discussed use called "LASIK Xtra®", an unapproved use of riboflavin during a LASIK procedure.

After discussion, the committee members voted 10 Yes, 4 No, 1 Abstain, to approved progressive keratoconus and 6 Yes, 4 No, 4 Abstain (and 1 member had departed the meeting) to approve corneal ectasia following refractive therapy.

Members commented on the low enrollment, the many deviations, the lack of data on the KXL device; some voted in favor of approval after noting "there is an unmet medical need."

9a. CDER Regulatory Briefing

The NDA was presented at the CDER Regulatory Briefing March 20, 2015, attended also by CDRH reviewers and management and Office of Combination Products (OCP) staff. The clinical presentation summarized published literature on corneal cross linking that used riboflavin products and UVA light sources; none of the published studies used the drug and device proposed for marketing in NDA 203324. The safety data were not presented. Various flaws and issues with study design and conduct were identified, including low patient enrollment (compared to planned), change in the primary endpoint from Month 3 to Month 12, treatment of sham control patients with CXL after Month 3, multiple protocol deviations, multiple planned analyses of secondary endpoints that were not reported, and differences in the clinical trial and to-be-marketed product. A statistical presentation summarized efficacy, including the change in the primary endpoint from Month 3 to Month 12 and the use of the last observation carried forward (LOCF) approach. A presentation on the device discussed the limitation of the studies and device. Overall, the comments during the discussion of questions regarding the efficacy reported in the studies were encouraging; however, the different devices used in the trial and proposed for marketing as well as the adequacy of information linking the UV-X device to the KXL-System remained outstanding issues that needed to be addressed.

10. Pediatrics

The application included information on less than 10 patients 16 years or younger. While CDER clinical reviewers consider that efficacy can be extrapolated to patients as young as 14 years of age, some Advisory Committee members commented they did not support extrapolation of efficacy from adults. CDRH defines pediatric patients as 21 years or younger, and there a total of 33 patients meeting this definition.

The applicant has orphan designation for the indications of 'keratoconus' and 'corneal ectasia following refractive surgery,' therefore the Pediatric Research Equity Act requirements are not applicable to this NDA.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection/CDER

Overall the Office of Compliance found facilities acceptable and issued a recommendation of Acceptable

11.2 Compliance Inspection/CDRH

Regarding the KXL Device, the Office of Compliance concluded that NDA-203324 is approvable from the perspective of the Medical Device Regulations compliance group, (see also 11.5). A post-market inspection is recommended for Avedro Inc.

11.3 Office of Scientific Investigation (OSI) Audits

Investigators from the three studies were inspected in support of the application: Drs. Stulting, Price, Hardten, Hersh, and Donnenfeld were selected for inspection, all enrolled relatively large numbers of subjects and each of the five sites had significant impact on study results. Observational findings included the most recent consent form was not used for all patients and some adverse reactions were not reported (epithelial defect, ocular pain, flashing light). Otherwise, the data appeared to be acceptable. Inspection of Avedro disclosed that there were many instances of no monitoring visit reports. Therefore, a third-party audit of Dr. Stulting's records was requested in the March 14, 2014, Complete Response letter, and led to OSI working to resolve potentially discrepant observations related to adverse event reporting between the 2014 FDA inspection and the subsequent third party audit. OSI examined the discrepancies and noted the following:

"Violations observed during the 2014 inspection of Dr. Stulting are outlined in the March 14, 2014 Clinical Inspection Summary in DARRTS. Significant observations based upon review of the EIR, Dr. Stulting's written response to the Form FDA 483, and follow-up inspection conducted at Emory Vision in 2015 include failure to follow the investigational plan (inclusion of subjects who did not meet eligibility criteria) and informed consent violations (informed consent document not dated by a subject at the time of signature).
There was no apparent under-reporting of AEs in the NDA related to Study UVX-001, although interpretation of severity and relatedness to study treatment were not defined in the protocol or included in source documents while Dr. Stulting had access to the records; interpretation regarding severity and attribution of AEs is left to the discretion of the review division. The data submitted in the NDA from Dr. Stulting's site appear reliable for use in support of the indication."

Comment: This response provides a satisfactory response to the Complete Response letter request regarding the BioMedical Inspection.

11.4 Financial Disclosure

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. The Clinical Investigator Financial Disclosure Review Template is included in Appendix 9.3 of the clinical review dated 3/7/2014.

11.5 Other Regulatory Issues – Center for Devices and Radiologic Health

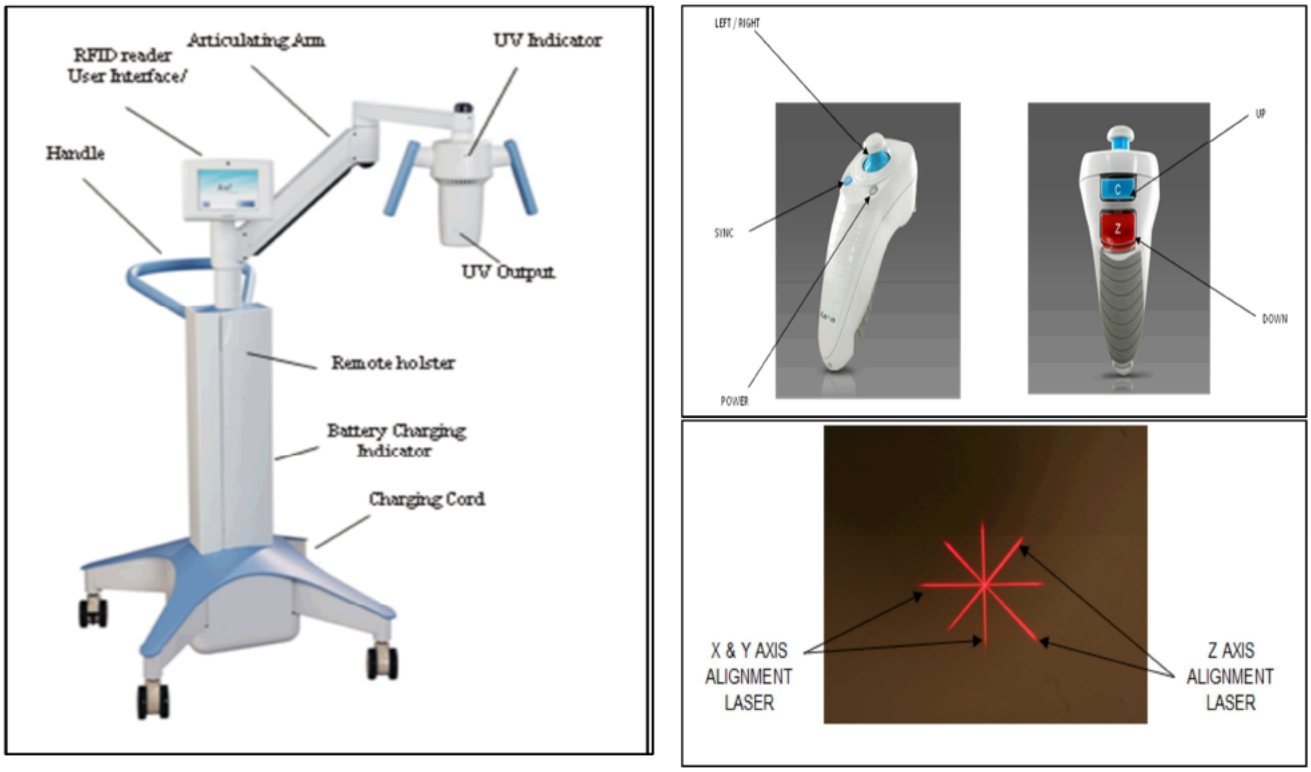
This is a combination product consisting of the drug component (two formulations of riboflavin) and the portable UV-A light source for the KXL System. The device's light emitting diode (LED) is used to deliver a metered dose of UVA light (365 nm wavelength) in a circular pattern onto the cornea after during the CXL procedure. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Further details on the device characteristics and operation are included in Dr. Boyd's CDTL review and Dexiu Shi's engineering review. There has been discussion of the differences between the two devices, and no agreement was reached that the two devices can be bridged.

The similarities between the UVX and KXL Systems include the following parameters:

UV source, UV irradiance, UV exposure time, UV emission, operating, EMI/EMC, and safety classification. CDRH has determined that the maximum allowable treatment parameters for UVA radiation at a wavelength of 365 nm will be limited to 3mW/cm^2 for 30 minutes and a maximum energy density of 5.4 J/cm^2 by the Radio Frequency Identification (RFID) activation card (this is the same for the two devices).

Differences between the devices include the potential patients positioning (although only supine position was used in studies), available UV beam diameter, power monitoring, UV light emission; UV focal alignment, UV focal plane, software, device dimensions and weigh, and power supply.

The following figures show the Overview Illustration of the KXL System, Wireless Remote and X, Y & Z alignment using lasers. Avedro considers this device an improvement to the earlier device.



Source: 3.2.R Regional Information, Dexiu Shi engineering review

The Complete Response letter dated March 14, 2014, included Device Constituent Part Deficiencies #5-#12. Based on the CDRH Clinical Review, and Engineering, Software, Energy Safety and Electromagnetic Compatibility reviews, it appears that the majority of the deficiencies were addressed.

Device deficiency #5 regarding the two devices has been addressed by the applicant. The CDRH Clinical Reviewer comments on the differences between the devices and defers to other CDRH colleagues regarding their significance. One of the differences noted is the 9.5 mm diameter

with the UV-X device compared to the 9.0 mm diameter with the KXL-System device. The Complete Response letter for this review cycle will request additional information on the two devices (See Appendix A).

Device deficiency #6 regarding the RFID card asks about optical radiation hazard: the applicant agreed to modify the software of the to-be-marketed device to implement a software lock-out of the irradiated power above 3 mW/cm2, and validation has been completed, adequately addressing this deficiency.

Device deficiency #7 regarding the (b) (4) validation activities: The applicant addressed this, the CDRH Clinical Reviewer defers to CDRH colleagues and the CDRH Engineering review states that validation and the response is satisfactory (p 21, 28)

Device deficiency #8 regarding electromagnetic compatibility (EMC): The CDRH Clinical reviewer defers to CDRH colleagues; and the CDRH EMC reviewer agrees the deficiency has been addressed.

Device deficiency #9 regarding immunity pass/fail criteria IEC 60601-1-2:2007 – the CDRH Clinical reviewer defers to CDRH colleagues and the EMC Senior Engineer requests additional EMC testing (review 3/24/2015). The deficiency will be communicated to the applicant.

Device deficiency #10 regarding immunity tests for which IEC 60601-1-2:2007 requests specific information: the CDRH Clinical reviewer defers to CDRH colleagues and the EMC Senior Engineer request additional EMC testing (review 3/24/2015). This deficiency will be communicated to the applicant.

Device deficiency #11 regarding IEC 60601-1-2:2007 specifies requirements for testing and for labeling. The deficiency (labeling) will be communicated to the applicant.

Device deficiency #12 regarding MRI warnings in the Operator's Manual: specifies requirements for testing and for labeling. The deficiency (labeling) will be communicated to the applicant.

The responses by Avedro to the March 14, 2014, deficiencies have raised additional CDRH questions in the following areas:

- Outstanding deficiencies listed above.
- The similarities and differences between the UV-X device used in clinical studies and the KXL System proposed for marketing, and request for additional information from the applicant.
- The clinical trial design, analysis and results, specifically, requests for various addition analyses of the data by age, by corneal thickness, by illumination diameter.
- Request for a thorough literature review including studies of the to be marketed drug/device; studies using KXL with other illumination parameters
- Additional analyses of safety, potentially for labeling purposes.

Comment: The outstanding device-related deficiencies will be included in the Complete Response letter. While the CDRH reviewers consider the information on the KXL System

insufficient to bridge to the UV-X device used in the clinical studies, the CDER Clinical Reviewers consider the similarities relevant and do not conclude that the differences between the UV-X and KXL System devices impact the safe and effective use of the device. The CDRH reviewers consider there is insufficient data to determine whether the KXL System can be used safely and effectively.

Since studies using the KXL System are not included in the application and CDRH does not consider information on the KXL System sufficient for approval. An adequate and well controlled study of corneal collagen cross-linking in patients with progressive keratoconus and patients with corneal ectasia (most commonly LASIK), using the to-be-marketed KXL System will be requested. Alternatively, the applicant may explore whether there is sufficient clinical information to bridge the KXL System to the IROC UV-X device used in the clinical studies (e.g., by providing literature or Avedro data), and provide further comparison between the devices, as detailed in Appendix A.

12. Labeling

Labeling discussions were deferred until the deficiencies in the application can be resolved. DMEPA provided label recommendations.

- **Package insert (PI):** review deferred
- **Device User Manual:** some labeling recommendatinos will be provided to the applicant
- **Carton and Container Labels**: changes recommended by DMEPA sent to Avedro
- **Proprietary Name**: DMEPA concluded that the newly proposed proprietary names Photrexa Viscous and Photrexa are acceptable. The previous trade name included (b) (4) (b) (4) and was turned down (b) (4)

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

A complete response letter will be issued that outlines the deficiencies for this application, and provides additional comments for consideration (Appendix A).

13.2 Risk Benefit Assessment

The risk benefit assessment is deferred until the deficiencies associated with this application are addressed.

13.3 Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)

Not applicable at this time

APPENDIX A: Detailed list of Deficiencies and Additional Comments

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. As discussed during the February 24, 2015, Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee, the application does not include clinical studies that were conducted with the to-be-marketed KXL-System (the device constituent part). Clinical studies UVX-001, UVX-002 and UVX-003 were conducted with the IROC UV-X device, as stated in the Avedro briefing document and the application. We find that the information submitted to establish similarity of the two device constituent parts is not sufficient. Therefore, the application is deficient under 21 CFR 314.126 in that it does not include adequate and well-controlled studies of the drug/device combination using the to-be-marketed device.[2]

   To address this deficiency, you should conduct a clinical study (or studies) showing that Photrexa Viscous and Photrexa with the KXL-System when used in the corneal collagen cross-linking procedure is safe and effective in the treatment of patients with progressive keratoconus and patients with corneal ectasia following refractive surgery. The design of this new clinical study (or studies) should be discussed with the Agency before the study is (or studies are) initiated. We recommend a meeting with the Agency be scheduled to discuss the design of the study (or studies)..

   Alternatively, if you believe that it is possible to provide sufficient clinical information to bridge the combination product device constituent, KXL System, to the IROC UV-X device used in the above-named clinical studies (e.g., by providing literature or Avedro data), then you may propose such an alternative.

   If you propose such an alternative, you need to provide the following information:

2. In the March 14, 2014, Complete Response letter, we requested clarification regarding your list of device differences between the IROC UV-X and the KXL System. In your September 29, 2014, resubmission, you indicate that the original list was not comprehensive, and therefore, you provided new information. However, the additional information you provided in your response does not support your rationale for equivalence between the two systems.

[2] Specifically 21 CFR 314.126(d) states that, For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation. Your application is for a combination product, consisting of a drug constituent and a device constituent. We agree that the drug constituent is consistent with this section of the regulations. However, as noted above, because the information submitted to establish similarity of the two devices is not sufficient, the device constituent is not compliant with this section of the regulations. Therefore, we are requesting a clinical study (or studies) with the to-be-marketed device constituent, the KXL-System.

Moreover, in light of your presentation at the February 24, 2015, Advisory Committee meeting, and your correspondence received March 16, 2015, there appears to be additional differences, which you did not include in your resubmission; e.g., the focusing differences between the two device constituents. Without a complete description and assessment of the differences, e.g., spatial distribution of effective ultraviolet (UV) exposure to the cornea, we cannot determine if these differences could result in increased radiation to the sub-corneal ocular structures or even within the cornea. Further, without a complete assessment of the differences between the two systems it cannot be determined if additional clinical or preclinical data may be needed beyond what is described in this letter. So that we have a more complete picture of the differences between these systems, please provide the following additional information:

a. To address potential UV irradiance concerns to sub-corneal structures as well as being able to assess how well the energy is distributed across the cornea itself in the X, Y and Z directions, provide a complete and detailed description and explanation of the optical systems of both devices. For example, describe all important components such as light sources, lenses, mirrors, filters, shutters, limiting apertures, beam homogenizers, etc. Include dimensions, distances, angles of divergence (or convergence) at the cornea, and accurate ray trace diagrams. Include explanations of any features intended to modify the beam energy distribution, compensate for corneal curvature, or limit scattered radiation beyond the nominal beam diameter.

b. To demonstrate the effect of beam propagation differences between the two devices and the potential of how that beam differs on the cornea, provide beam irradiance maps at the corneal plane for both devices. These maps should be accurate out to the full extent of the beam, and the spatial resolution of the measurements should be specified. These maps should show the effect of the beam propagation differences and how the beam differs on the cornea. Also, please explain any differences between the KXL map in the September 2013 submission and the KXL map in the September 29, 2014 resubmission that you provided (b) (4)

c. For both device constituents, provide a detailed description of all features and procedures used in the clinical trial to limit patient eye movements during the cross-linking procedure, and those for use with the KXL System. For example, describe what fixation targets, instructions to patient and physician, eye position monitoring procedures, and fail-safe provisions in case of excessive movement were employed during the studies and how does that differ from what is provided for the KXL System. In addition, for both device constituents, please provide all available evidence regarding actual sequences of eye movements during the procedure; e.g., a description of any methods used for quantitative eye movement measurements, analyses of across-patient variations, changes in fixation accuracy over time, and the effects of eye movements on the effective beam size and exposure pattern.

d. Provide measurements or best estimates of the location of the focal plane relative to the cornea for both devices. Also provide data regarding the accuracy and precision of the actual vs. the intended focal depth.

e. Provide a comparative analysis of the 3-D distribution of UV energy in the corneal stroma for the two devices, taking into account any differences in beam homogeneity, eye movement effects, focal planes, beam divergence angles, maps of percent reflectance from the curved front corneal surface.

3. Electromechanical Compatibility (EMC)

a. In your September 29, 2014, resubmission in response to Deficiency #9, of our March 14, 2014, Complete Response letter, the EMC test reports identified modifications that were made to the KXL System in order to pass the IEC 60601-1-2 tests. You confirmed that all modifications listed in the test report will be implemented in the marketed version of the device. However, an additional change (b) (4) was made after the original EMC test was completed and found acceptable. The change involved (b) (4) Because of this significant modification, EMC testing was to be repeated to ensure the KXL System (b) (4) still meets the IEC 60601-1-2 standard. You have not provided the new test report for review. Please provide the new test report once EMC testing of the KXL System (b) (4) is completed. This information is needed so that we can assess conformity of the "to be marketed" Photrexa/ KXL UV irradiation system with IEC 60601-1-2:2007.

b. In our March 14, 2014, Complete Response letter Deficiency #10, we said that in order to demonstrate conformity with the IEC 60601-1-2: 2007 standard, not only evidence of meeting the testing requirements, but evidence of meeting the labeling requirements should be provided. As requested, in your September 29, 2014, resubmission you have modified the system technical description in the Operator's Manual to include four tables of EMC guidance, based on compliance of the device with the individual EMC test standards. However, we had not noticed previously that the correct "U_T" was completely missing from the Compliance level column. The current specifications in the Compliance level column are not properly labeled. To comply with IEC 60601-1-2: 2007, please change, in the Voltage dips row, (b) (4) to "0% U_T for 0.5 cycles", (b) (4) to "40% U_T for 5 cycles", (b) (4) to "70% U_T for 25/30 cycles", and (b) (4) to "0% U_T for 250/300 cycles".

ADDITIONAL COMMENTS

In addition, we have the following comments, which are not deficiencies, for your consideration as you work to address the above deficiencies. These may provide additional information that helps inform the design or analysis of the new clinical study and or existing literature and Avedro data.

1. During the Advisory Committee meeting, there was discussion about the choice of the appropriate primary endpoint to demonstrate treatment benefit in the progressive keratoconus and corneal ectasia patient populations. Please review and summarize available published information on the correlation of Kmax with patient benefit in a clinically meaningful endpoint (e.g., visual function) and/or include in the next clinical study plans to collect prospectively information on Kmax along with visual function or other clinically relevant endpoints to provide evidence that the change in Kmax following corneal collagen cross-linking correlates with a clinical benefit to the patient. The clinical benefit can be a patient reported outcome, caregiver reported outcome, or a clinical observer outcome.

2. The Advisory Committee discussion identified a number of trial design concerns including the disease definition and entry criteria. In your new study (or studies) for the proposed indication(s) we request you consider inclusion and exclusion criteria for progression of disease, types and number of prior refractive procedures (including non-laser based refractive procedures, time between prior refractive treatment and enrollment in the clinical trial (if known) for these eyes, exclusion for previous corneal collagen crosslinking.

3. We recommend you consider evaluating the existing study data to explore the following:

    a. Outcomes for eyes which had a pachymetry <400 microns versus > 400 microns, and results for patients who received Photrexa Viscous only, or who received both Photrexa Viscous and Photrexa.
    b. Outcomes based on the original corneal thickness versus corneal thickness after treatment was <400 microns or > 400 microns.

4. Use of published literature: If you intend to provide clinical literature to support the use of the to-be-marketed combination product with the KXL System, the literature should be based on a comprehensive literature search stratified by key parameters of interest. [3]

    In addition to results, please provide detail regarding how this literature review was performed. Using the PRISMA guidelines, indicate the database(s) searched, search terms, reasons for excluding articles and including them. For this process please give the number of articles screened, assessed for eligibility and included in the review with reasons for exclusion at each stage ideally with a flow diagram. Also indicate which publications represent trials, which were case series, etc. This is requested so that we can determine the adequacy of the review and any potential sources of bias. Please provide PDFs of these complete articles.

    a. Identify the search criteria and methodology to identify the strengths and weaknesses of the articles.

[3] Please refer to the FDA Guidance for - Industry Applications Covered by Section 505(b)(2), http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf
FDA may request additional information on the clinical protocols used, line listing, and inspection of the clinical site.

b. The publications should identify specific drug/device combination product and the procedure method that was studied
c. The publications, where possible, are recommended to describe the specific drug/device combination product you are requesting to market. We note that at the Advisory Committee meeting that you noted that there may not be any literature using the combination product as submitted to the NDA. If you wish to rely on other clinical literature, a strong justification should be provided. Please include in your discussion if any of this literature addresses the concern that differences between the UV-X and KXL systems may affect safety and effectiveness outcomes.
d. Please submit any existing publications or manuscripts presenting any data collected in the pivotal trials from this NDA

5. Corneal haze is reported in your pivotal trial results. We recommend that you consider grading corneal haze at all visits in any future trial (s) and provide a discussion of any impact of the haze on visual function.

6. We recommend that you utilize observed data only (no LOCF) in the primary analysis of corneal endothelial cell count (ECC) in any future trials. We recommend that you include procedures to identify non-physiologic ECC values at the study visits.

7. We recommend that for any new clinical trial, the protocol should comprehensively describe all investigator training and details of procedures. The protocol study methodology, e.g. epithelial debridement procedure, should contain adequate detail to ensure that study procedures are standard across all study sites.

LABELING

In the EMC guidance tables mentioned above, a comma (,) was used as the decimal separator as required by the IEC standard. However, while using the comma for the decimal separator is the convention in Europe, it is not the convention in the US. To assure the usability of the Operators Manual in the US, please use the period (.) where needed in the EMC guidance tables for US version of the Operators Manuals.

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/s/

RENATA ALBRECHT
03/29/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203324
Priority or Standard	Priority
Submit Date(s)	September 29, 2014
Received Date(s)	September 29, 2014
PDUFA Goal Date	March 29, 2015
Division / Office	Division of Transplant and Ophthalmology Products/Office of Antimicrobial Products
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	March 16, 2015
Established Name	riboflavin 5'-phosphate ophthalmic solution 0.146%, riboflavin 5'-phosphate in 20% dextran ophthalmic solution 0.146%, and KXL System
(Proposed) Trade Name	
Therapeutic Class	photoenhancer
Applicant	Avedro, Inc.
Formulation(s)	ophthalmic solution
Dosing Regimen	1 drop topically on the eye every 2 minutes for 30 minutes

Indication(s)	treatment of progressive keratoconus and corneal ectasia following refractive surgery
Intended Population(s)	progressive keratoconus and corneal ectasia following refractive

Template Version: March 6, 2009

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

NDA 203324, Photrexa Viscous (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL with 20% dextran and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL and KXL System, is recommended for approval for the treatment of progressive keratoconus and for the treatment of corneal ectasia with the revisions to the labeling found in this review.

The applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 14, 2014, as approvability issues.

1.2 Risk Benefit Assessment

Keratoconus is a naturally-occurring ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in corneal optical irregularities with increasing myopia, irregular astigmatism, and consequential loss of best corrected visual acuity (BCVA). Onset of keratoconus generally occurs during puberty or early adulthood and profoundly affects patients who develop the condition. If left untreated, patients experience progressive vision impairment, which may result in the need for corneal transplantation.

Corneal ectasia is a well-described complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy. It is a condition similar to keratoconus, but occurs postoperatively. Ectasia may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of both uncorrected visual acuity (UCVA) and BCVA.

There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery. For both keratoconus and corneal ectasia, early intervention usually involves 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 address the optical irregularity of the cornea. Surgically-implanted intrastromal ring segments may be used to improve contact lens wear in patients who are contact lens intolerant. These treatments do not halt the

progression of keratoconus. Corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal transplantation is not without risk – postoperative complications include transplant failure, rejection, secondary cataract, secondary glaucoma, and recurrence of keratoconus in the transplanted graft.

The goal of corneal collagen cross-linking (CXL) is to biomechanically stabilize the weak cornea in keratoconus and postoperative corneal ectasia and decrease the clinical progression of these diseases. In the crosslinking procedure, riboflavin is administered topically to the eye (typically one drop every 2 minutes for 30 minutes). After riboflavin saturation through the corneal stroma, exposure to ultraviolet A (UVA) light (365 nm; 3 mW/cm^2 irradiation; 30 minutes' duration) induces crosslinking.

Normally riboflavin ophthalmic solution containing 20% dextran is used. However, if corneal thickness is < 400 µm riboflavin ophthalmic solution containing no dextran is used until the corneal thickness is at least 400 µm.

The original primary efficacy endpoint for the applicant's clinical trials was as the difference between the CXL group and the control group in maximum keratometry (Kmax) from baseline to Month 3. At the time the studies were initially planned, the Agency recommended a 12 month endpoint but the applicant believed that the primary efficacy endpoint could be analyzed at 3 months post-procedure based on their review of the existing literature. The applicant reviewed subsequent additional literature which suggested to them that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize.

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for both indications.

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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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. The loss of control subjects makes the analysis of observed data challenging to interpret due to the decreasing sample size at later time points.

The most common adverse events for both the keratoconus and corneal ectasia indications occurring at 10% to 92% in UVX-001, -002, and -003 were corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following the corneal epithelial debridement which accompanied the procedure.

A joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee (OP-MDAC) was held on February 24, 2015:

> When asked: Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for progressive keratoconus? Yes/No

The panel voted: **YES:** 10 **NO:** 4 **ABSTAIN:** 1

> When asked: Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for corneal ectasia following refractive surgery? Yes/No

The panel voted: **YES:** 6 **NO:** 4 **ABSTAIN:** 4 **NO VOTE:** 1

The applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 14, 2014, as approvability issues.

The benefits of the CXL procedure are considered to outweigh the risks for both indications.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Avedro's riboflavin ophthalmic solution/UVA irradiation is a combination product consisting of a UVA 365 nm wavelength light source and riboflavin administered in conjunction with the UVA light as a photosensitizer.

Drug Constituent- Riboflavin
Photrexa Viscous (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL with 20% dextran and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL contain riboflavin 5'-phosphate sodium, sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic, and sterile water for injection. Photrexa Viscous contains 20% dextran 500 and Photrexa does not.

Device Constituent- KXL System
The KXL System is an electronic medical device that delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of Photrexa or Photrexa Viscous (riboflavin ophthalmic solution). UVA flux and irradiation time at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System.

Figure 2.1: Overview Illustration of the KXL System

The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient's cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

The KXL System includes a Radio Frequency Identification (RFID) reader and RFID activation card. The RFID activation cards are supplied with Photrexa Viscous or Photrexa (riboflavin ophthalmic solution). The software allows treatment only if a valid RFID activation card has been identified by the RFID reader of the system console. For the KXL System, software lock-out provides the maximum allowable treatment parameters will be limited to 3mW/cm^2 for 30 minutes and a maximum energy density of 5.4 J/cm^2.

The user will not be able to change the induction, power and treatment time.

The following treatment parameters provided by the RFID activation card

- Induction Period: (b) (4) 30 minutes
- Irradiance: 3 mW/cm^2
- Total Energy: 5.4 J/cm^2

- Exposure Time: 30 minutes

Table 2.1 shows excerpts from the KXL System specifications.

Table 2.1.1: KXL System Specifications

Specification	Description
Electrical	Battery Powered: 12V 35 Ah SLA Line voltages 100-240 volts AC, (b) (4) Current (b) (4) Single Phase RMS, 50/60 Hz, (b) (4) Remote 2x AAA batteries
User accessible Fuses	250 V~ (b) (4)
Energy Delivery	UV Radiation 3 mW/cm^2 365 nm
External Interfaces	USB 2.0
Battery Life (normal operating conditions)	16 hours

The Optics Head houses the UVA irradiation mechanism. UVA radiation is generated by (b) (4) UV LED. The LED is manufactured to emit UVA radiation at a wavelength of 365 nm. (b) (4)

(b) (4) A fixed aperture mounted in the UVA irradiation beam path is used to produce a uniform circular area of irradiation at the treatment plane with an approximate diameter of 9 mm.

To correctly position the UV beam onto the cornea, two targeting lasers are used. (b) (4) Both lasers are controlled (b) (4)

Device Constituent Part Difference: Clinical trial device vs. the proposed for market device

The device used in the three Phase 3 trials differed from the device proposed for approval in this NDA (Avedro KXL) as summarized in Table 5 below. The KXL-System was not used in the three Phase 3 trials. Table 5 summarizes the device similarities followed by the differences.

Table 5: Similarities and Differences between the UVX and Avedro KXL Devices

Parameter	Clinical trial device (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL System (device to be marketed)	Comparison Comment
Patient Contact	Non-contacting	Non-contacting	Same
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
Operating	+10C - +40C 30-75% RH, non-condensing 700-1060 mbar	+10C - +40C 30-75% RH, non-condensing 700-1060 mbar	Same
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

Parameter	Clinical trial device (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL System (device to be marketed)	Comparison Comment
Patient Position	Supine or Sitting	Supine Only	The Clinical Trial Device 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.
Available UV Beam (Ø)	7.5 mm 9.5 mm 11.5 mm	9.0 mm	The Clinical Trial Device had three available beam diameters while the KXL System only includes the 9 mm setting.
Power Monitoring	Stand-alone commercial power meter, used at start-up.	Continuous, on-board monitoring using two independent dedicated UV photodiodes	The Clinical Trial Device 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 does not require the user to manually check calibration prior to treatment.
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.

Parameter	Clinical trial device (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL System (device to be marketed)	Comparison Comment
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 Clinical Trial Device.
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; both systems have methods for the user to determine the correct focal plane for treatment.
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.
Device Dimensions	32x5x5 cm	60x60x150 cm, maximum extended position.	The dimensions of the two systems differ.
Device Weight	<10 kg	45 kg	The weights of the two systems differ.

Parameter	Clinical trial device (used in UVX-001, UVX-002 and UVX-003)	Avedro KXL System (device to be marketed)	Comparison Comment
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.

2.2 Tables of Currently Available Treatments for Proposed Indications

There is currently no FDA-approved drug in the United States (US) for the treatment of progressive keratoconus or corneal ectasia following refractive surgery.

One device has labeling for use in patients with keratoconus (KC), INTACS. INTACS prescription inserts are intended for the reduction or elimination of myopia and astigmatism in patients with KC, who are no longer able to achieve adequate vision with their contact lenses or spectacles, so that their functional vision may be restored and the need for a corneal transplant procedure may potentially be deferred.

2.3 Availability of Proposed Active Ingredient in the United States

There are no approved riboflavin ophthalmic solutions in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Riboflavin (Vitamin B2) is a water-soluble vitamin that is the parent of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze many oxidation/reduction reactions in the body. Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photosensitizer.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is a combination product submitted under NDA 203324, which was studied under two INDs.

This is a 505(b)(2) application. The applicant is not relying upon a listed product. A majority of the toxicological data for riboflavin was generated following oral administration because of its use in food or as a dietary supplement. Topical riboflavin with concurrent exposure to UVA light has been used for the treatment of keratoconus and corneal ectasia and both in vitro and in vivo nonclinical studies have been conducted using this methodology. The applicant has conducted corneal crosslinking clinical trials utilizing the final formulations (s) of the to be- marketed riboflavin.

In July 2007, Doyle Stulting, MD, an ophthalmologist and Professor at Emory University opened an IND (IND 78,933) to study progressive keratoconus and corneal ectasia following refractive procedures. Dr. Stulting's studies were identified as UVX-001 Keratoconus and UVX-001 Corneal ectasia.

Dr. Stulting's study was performed in association with Peschke Meditrade and Peschke Meditrade was involved in discussions between Dr. Stulting and the Division of Anti-Infective and Ophthalmology Products concerning the UVX-001 protocol. The original protocol design envisioned a 3 month clinical trial with the potential for additional follow-up. The Division was concerned that a 3 month endpoint would not allow enough time to demonstrate a measurable clinical effect from the corneal cross-linking and strongly recommended a 12 month endpoint.

The Division provided comments on Protocol UVX-001 on September 11, 2007, and subsequently held a teleconference with these IND holders to discuss potential modifications to Protocol UVX-001, including timing of the primary endpoint. Dr. Stulting and Peschke Meditrade were concerned that patients in the sham control group would not be willing to wait more than 3 months to have their eyes treated recognizing the potential lifetime consequences of the disease. Based on the availability of corneal cross-linking by a number of private practitioners in the United States, the publication of cross-linking successes and the lack of any enforcement action by the FDA against US practitioners promoting corneal cross-linking, Dr. Stulting and Peschke Meditrade believed that a US trials could not be conducted if sham control subjects had to wait more than 3 months to have their eyes treated or to have their contralateral eye treated. The FDA insisted that the trials include at least 12 months of follow-up following any eye treated study eye, contralateral eye or sham control eye crossed over to treatment. Dr. Stulting and Peschke Meditrade chose to accept the risk that there might not be enough time to demonstrate the benefit of corneal cross-linking, maintaining that they could not conduct the trial without the ability to allow a 3 month cross-over. Protocol UVX-001 was amended on September 14, 2007, and October 12, 2007, to become a randomized, one year study. With the consideration that the cross-over was not a safety issue and in the absence of definitive proof that the study would fail at 3 months, the study was permitted to proceed.

In November 2007,Peschke Meditrade opened their own IND (IND 77,882) and proposed two multicenter studies, patterned after Dr. Stulting's protocol. Protocol UVX-002 would include patients with progressive keratoconus. Protocol UVX-003 would include patients with corneal ectasia follow corneal refractive procedures.

In 2010, during the conduct of trial UVX-001, Dr. Stulting left Emory University and opened another practice in Atlanta, GA, near Emory University. Emory University did not allow Dr. Stulting to transfer the clinical trial to his new practice. Emory closed the study without completing the enrollment of the study and without completing the follow-up of some of the patients previously treated.

In 2010, citing a lack of funding, Peschke Meditrade stopped new enrollment of UVX-002 and UVX-003. Follow-up of patients previously treated continued.

Peschke Meditrade sold the data and rights to UVX-001, UVX-002 and UVX-003 to Avedro in May 2010. Sponsorship of IND 77,882 was transferred to Avedro, Inc. on May 7, 2010. Avedro, Inc. received orphan-drug designation "for corneal cross-linking for the treatment of keratoconus (sic)" on September 2, 2011, and "treatment of corneal ectasia following refractive surgery" on December 2, 2011. A pre-NDA Meeting was held on September 21, 2011. CMC indicated that the briefing document was inadequate and requested additional information on the composition of the material used for the Phase 3 studies and the composition of the proposed commercial formulation. Clinical stated it was not possible to determine whether the clinical program will be sufficient to support approval based on the information previously submitted. Clinical would need to review the final study report for study UVX- 001, -002 and -003 to determine whether it is appropriate to combine patients from -001 into - 002 and -003. The lack of statistical significance between groups in the patients treated for keratoconus at Month 3 was noted as potentially problematic.

Avedro wrote the Statistical Analysis Plan in December/January of 2012. Avedro also completed the data entry and performed the data clean-up and performed the data analysis. The original protocol described an interim analysis of all data at 3 months. While Avedro did not perform the interim analysis, one of the investigators in studies UVX-002 and UVX-003 (Peter Hersh, MD) performed and published an analysis of the data at his site.

Avedro, Inc. submitted a New Drug Application (NDA) on March 8, 2012, for their riboflavin ophthalmic solution /KXL System. Avedro, Inc received a refuse to file letter dated May 4, 2012. The application was not sufficiently complete to permit a substantive review. The Agency refused to file this application under 21 CFR 314.101(d). A post "Refuse-to-File" meeting was held with Avedro, Inc. on May 31, 2012, to discuss the Agency's comments in the RTF letter dated May 4, 2012.

A CMC Type A meeting was held on August 15, 2012, where Avedro committed to revise the commercial formulation information proposed in the NDA to be consistent with the clinical formulations used in the clinical trials.

A general advice letter was send on October 19, 2012, in response to the September 24, 2012, submission seeking Agency advice on Avedro's plan for cGMP manufacturing of the drug substance, riboflavin 5'-phosphate sodium and drug product process validation and registration stability.

NDA 203324 for the Photrexa Viscous /Photrexa/KXL-System was submitted September 16, 2013. Avedro was issued a Complete Response letter on March 14, 2014, and asked to provide additional information on the drug constituent part, the drug facility inspections, the device constituent part, clinical/statistical information, clinical site inspections and other comments. On August 6, 2014, Avedro met with FDA to go over their proposed responses to the outstanding items and submitted a complete response to the NDA on September 29, 2014.

2.6 Other Relevant Background Information

The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for these combination products under RFD070013.

The final Statistical Analysis Plan (SAP) for Progressive Keratoconus was dated December 16, 2011. The SAP described changes from the planned analyses in the protocol. These changes were:

1. Efficacy data would be summarized in 3 ways: (1) the UVX-001 keratoconus data pooled with the UVX-002, (2) the UVX-001 keratoconus data alone and (3) the UVX-002 data alone.

2. The original protocol defined Month 3 as the primary time point for analysis of improvement in Kmax. The final SAP extended the primary time point for analysis to Month 12, and a last observation carried forward analysis strategy was added.

3. Although no formal interim analysis was planned, the SAP incorporated an adjustment to the alpha-level to account for the analyses at Month 3 and Month 12.

The final SAP for Corneal Ectasia was dated January 18, 2012. The statistical analysis plan described changes from the planned analyses in the original protocol. With the exception that the pooled analyses included UVX-001 corneal ectasia data and UVX-

003 data, changes were identical to those described above in the SAP for Progressive Keratoconus.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The Advisory Committee voted that substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for progressive keratoconus. The Committee also voted that substantial evidence of efficacy and safety had been demonstrated to support approval for corneal ectasia following refractive surgery. It was clear however that there were significant issues with the trials. These issues included, but are not necessarily limited to:

1. Incomplete enrollment of the clinical trials with none of the trials enrolling the planned number of patients.

   Dr. Stulting enrolled of only about one third of the planned number of patients, and the follow-up of some of these patients was interrupted by his move to another clinical site. Emory University did not allow Dr. Stulting to take the study with him or and did not arrange for the protocol to be continued at Emory by another investigator.

Enrollment of the multicenter trials was stopped prior to completing the planned enrollment, reportedly due to financial concerns. Enrollment was not resumed by the new owner of the clinical trials. Eighty-six percent (86%:277/320) of planned patients enrolled. The circumstances raise questions about whether a premature look at the data led to the discontinuation of enrollment.

2. A lack of statistical rigor.

   The statistical analyses plan was written late in the process. It was written prior to all planned patients being enrolled in the trial, but after all of the patients that were actually enrolled in the trial completed their follow-up.

   The primary endpoint was changed 3 to 12 months, changing the reported result of a failed study in patients with keratoconus to a successful study in patients with keratoconus. While the FDA's Clinical Review Division recommended the

12 month endpoint, the Division did not recommend allowing control patients to have treatment prior to reaching their final endpoint.

The protocol allowed for an interim look without appropriate adjustments for multiplicity. There was a publication of partial results of the trial (i.e., from one site).

Study results were sold to another sponsor reportedly prior to an analysis of the data.

3. Large percentages of the control patients crossed over to the treatment group prior to reaching the Statistical Analysis Plan's defined endpoint.

Almost all sham eyes crossed over or were lost to follow-up prior to Month 12. While the original protocol defined Month 3 as the primary endpoint and allowed cross-over at that point in time, the Statistical Analysis Plan defined the primary endpoint at Month 12. Most control/sham eyes were crossed over prior to the newly defined endpoint. The result is that the almost all data in the sham/control group at the primary endpoint is based on a last observation carried forward analysis.

Percentage of Sham Eyes Lost or Crossed Over

	Month 6	Month 12
UVX-001 Keratoconus	38%	100%
UVX-001 Corneal Ectasia	48%	100%
UVX-002 Keratoconus	72%	97%
UVX-003 Corneal Ectasia	70%	97%

4. There were a large number of protocol deviations in each of the clinical trials.

UVX-001 427 Deviations

- Over ½ for not collecting IOP measurement
- The vast majority of the deviations were related to timing or measurement which are unlikely to result in any clinical concerns, but are examples of non-adherence to the protocol.

UVX-002 422 Deviations

- Approximately ½ for collecting info outside protocol window while others were evenly split between missing different elements.

- The vast majority of the deviations were related to timing or measurements which are unlikely to result in any clinical concerns, but are examples of non-adherence to the protocol.

UVX-003 745 Deviations

- Almost 1/3 from a single site missing IOP measurements while others were split between missing elements or outside windows.
- The vast majority of the deviations were related to timing or measurements which are unlikely to result in any clinical concerns, but are examples of non-adherence to the protocol.

5. The protocol specified primary endpoint, Kmax at 3 months, was not met for patients with keratoconus, while the Statistical Analysis plan primary endpoint, Kmax at 12 months was met.

6. The device used in the clinical trial was not the same as the device proposed to be marketed.

The similarities include:

Parameter	IROC UV-X	Avedro KXL	Comparison
Patient Contact	Non-contacting	Non-contacting	Same
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
Operating	+10C - +40C 30-75% RH, non-condensing 700-1060 mbar	+10C - +40C 30-75% RH, non-condensing 700-1060 mbar	Same
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

Differences include the size, shape, power supply and software in the device and the distance between the device and patient during use.

Parameter	IROC UV-X	Avedro KXL
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.
Device Dimensions	32 x 5 x 5 cm	60 x 60 x 150 cm
Device Weight	<10 kg	45 kg
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
Power Monitoring	Stand-alone commercial power meter, used at start-up.	Continuous, on-board monitoring using two independent dedicated UV photodiodes
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
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.
UV Focal Plane (working distance– instrument exit to patient corneal apex)	50 mm nominal	150 mm nominal

An additional difference between the device used in the Phase 3 clinical trials and the device proposed for marketing was that the device in the clinical trials had 3 possible diameter settings for application of the light source, 7.5mm,

9.5mm and 11.5mm. The device proposed for marketing has a single, 9mm diameter.

In the clinical trials only the 9.5mm and the 11.5mm settings were used and the majority of patients were treated with the 9.5mm setting.

Illumination Diameter	UVX-001 Ectasia	UVX-001 Keratoconus	UVX-002 Keratoconus	UVX-003 Ectasia
Medium (9.5 mm)	24	29	61	56
Large (11.0 mm)	--	--	10	7

It is unclear whether this difference in diameter could result in any clinical differences. The devices deliver a uniform UV irradiance of 3.0 ± 0.3mW/cm^2. The difference between a 9mm and 9.5mm diameter is 0.25mm at the edge of the circle. The difference between a 9mm and an 11.5mm diameter is 1.25mm at the edge of the circle. The ability of any individual to keep their eye still and not permit a 1.25mm movement in any direction for 30 minutes is highly unlikely.

7. The clinical course of keratoconus variable and patients with or without progression during a period prior to the clinical trial may or may not have had progression during the clinical trial.

   It is not possible to predict when keratoconus progression will occur. The rate of progression is often not constant. One of the reasons for conducting a randomized, controlled trial was to balance unknown progression rates between groups.

   While a portion of the clinical trial population only met a criterion for a small amount of progression, the randomization of patients should minimize the impact.

8. There were only a small number of pediatric patients enrolled in the clinical trials. There are multiple studies of corneal cross-linking with riboflavin in pediatric patients demonstrating similar results as seen in adults.

9. The database originally submitted by the applicant included typographical errors precluding accurate analyses of some of the clinical parameters. The applicant was asked to fix these errors in the Agency's Complete Response letter following the original submission and in subsequent interactions with the applicant. While there are a variety of opinions about the clinical utility of performing meticulousness data analysis of some of the datasets which contained the errors, the errors raised questions about the applicant's ability to perform a quality review of the datasets.

3.2 Compliance with Good Clinical Practices

The clinical trials reviewed in this application were conducted in accordance with good clinical trial practices.

3.3 Financial Disclosures

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2.

See Section 3.3 and Appendix 9.3 of the original Medical Officer's review dated 3/7/2014.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Photrexa Viscous (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL with 20% dextran and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL are indicated (b) (4)

The Photrexa Viscous and Photrexa drug product solutions contain riboflavin 5'-phosphate sodium, sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic, and sterile water for injection. Photrexa Viscous contains 20% dextran 500 and Photrexa does not.

(b) (4) Except for dextran 500 the excipients are compendial. Dextran 500 is a novel excipient. As with other dextrans, it is a water-soluble polymer of glucose.

The drug product is manufactured (b) (4) with some testing carried out by outside laboratories. An Overall recommendation of Approve has been made by Compliance. The Overall Re-evaluation Date is 4/4/16. The manufacturing process is described in reasonable detail and the in-process controls are reasonable.

The container-closure solution is a 3 mL clear glass syringe fitted with a plunger with a rubber stopper and a plastic rigid tip cap. The syringe is packaged in a Tyvek pouch and this pouch is placed inside a foil pouch.

Twelve months of satisfactory stability data are provided for three batches of each formulation. The expiration dating period is 18 months.

The compositions of the final solutions are as follows:

Component	Photrexa Viscous		Photrexa	
	Amount	mg/g	Amount	mg/g
Sodium phosphate, monobasic	(b) (4)			
Sodium phosphate, dibasic				
Sodium chloride				
Riboflavin				
Dextran 500				
Sterile water for injection				
Total				

*Equivalent to 1.46 mg/mL riboflavin 5'-phosphate (MW of riboflavin phosphate = 456.349)

As modified in the applicant's amendments of 9/29/14 and 11/14/14, the drug product specification is as follows:

Table 1: Drug Product Specifications

Test Description	Method	Acceptance Criteria
Appearance	Visual	A glass syringe containing a clear yellow solution, no visible particulates, and no leakage. May contain a minimal bubble
Identification	RP-HPLC	Retention time ((b) (4)%) and UV spectra conform
Assay	RP-HPLC	(b) (4)% LC ((b) (4) mg/ml)
Riboflavin 5'-monophosphate	RP-HPLC	Not less than (b) (4)% Relative Area
pH	USP <791>	(b) (4)
Sterility	USP <71>	No Growth
Viscosity	USP <911>	Photrexa: (b) (4) cP Photrexa (b) (4) cP
Osmolality	USP <785>	Photrexa: (b) (4) mOsm/kg Photrexa (b) (4) mOsm/kg
Particulate Matter	USP <789>	(b) (4) particles/mL (b) (4) particles/mL particles/mL
Endotoxin	USP <85>	(b) (4) EU/mL
Degradants	RP-HPLC	Specified: (b) (4) RRT (b) (4)% RRT % RRT % Each Unspecified: (b) (4)% Total: (b) (4)%

4.2 Clinical Microbiology

Not applicable to this review.

4.3 Preclinical Pharmacology/Toxicology

See original Pharmacology/Toxicology review dated 2/26/2014.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See the original Medical Officer's review dated 3/7/2014.

4.4.2 Pharmacodynamics

See the original Medical Officer's review dated 3/7/2014.

4.4.3 Pharmacokinetics

See the original Medical Officer's review dated 3/7/2014.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Table of Clinical Studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Diagnosis of Patients	Duration of Treatment
UVX-001	Safety and Efficacy	Randomized sham-controlled	Photrexa/Photrexa Viscous 0.12% solution; clinical trial device - UVA light (365 nm; 3 mW/cm^2) Single Treatment	107; (53 drug; 54 sham)	Patients with progressive keratoconus and corneal ectasia following refractive surgery	Pre-treatment and during irradiation: Photrexa/Photrexa Viscous 0.12% solution 1 drop every two min for 30 min Clinical trial device: UVA light: 30 min
UVX-002	Safety and Efficacy	Randomized sham-controlled	Photrexa/Photrexa Viscous 0.12% solution; clinical trial device - UVA light (365 nm; 3 mW/cm^2) Single Treatment	147; (73 drug; 74 sham)	Patients with progressive keratoconus	Pre-treatment and during irradiation: Photrexa/Photrexa Viscous 0.12% solution 1 drop every two min for 30 min Clinical trial device: UVA light: 30 min
UVX-003	Safety and Efficacy	Randomized sham-controlled	Photrexa/Photrexa Viscous 0.12% solution; clinical trial device: UVA light (365 nm; 3 mW/cm^2) Single Treatment	130; (67 drug; 63 sham)	Patients with corneal ectasia following refractive surgery	Pre-treatment and during irradiation: Photrexa/Photrexa Viscous 0.12% solution 1 drop every two min for 30 min Clinical trial device: UVA light: 30 min

Source: 5.2 Tabular Listing of All Clinical Studies

5.3 Discussion of Individual Studies/Clinical Trials

See the original Medical Officer's review dated 3/7/2014

6 REVIEW OF EFFICACY

Efficacy Summary

6.1 Resubmission after Complete Response

Text in italics represents CDER Medical Officer/Reviewer Comments.

The applicant's responses to the Complete Response letter are located in SDN-032 (eCTD seq 0027) submitted 7/14/2014, and SDN-033 (eCTD seq 0028) submitted 9/29/2014.

The Complete Response letter dated March 14, 2014, cited the following items as approvability issues.

6.1.1 The DRUG CONSTITUENT PART

1. The validation of the HPLC method is inadequate. Please submit the Method Validation report for the drug product HPLC method.

The CMC review #2 dated 3/5/2015 finds the validation of the HPLC method acceptable (see P.5.2 Analytical Procedures and P.5.3 Validation of Analytical Procedures).

2. The specifications for the proposed drug products are inadequate. The specifications should be based on the specifications submitted in the amendment submitted November 27, 2013. The description of your two products should be as noted in your amendment submitted February 14, 2014. The degradants should be specified and have acceptance criteria that are based on data from the methods validation report and the stability data provided in the amendment submitted February 14, 2014 as well as any more recent stability data. Include tests for specified, unspecified, and total degradants in your response. In general the recommendations of Q3B should be followed.

The CMC review #2 dated 3/5/2015 finds the revised specifications acceptable (see P.5.1 Specification(s)).

3. The stability data for your two products cannot be evaluated without appropriate drug product specifications as noted above. Please revise your batch analyses and stability data in accordance with the modified specifications.

The CMC review #2 dated 3/5/2015 finds the revised batch analyses and stability data acceptable. Twelve months of satisfactory stability data are provided for three batches of each formulation. The expiration dating period is 18 months (see page 9 of the CMC review).

6.1.2 DRUG FACILITY INSPECTIONS

4. A recent inspection of the (b) (4) manufacturing facility noted deviations from current Good Manufacturing Procedures (cGMP) for this application. Our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

The CMC review #2 dated 3/5/2015 notes that an overall recommendation of Approve has been made by Compliance. The Overall Re-evaluation Date is 4/4/16 (see below and pages 9 and 72 of the CMC review).

(b) (4)

6.1.3 DEVICE CONSTITUENT PART

5. You have submitted information regarding the differences between the specifications of the device used in the clinical studies (UV-X Illumination System) and the device proposed for approval (the KXL system). This information was to evaluate the impact

that differences may have had on study safety and effectiveness results and their applicability to expected post-market device performance. Your submission on February 21, 2014 raised the following concerns:

a. You were asked to clarify whether the differences listed in Table 8 include all differences between the device used in each of your three clinical studies and the device proposed for marketing approval (including, but not limited to, device description, laser settings and/or parameters, software, and instructions for use). If not, you were asked to provide this information. In your response, you describe the differences in Table 8 and state that "…device specifications which directly impact dose of the UV light are equivalent between the UV-X Illumination System and the KXL System." However, this response is inadequate because you have not clarified whether the list of differences in Table 8 encompasses all differences between the device studied and the device you intend to market. Therefore, please clearly state whether the differences listed in Table 8 include all differences between the device used in each of your three clinical studies and the device proposed for marketing approval (including, but not limited to, device description, laser settings and/or parameters, software, and instructions for use.) If not, please provide a description of all additional differences and discuss whether any of these differences could impact the safety or effectiveness of the device.

In the Type A Meeting Briefing Package, Section 3.5 (SN 0027, Module 1.6.2), Avedro provided tables outlining the differences between the device and instructions for use used in the clinical studies compared to the device proposed for marketing approval.

At the 06 August 2014 Type A Meeting, Avedro explained that (b) (4) *was an administrative error in the table that was included in the briefing book. Avedro confirmed that the instructions for use in the KXL User Manual will be the same as during the clinical study.*

This response is acceptable.

6.1.3.1 Optical Radiation Hazard

6. You have indicated that you intend to use a Radio Frequency Identification (RFID) activation card to determine the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage. We previously expressed concern regarding the adequacy of this method to control for safety (i.e., excessive power delivery to the eye). In addition to RFID security issues, there are also electromagnetic compatibility (EMC) concerns regarding the use of RFID integration in the device. Therefore, for adequate control of the energy output of your device,

please modify the software of your device to implement a software lock-out of irradiated power above 3 mW/cm^2.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.6 (SN 0027, Module 1.6.2). Avedro agrees to modify the software of the to-be-marketed device to implement a software lock-out of the irradiated power above 3 mW/cm^2. The user will not be able to change the induction, power and treatment time. With this implementation, the RFID activation card will no longer be used to set the treatment parameters; however, it will still be used to enable the treatment to start. Validation of the software lock-out has been completed.

This response is acceptable.

7. You indicate that the (b) (4) validation activities for the Homogeneity Measurement Master Validation plan (VAL-0005) are ongoing. Please provide the results of your validation activities.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.7 (SN 0027, Module 1.6.2). The validation activities for the Homogeneity Measurement Master Validation plan have been completed and results are provided in Final Report VAL-00005-RPT.

This response is acceptable.

6.1.3.2 Electro Magnetic Compatibility

The following deficiencies refer to a Request #6 - #8 and #10 - #12, respectively, in the agency Information Request (IR) letter dated February 11, 2014.

8. In your table of "recognized standards" with which the KXL System is claimed to comply, for many of the standards listed, there was no edition or date information. Requirements of standards can differ considerably from one edition to the next. Therefore, edition or date of publication information is needed. Please note that FDA does not recognize EN standards, and there were several on the list. Conformity with IEC 60601-1-2 was claimed. However, the EMC test report cited EN 60601-1-2. While the two standards are essentially identical, we asked you to be consistent in the claims of conformity. Finally, we asked you to submit an FDA Form 3654 for each standard to which conformity was claimed.

You submitted a revised Table 6: List of Recognized Consensus Standards and an FDA Form 3654 for each standard to which conformity is claimed. This is partially acceptable because the table and forms have the errors listed below. Please correct them.

a. In Table 6, ISO 14971:2007/(R)2010 is listed, with recognition number 5-70. ISO does not reaffirm standards. The (R) designation and the recognition number are for the AAMI ANSI ISO version of the standard. The corresponding FDA Form 3654 lists the standard correctly.

b. In Table 6, the recognition number for IEC 60601-1:2005 (Edition 3) is incorrect. The number shown (5-77) is for Edition 3.1. The number shown on the corresponding FDA Form 3654 (5-78) is the correct recognition number for IEC 60601-1:2005 (Edition 3.0).

c. While Table 6 and the corresponding FDA Form 3654 claim conformance to IEC 60601-1-2:2007, according to the EMC test report, the device is actually in conformance with EN 60601-1-2:2007. Because the IEC and EN versions are identical, this response is acceptable. However, while the FDA Form 3654 correctly cites recognition number 5-53, the number listed in Table 6, 5-54, is incorrect. Recognition number 5-54 is the AAMI ANSI IEC version of the standard.

d. Table 6 cites conformity with IEC 60601-1-6:2010, Edition 2.0, recognition number 5-85. This is partially incorrect. The correct Edition number is Edition 3.0.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.8 (SN 0027, Module 1.6.2). The information contained in the List of Recognized Consensus Standards table has been revised to correct the errors noted in items a, b, c, d and f above (see Table 7).

Table 7: List of Recognized Consensus Standards

STANDARD	FDA RECOGNITION NUMBER	TITLE
AAMI/ANSI/ISO 14971:2007/(R)2010	5-70	Medical devices – Application of risk management to medical devices
ISO 13485:2003	--	Medical devices – Quality management systems – Requirements for regulatory purposes
IEC 60601-1:2005, Ed. 3, Corr. 1 (2006), Corr. 2 (2007)	5-78	Medical Electrical Equipment: General Requirements for Basic Safety and Essential Performance
IEC 60601-1-2:2007 ED 3.0	5-53	Medical Electrical Equipment – Part 1-2: General Requirements for Safety – Collateral Standard: Electromagnetic Compatibility – Requirements and Tests
IEC 60601-1-6:2006 ED 2.0	--	Medical Electrical Equipment – Part 1-6: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Usability
IEC 60825-1:2007 Ed.2 + Corr. 1:2008	12-220	Safety of laser products - Part 1: Equipment classification and requirements
IEC 62471:2006 ED 1.0	12-249	Photobiological safety of lamps and lamp systems

Table 7: List of Recognized Consensus Standards (Continued)

STANDARD	FDA RECOGNITION NUMBER	TITLE
ISO 15223-1:2012	5-73	Medical Devices. Symbols to be used with Medical Device Labels, Labeling and Information to be supplied. General Requirements.
IEC 62304:2006/AC:2008	13-8	Medical Device Software-Software Life Cycle Processes
IEC 62366:2008	5-50	Medical Devices-Application of usability engineering to medical devices

This response is acceptable.

e. The FDA Form 3654 for IEC 60601-1-6 cites Edition 2 (2006) and recognition number 5-85. Edition 2 is no longer recognized by FDA, and recognition number 5-85 is recognition of Edition 3 (2010).

To address item #e, FDA Form 3654 for IEC 60601-1-6 has been updated and is consistent with the testing performed in the submitted 60601-1 Test Report.

This response is acceptable.

f. Table 6 cites conformity with IEC 62471:2008 ED 1.0 and recognition number 12-249. Edition 1.0 was published in 2006.

See Avedro response to 8 a-d above. This response is acceptable.

g. The following standards are listed in Table 6 and for each one there is also an FDA Form 3654 in the submission:

- CISPR 11
- IEC 61000-4-2
- IEC 61000-4-3
- IEC 61000-4-4
- IEC 61000-4-5
- IEC 61000-4-6
- IEC 61000-4-8
- IEC 61000-4-11

These are all normative references of IEC 60601-1-2 and therefore do not need to be listed separately. Also, IEC 60601-1-2 specifies some modifications and additions to these standards, so assuming that the modifications and additions were used, a declaration of conformity to these standards would need to list or describe those modifications and additions. The EMC basic immunity standards are primarily test methods. They have menus of test levels and menus of pass/fail criteria, so a declaration of conformity would need to specify the test level and pass/fail criteria that were used.

If you decide to keep these declarations, [FDA Forms 3654 specify the version and date of publication], please add this information to Table 6 of the application.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.8 (SN 0027, Module 1.6.2). To address item #g, FDA Form 3654 for IEC 60601-1-2 has been updated and is consistent with the testing performed in the submitted VAL-00095-RPT.

This response is acceptable.

9. The immunity pass/fail criteria specified in the EMC test report did not conform to IEC 60601-1-2:2007. The standard lists degradations that are not allowed if associated with Basic Safety or Essential Performance. However, you had not specified the performance that was determined to be the Essential Performance of the KXL System. It is possible that this could be derived from the specification of Criterion A; however, we asked you to specify the Essential Performance explicitly. We recommended that any future EMC testing to IEC 60601-1-2 that you submitted should include immunity pass/fail criteria that conform to the requirements of the

standard. Also, as mentioned below, IEC 60601-1-2 requires that the Essential Performance statement be included in the technical description.

You responded with the following Essential Performance Statement: The KXL system delivers to the cornea UV-A radiation of nominally 365 nm wavelength at an irradiance of 3 mW/cm^2 over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm^2.

You committed that future EMC testing would include testing to IEC 60601-1-2:2007, including immunity pass/fail criteria that conform to the requirements of the standard. In addition, you committed to updating the operators manual to include the Essential Performance statement.

The Essential Performance statement is acceptable. Your promise to conform to the immunity pass/fail requirements of IEC 60601-1-2 is also acceptable. We note that you intend to include the Essential Performance statement in the operator's manual. Please submit the revised operator's manual and confirmation of inclusion of the Essential Performance statement.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.9 (SN 0027, Module 1.6.2). The EMC testing as described above has been performed and results are presented in the provided Report VAL-00091-RPT. In addition, the KXL Operator's Manual was revised to include the Essential Performance statement and is provided.

This response is acceptable.

10. Three immunity tests for which IEC 60601-1-2:2007 specifies the following:

> For ME EQUIPMENT and ME SYSTEMS that have, for power input, multiple voltage settings or autoranging voltage capability, the test is performed at the minimum and maximum RATED input voltages.

The three tests to which this applies are IEC 61000-4-4 (Transient bursts), IEC 61000-4-5 (Surge), and IEC 61000-4-11 (Voltage dips and interruptions). For these three tests, the EMC test report showed that the testing was performed only at (b) (4) VAC/ (b) (4) Hz. We noted that the AC input specifications of the KXL System are 100-240 VAC. Please perform these tests as specified by IEC 60601-1-2, i.e. repeat them at 100 VAC and submit the results of the testing.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.10

(SN 0027, Module 1.6.2). The three immunity tests as described above have been performed and results are presented in the provided Report VAL-00095-RPT.

This response is acceptable.

11. IEC 60601-1-2:2007 specifies requirements for testing and for labeling. In order to demonstrate conformity with the standard (which you claim), in addition to evidence of meeting the testing requirements of the standard, you need to submit evidence of meeting the labeling requirements. This includes the items listed below. We were not able to find any of these items in the Operator's Manual:

    a. We asked you to modify the system technical description to include the following items:

        i. A statement of the performance that was determined to be Essential Performance;

        ii. A warning that the equipment should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, the equipment should be observed to verify normal operation in the configuration in which it will be used.

        iii. Four tables of EMC guidance based on compliance of the device with the individual EMC test standards.

        iv. For devices that incorporate RF transmitters: each frequency or frequency band of transmission, the type and frequency characteristics of the modulation and the EFFECTIVE RADIATED POWER.

        v. For devices that incorporate RF receivers: each frequency or frequency band of reception; the preferred frequency or frequency band, if applicable, and the bandwidth of the receiving section of the ME EQUIPMENT or ME SYSTEM in those bands; and a warning that the ME EQUIPMENT or ME SYSTEM may be interfered with by other equipment, even if that other equipment complies with CISPR EMISSION requirements.

    b. We asked you to modify the system Instructions for Use to include the following items:

        i. A statement that medical electrical equipment needs special precautions regarding electromagnetic compatibility (EMC) and needs to be installed

and put into service according to the EMC information provided in the Instruction Manual.

ii. A statement that portable and mobile RF communications equipment can affect medical electrical equipment.

You have committed to updating the operators manual to include all the items above. Please submit complete versions of the operators manual, which include the above statements.

The KXL System incorporates a wireless remote control and radio frequency identification (RFID) capabilities. As noted above, we now request that your provide a software lockout of powers in excess of 3mW/cm^2. Thus, RFID concerns will no longer be applicable in the absence of a RFID mechanism. However, we do still have remaining concerns regarding the effective radiated power of the wireless device. You have indicated that the KXL system minimizes coexistence problems by only enabling the remote receiver at specific portions of the treatment. Specifically, the remote receiver is enabled for 15 seconds at the Preparing System screen. If the physician chooses to continue without a remote, the power to the remote receiver is disabled. Likewise, the power to the receiver is removed when a treatment is complete. Therefore, coexistence testing is not needed.

The information available on the FCC website for FCC ID SXJ87027-T shows that the wireless technology used is the (b) (4) transmitter and receiver. According to www.thetechnologyreview.com, the wireless standard used is Bluetooth. Bluetooth is known to interfere with wireless LAN services such as Wi-Fi. Furthermore, while you discussed the low duty cycle of the receiver, you did not mention a duty cycle for the transmitter, so the assumption is that it is on continuously. Please submit wireless coexistence test results for this service or a valid rationale for not performing wireless coexistence testing.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.11 (SN 0027, Module 1.6.2). A copy of the KXL Operator's Manual, revised to include the items listed in section a) and b) above, is provided.

The information presented on www.thetechnologyreview.com is correct but incomplete. Bluetooth is a defined wireless standard, designed to allow devices from multiple manufacturers to be compatible with one another. Where in the past wireless chip sets were designed to pair with only one another, Bluetooth allows devices from many different manufacturers to work together by following a common protocol. Additionally, multiple Bluetooth devices can pair to one host, versus one to one. Bluetooth is based on a standard 2.4GHz wireless chip set, but there are protocols and technologies that are unique to Bluetooth, and not every device working on the same frequency band can

be considered Bluetooth. Bluetooth is a trademark, and the technology has unique patents that are needed to make it work. Therefore having a 2.4GHz chipset and even frequency hopping does not make it Bluetooth.

The remote used by Avedro does not conform to the Bluetooth standard, and more importantly is specifically meant to pair only on a one-to-one basis. Wireless coexistence testing was performed (b) (4) *that isISO/IEC 17025 accredited. As outlined in the submitted protocol (KXL Wireless Coexistence Testing Protocol), 802.11 coexistence tests for interference between one or more non-802.11 devices operating within the 2.4 GHz band with 802.11 devices also in the 2.4 GHz band. These tests are designed to compare standard 802.11 traffic with a separate occurrence of identical traffic but with the non-802.11 device(s) operating simultaneously.*

Results of the testing are provided in the submitted final report (KXL Wireless Coexistence Testing Report). Based on the results observed using different traffic types and network topologies, there were no instances observed where the device being tested, operating at the same radio frequency as the 802.11 network(s), negatively impacted the performance of the 802.11 network(s).

The wireless transmitter does have a sleep mode. After 5 minutes of inactivity (no commands to transmit, such as a button push or thumb-toggle movement), the transmitter goes into sleep mode and stops transmitting by design. It can be woken-up only by re-pairing to the receiver.

This response is acceptable.

12. We were not able to find any MRI warnings in the Operator's Manual. We noted that while it is not likely that the device would be taken into the controlled access area of an MRI system, proper precaution is advised for inclusion in your labeling. Thus, an MRI warning should be included in the Operator's Manual and a warning symbol should be included on the device label. These should conform to ASTM F2503, Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment. We asked you to include the "MR Unsafe" symbol on the device label, use the terminology specified by ASTM F2503 (MR Unsafe) in a warning in the Operator's Manual, and show and explain the symbol in the manual. It might be necessary to explain or elaborate on "MR Unsafe", such as "MR Unsafe – keep away from magnetic resonance imaging (MRI) equipment".

    You said that you commit to updating the operators manual and device label to include these items. Please submit the revised operator's manual and a reproduction of the device label and review of these items.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.12 (SN 0027, Module 1.6.2). The KXL Operator's Manual and device label were revised to include the information as requested. A copy of the revised KXL Operator's Manual, including a reproduction of the device label, was provided.

This response is acceptable.

6.1.4 CLINICAL/STATISTICAL DEFICIENCES

13. There is insufficient data from adequate and well controlled trials to establish the efficacy of riboflavin ophthalmic solution and KXL System for the proposed indications.

    a. In your February 2014 submission, you state that seventeen subjects were treated with the large aperture (or illumination diameter) setting based on investigator discretion while the remaining subjects were treated with the medium aperture setting. You state that ten of the 17 subjects treated with the larger aperture were enrolled in the UVX-002 study and the remaining seven were in the UVX-003 study. While the efficacy analyses you provide are consistent with this response, the safety analyses tables (Tables 14.3.1.11) include data from ten subjects each in studies UVX-002 and UVX-003 (implying that the total number of subjects receiving the larger diameter could be twenty). Please clarify this discrepancy and provide corrected analyses.

A summary of the number of subjects by illumination diameter 11.0 mm (large) that was included in the efficacy and safety analysis by study is presented in Table 8.

Table 8: Number of Study Subjects by Illumination Diameter

Illumination Diameter	UVX-002	UVX-003
Large (Efficacy Analysis)	10	7
Large (Safety Analysis)	10	10

The number of subjects included in the UVX-002 study efficacy and safety analysis (large aperture) is the same. However, the number of subjects included in the UVX-003 study efficacy and safety analysis (large aperture) is not. The reason why there were only 7 subjects included in the UVX-003 efficacy analysis versus 10 in the safety analysis was due to the fact that three subjects with the large aperture did not have a baseline Kmax measurement and therefore were excluded from any calculations involving change from baseline for Kmax. Because they were exposed to treatment,

they were included in the safety analysis. Based on this clarification, the tables provided in the February 2014 submission are correct.

This response is acceptable.

b. With regard to the variable illumination diameter in the device studied, you state that "investigators were instructed to select the medium aperture setting prior to irradiation based upon ease of alignment over the clear cornea and centration to the limbus diameter". However, you do not mention specific instruction regarding protection of limbal stem cells. Please clarify whether investigators were instructed to maintain a pre-specified margin from the corneal limbus. Please describe any other risk mitigation measures in place to protect limbal stem cells (such as use of a metal shield). Please also discuss any risk mitigation measures (to prevent or minimize damage to limbal stem cells) which are planned for the device to be marketed.

In the UVX clinical studies, investigators were not instructed to maintain a pre-specified margin from the corneal limbus. In these studies, the central corneal epithelium was removed without violation of the limbal epithelial cells. The light source was placed by the physician over the center of the cornea and did not impinge on the limbus. Investigators were instructed to maintain centration of the light on the cornea throughout the procedure, minimizing any direct UV light to the limbus.
With these measures in place, no adverse events associated with limbal stem cell damage were observed above control levels in the UVX clinical studies; therefore, no additional shielding is necessary. In addition, the risks and benefits of adding additional shielding have not been evaluated.

Plans for the marketed process are based upon the process used for the Phase 3 studies and do not include additional shielding as no risks were identified. As a risk mitigation measure, specific instructions will be added to the product labeling calling for the physician to avoid direct illumination of the limbus and to conduct slit lamp examination during follow up standard of care visits to monitor any potential safety signals.

This response is acceptable.

c. Please provide the location in the application, or provide new analyses of safety data by study visit at month 3, month 6, month 9 and month 12 for each study and each treatment arm to see what adverse events resolved, which continued to be reported and any which may have appeared later in the study

An analysis of the safety data by visit for each study is provided in Table 9 through Table 12. These tables summarizing treatment emergent adverse events (TEAEs) are organized by preferred term in decreasing frequency using a cut-off of ≥2% of subjects in the CXL group and then alphabetically for terms of like incidence, where appropriate. For each indication, the most common TEAEs observed in the CXL group between baseline and Month 3 were expected sequelae following corneal epithelial debridement and occurred at a higher incidence than observed in control subjects, who did not undergo the epithelial debridement procedure or exposure to UVA light. The most common reported ocular TEAEs over all treatment groups regardless of indication were corneal opacity (haze), corneal epithelium defect, punctate keratitis, vision blurred, and eye pain.

The TEAEs observed in the CXL group through Month 12 were generally consistent for both indications, indicating that TEAEs generally develop in the short-term with few late-onset complications. These data are consistent with the overall safety profile.

Table 9: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-001 Keratoconus (Safety Population)

	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Number (%) of Subjects Reporting Any AEs[a]	127:29(100.0%)	14:11(37.9%)	12:9(31.0%)	3:3(10.3%)	10:7(24.1%)	0	10:7(24.1%)	0
Eye Disorders	123:29(100%)	11:9(31.0%)	9:7(24.1%)	3:3(10.3%)	8:6(20.7%)	0	8:5(17.2%)	0
Corneal opacity	29:23(79.3%)	1:1(3.4%)	3:3(10.3%)	1:1(3.4%)	1:1(3.4%)	0	2:2(6.9%)	0
Corneal striae	15:14(48.3%)	4:4(13.8%)	2:2(6.9%)	0	--	--	1:1(3.4%)	0
Corneal epithelium defect	15:13(44.8%)	0	--	--	1:1(3.4%)	0	--	--
Punctate keratitis	11:11(37.9%)	0	--	--	2:2(6.9%)	0	--	--
Vision blurred	7:7(24.1%)	0	0	1:1(3.4%)	--	--	--	--
Eye irritation	5:5(17.2%)	0	1:1(3.4%)	0	--	--	--	--
Visual acuity reduced	5:5(17.2%)	2:2(6.9%)	1:1(3.4%)	1:1(3.4%)	1:1(3.4%)	0	--	--
Eye pain	4:4(13.8%)	0	--	--	1:1(3.4%)	0	--	--
Photophobia	4:4(13.8%)	0	--	--	--	--	--	--
Conjunctival hyperaemia	3:3(10.3%)	0	--	--	--	--	1:1(3.4%)	0
Eye oedema	3:3(10.3%)	0	--	--	--	--	--	--
Foreign body sensation in eyes	3:3(10.3%)	0	--	--	--	--	--	--
Dry eye	2:2(6.9%)	0	--	--	--	--	--	--
Eye discharge	2:2(6.9%)	1:1(3.4%)	--	--	1:1(3.4%)	0	1:1(3.4%)	0
Eye pruritus	2:2(6.9%)	0	--	--	--	--	1:1(3.4%)	0
Glare	2:2(6.9%)	0	--	--	--	--	--	--
Ocular hyperaemia	2:2(6.9%)	0	--	--	--	--	--	--
Anterior chamber cell	1:1(3.4%)	0	--	--	--	--	--	--
Anterior chamber flare	1:1(3.4%)	0	--	--	--	--	--	--
Corneal oedema	1:1(3.4%)	0	--	--	--	--	--	--
Iridocyclitis	1:1(3.4%)	0	--	--	--	--	--	--
Kayser-Fleischer ring	1:1(3.4%)	1:1(3.4%)	--	--	--	--	--	--
Lacrimation increased	1:1(3.4%)	0	--	--	1:1(3.4%)	0	1:1(3.4%)	0

Table 9: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-001 Keratoconus (Safety Population) (Continued)

	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Metamorphopsia	1:1(3.4%)	0	--	--	--	--	--	--
Visual impairment	1:1(3.4%)	1:1(3.4%)	--	--	--	--	--	--
Vitreous detachment	1:1(3.4%)	0	--	--	--	--	--	--
Blepharitis	--	--	1;1(3.4%)	0	--	--	--	--
Meibomianitis	--	--	1;1(3.4%)	0	--	--	--	--
Iritis	--	--	--	--	--	--	1:1(3.4%)	0
Other Ocular TEAEs								
Corneal scar	3:3(10.3%)	3:3(10.3%)	3:2(6.9%)	0	2:2(6.9%)	0	2:2(6.9%)	0
Eye complication associated with device	1:1(3.4%)	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 10: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-001 Ectasia (Safety Population)

	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=24)	Control Group (N=25)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Number (%) of Subjects Reporting Any AEs[a]	94:23(95.8%)	14:9(36.0%)	15:7(29.2%)	0	7:6(25.0%)	0	6:5(20.8%)	0
Eye Disorders	91:23(95.8%)	13:9(36.0%)	14:7(29.2%)	0	7:6(25.0%)	0	5:4(16.7%)	0
Corneal opacity	29:22(91.7%)	4:4(16.0%)	5:4(16.7%)	0	4:4(16.7%)	0	--	--
Corneal epithelium defect	12:10(41.7%)	1:1(4.0%)	1:1(4.2%)	0	--	--	--	--
Eye pain	10:6(25.0%)	0	--	--	--	--	--	--
Photophobia	6:6(25.0%)	0	--	--	--	--	--	--
Punctate keratitis	5:5(20.8%)	1:1(4.0%)	1:1(4.2%)	0	2:2(8.3%)	0	2:2(8.3%)	0
Lacrimation increased	4:4(16.7%)	1:1(4.0%)	--	--	--	--	--	--
Vision blurred	4:4(16.7%)	0	1:1(4.2%)	0	--	--	--	--
Corneal striae	3:3(12.5%)	2:2(8.0%)	1:1(4.2%)	0	--	--	--	--
Ocular discomfort	3:3(12.5%)	0	--	--	--	--	--	--
Anterior chamber flare	2:2(8.3%)	0	--	--	--	--	--	--
Corneal disorder	2:2(8.3%)	0	--	--	--	--	--	--
Dry eye	2:2(8.3%)	1:1(4.0%)	--	--	1:1(4.2%)	0	1:1(4.2%)	0
Foreign body sensation in eyes	2:2(8.3%)	0	--	--	--	--	--	--
Visual acuity reduced	2:2(8.3%)	0	2:2(8.3%)	0	--	--	2:2(8.3%)	0
Corneal oedema	1:1(4.2%)	0	--	--	--	--	--	--
Diplopia	1:1(4.2%)	0	--	--	--	--	--	--
Eye irritation	1:1(4.2%)	1:1(4.0%)	--	--	--	--	--	--
Eyelid oedema	1:1(4.2%)	0	--	--	--	--	--	--
Visual impairment	1:1(4.2%)	0	--	--	--	--	--	--
Ulcerative keratitis	--	--	1:1(4.2%)	0	--	--	--	--
Vitreous floaters	--	--	1:1(4.2%)	0	--	--	--	--
Ocular hyperaemia	--	--	1:1(4.2%)	0	--	--	--	--

Table 10: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-001 Ectasia (Safety Population) (Continued)

	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=24)	Control Group (N=25)	CXL Group (N=24)	Control Group (N=25)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Other Ocular TEAEs								
Corneal scar	2:2(8.3%)	1:1(4.0%)	1:1(4.2%)	0	--	--	1:1(4.2%)	0
Eye injury	1:1(4.2%)	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.

Table 11: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-002 Keratoconus (Safety Population)

	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=73)	Control Group (N=74)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Number (%) of Subjects Reporting Any AEs[a]	171:56(76.7%)	34:23(31.1%)	16:14(19.2%)	5:3(4.1%)	8:8(11.0%)	1:1(1.4%)	19:15(20.5%)	0
Eye Disorders	167:56(76.7%)	32:22(29.7%)	14:12(16.4%)	4:3(4.1%)	7:7(9.6%)	1:1(1.4%)	17:15(20.5%)	0
Corneal opacity	42:34(46.6%)	1:1(1.4%)	3:3(4.1%)	0	3:3(4.1%)	0	2:2(2.7%)	0
Eye pain	13:13(17.8%)	3:3(4.1%)	--	--	--	--	--	--
Punctate keratitis	15:13(17.8%)	7:7(9.5%)	--	--	--	--	--	--
Corneal striae	11:11(15.1%)	4:4(5.4%)	4:4(5.5%)	0	--	--	--	--
Corneal epithelium defect	11:10(13.7%)	1:1(1.4%)	2:2(2.7%)	0	--	--	--	--
Vision blurred	11:8(11.0%)	1:1(1.4%)	--	--	--	--	--	--
Conjunctival hyperaemia	7:7(9.6%)	0	--	--	--	--	--	--
Eyelid oedema	5:5(6.8%)	0	--	--	--	--	--	--
Visual acuity reduced	5:5(6.8%)	6:6(8.1%)	0	2:2(2.7%)	--	--	5:5(6.8%)	0
Dry eye	4:4(5.5%)	1:1(1.4%)	--	--	--	--	--	--
Eye oedema	4:4(5.5%)	0	--	--	--	--	--	--
Photophobia	4:4(5.5%)	0	--	--	--	--	--	--
Anterior chamber flare	3:3(4.1%)	0	--	--	--	--	--	--
Corneal disorder	3:3(4.1%)	0	--	--	--	--	--	--
Eye irritation	3:3(4.1%)	0	--	--	--	--	--	--
Lacrimation increased	3:3(4.1%)	0	--	--	--	--	--	--
Corneal oedema	2:2(2.7%)	0	--	--	--	--	--	--
Diplopia	2:2(2.7%)	1:1(1.4%)	--	--	--	--	--	--
Ocular hyperaemia	2:2(2.7%)	1:1(1.4%)	--	--	--	--	--	--
Corneal thinning	1:1(1.4%)	2:2(2.7%)	--	--	--	--	--	--

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 12: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-003 Ectasia (Safety Population)

	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=67)	Control Group (N=63)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Number (%) of Subjects Reporting Any AEs[a]	203:59(88.1%)	26:14(22.2%)	18:18(26.9%)	6:5(7.9%)	7:5(7.5%)	1:1(1.6%)	13:7(10.4%)	0
Eye Disorders	197:59(88.1%)	24:13(20.6%)	17:17(25.4%)	6:5(7.9%)	6:5(7.5%)	1:1(1.6%)	11:7(10.4%)	0
Corneal opacity	44:39(58.2%)	0	5:5(7.5%)	1:1(1.6%)	--	--	--	--
Eye pain	19:18(26.9%)	0	--	--	--	--	--	--
Corneal epithelium defect	18:14(20.9%)	1:1(1.6%)	--	--	--	--	--	--
Punctate keratitis	13:13(19.4%)	2:1(1.6%)	--	--	--	--	--	--
Dry eye	11:11(16.4%)	2:2(3.2%)	2:2(3.0%)	0	--	--	--	--
Photophobia	12:11(16.4%)	0	--	--	--	--	--	--
Vision blurred	10:10(14.9%)	2:2(3.2%)	2:2(3.0%)	1:1(1.6%)	--	--	--	--
Eye irritation	7:7(10.4%)	0	--	--	--	--	--	--
Visual acuity reduced	6:6(9.0%)	1:1(1.6%)	4:4(6.0%)	0	--	--	3:3(4.5%)	0
Corneal striae	6:5(7.5%)	2:2(3.2%)	--	--	--	--	--	--
Lacrimation increased	5:5(7.5%)	0	--	--	--	--	--	--
Ocular discomfort	5:5(7.5%)	0	--	--	--	--	--	--
Eyelid oedema	4:4(6.0%)	0	--	--	--	--	--	--
Anterior chamber flare	3:3(4.5%)	1:1(1.6%)	--	--	--	--	--	--
Conjunctival hyperaemia	3:3(4.5%)	3:3(4.8%)	--	--	--	--	--	--
Foreign body sensation in eyes	3:3(4.5%)	1:1(1.6%)	--	--	--	--	--	--
Keratitis	3:3(4.5%)	0	--	--	--	--	--	--
Meibomian gland dysfunction	4:3(4.5%)	1:1(1.6%)	--	--	--	--	--	--
Visual impairment	3:3(4.5%)	0	--	--	--	--	--	--
Anterior chamber cell	2:2(3.0%)	0	--	--	--	--	--	--
Asthenopia	2:2(3.0%)	0	--	--	--	--	--	--
Corneal oedema	2:2(3.0%)	0	--	--	--	--	--	--
Glare	2:2(3.0%)	0	--	--	--	--	--	--
Halo vision	2:2(3.0%)	0	--	--	--	--	--	--
Ocular hyperaemia	2:2(3.0%)	1:1(1.6%)	--	--	--	--	--	--

Table 12: Summary of Adverse Events Reported by ≥2% of Subjects in UVX-003 Ectasia (Safety Population) (Continued)

	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=67)	Control Group (N=63)	CXL Group (N=67)	Control Group (N=63)
MedDRA System Organ Class/ Preferred Term	**Month 3**		**Months 6**		**Month 9**		**Month 12**	
Injury, poisoning and procedural complications								
Corneal abrasion	2:2(3.0%)	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.

This response is acceptable.

d. Given that corneal collagen cross-linking is intended to stabilize the cornea and improve visual function, please discuss whether the loss of 15 letters or more in visual acuity represents a lack of efficacy or an adverse reaction/complication of the procedure.

In the UVX studies, a loss of visual acuity (as measured by BSCVA) of 15 letters or more was identified in the protocol as a safety parameter. A greater than or equal to

loss of 15-letters represented an adverse reaction/complication associated with the debridement of the cornea. As summarized in the UVX Clinical Study Reports, by Month 3, the proportion of subjects with BSCVA loss ≥15 letters decreases for the CXL group consistent with the healing process post-debridement.

By Month 12, only 1 (1.6%) CXL subject lost ≥15 letters in BSCVA in Study UVX-002 and 2 (3.8%) in UVX-003.

This response is acceptable.

14. Regarding studies UVX-001 and UVX-002, treatment of keratoconus:

    a. The clinical studies do not meet the protocol-specified primary endpoints at 3 months.

See Section 2.6 (Other Relevant Background Information) of this review.

The initial sponsor of the UVX clinical studies was Peschke Meditrade. Peschke Meditrade submitted the IND for Corneal Collagen Cross-linking on November 6, 2007. The primary efficacy criteria in the UVX studies was defined as a ≥1 D difference in the mean change in K_{max} between the CXL group and the control group.

Both Avedro's data as well as data in the published literature[1] indicate that a 3 month timeframe for analysis of cross-linking for keratoconus is too short of a time to evaluate the benefit of this procedure. On the basis of this new information, which was not available when the original protocol was prepared, Avefro believes that the appropriate time frame for efficacy analysis is at least 6 months.

Based upon this current understanding of healing post debridement, when Avedro obtained the UVX cross-linking studies from Peschke Meditrade, Avedro changed the timepoint of efficacy analysis from 3 months to 12 months. This change was incorporated prior to database lock and finalization of the statistical analysis plan. The primary endpoint, as previously agreed with the FDA, did not change and continued to be a ≥1 D difference in the mean change in Kmax between the CXL group and the control group.

This response is acceptable.

1 (Wollensak and Iomdina 2009; Caporossi 2010; Wittig-Silva 2014)

b. We acknowledge that you included an analysis of data at month 12 according to your statistical analysis plan, however, this analysis is not a direct comparison between the CXL arm and the control arm at month 12.

As the study design allowed subjects in 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. Therefore, the primary efficacy analysis used the LOCF method for imputing missing data for the control subjects who received subsequent CXL in the study eye. It must be noted that LOCF was used only for imputation of data for the control group. All data obtained for the CXL group was observed case data at each timepoint.

Avedro asserts that the LOCF analyses provided in NDA 203324 allows for a valid comparison between the CXL arm and the control arm and the results meet the standards for substantial evidence of effectiveness. It believes the LOCF approach minimizes the differences between treatment and control groups, making it more difficult to demonstrate a ≥1 D difference in mean change from baseline Kmax. The results of both pooled and individual analyses at 12 months all meet the endpoint with clinical significance (a ≥1 D difference in the mean change in Kmax between the CXL group and the control group) and statistical significance (p<0.05).

Table 13: Differences (Control minus CXL) between Treatment Groups in Mean Changes from Baseline Kmax (D) in the Randomized Study Eye of Keratoconus Subjects (LOCF)

Study	3 Months	6 Months	12 Months
UVX-001	0.4 D (p=0.51)	1.4 D (p=0.07)	1.9 D (p=0.02)
UVX-002	1.3 D (p=0.11)	2.3 D (p=0.01)	2.9 D (p=0.001)
Pooled	1.1 D (p=0.09)	2.0 D (p=0.003)	2.6 D (p=0.0001)

Avedro believes that the observed case data supports the extension of the timing of analysis of the primary endpoint, the utilization of LOCF analysis as well as treatment effect of cross-linking.

Table 14: Mean Changes from Baseline K_{max} in the Randomized Study Eye (ITT Population, Observed Values): UVX-001 (Keratoconus Subjects), UVX-002, Pooled UVX-001 and UVX-002

Visit	Statistic	UVX-001			UVX-002			Pooled Studies		
		CXL Group (N=29)	Control Group (N=29)	P-value	CXL Group (N=73)	Control Group (N=74)	P-value	CXL Group (N=102)	Control Group (N=103)	P-value
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
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
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

This response is acceptable.

c. The datasets provided for UVX-01 and UVX-002 contain errors. For example, Kmax cannot be negative or equal to zero as presented in Tables 14.2.1.1.2 and 14.2.1.1.3.

A review of the Kmax data from Studies UVX-001 and UVX-002 revealed two data points whose value was either negative or equal to zero.

In Table 14.2.1.1.2 (UVX-001 CSR)[2], the Month 1 Kmax result has a minimum value of -0 in the Control Group. This value originated from Subject (b) (6) *Upon review of the subject's source documents, the patient's Kmax value for this timepoint was -0.3 D, as documented on the Pentacam print out (see Figure 6 below). Avedro investigated the negative value with both the site and Pentacam and this appears to be an output printing error from the Pentacam.*

In Table 14.2.1.1.3 (UVX-002 CSR)[3], the Month 1 Kmax result has a minimum value of 0 in the Control Group. This value originated from Subject (b) (6) *. Upon reviewing the subject's source documents, the patient's actual Kmax value for this timepoint was 58.9*

2 See page 48 of the original Medical Officer's review dated 3/7/2014.

3 See page 52 of the original Medical Officer's review dated 3/7/2014.

D as documented on the Pentacam print out (See Figure 7 below), an apparent data entry error.

Figure 6: UVX-001 Subject (b) (6) Pentacam Measurement

Figure 7: UVX-002 Subject (b) (6) Pentacam Measurement

This response is acceptable.

d. The datasets provided for UVX-01 and UVX-002 for the Endothelial Cell Count data appear to contain errors because they include increases beyond that which might physiologically be expected. Please verify the data sets.

A review of the UVX-001 and UVX-002 data sets for Endothelial Cell Count (ECC) found 1 major data discrepancy. In Table 14.3.4 (UVX-001 CSR), the ECC change-from-baseline in the CXL group had maximum values of 2120 and 2032 cells/mm2 at Month 3 and Month 12, respectively. These values originated from subject (b) (6) for whom a baseline ECC was not performed. A baseline ECC value of "0" was incorrectly entered into the database, resulting in change-from-baseline values of 2120 and 2032 cells/mm2 at Month 3 and Month 12, respectively, for this subject. The subject was removed from the change-from-baseline analysis and a revised table summarizing the ECC data for the ITT Keratoconus population in study UVX-001 is presented below (see Table 19).

Table 19: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed Values (Keratoconus Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline: CXL Group (N=29)	Change from Baseline: Control Group (N=29)
Baseline	n	26	28		
	Mean	2663	2454		
	SD	309.63	369.13		
	Median	2641	2493		
	Min, Max	2174, 3311	1600, 3304		
Month 3	n	26	29	23	28
	Mean	2576	2548	–97	109
	SD	335.29	403.79	291.33	243.3
	Median	2543	2530	–81	106
	Min, Max	1910, 3304	1615, 3387	–759, 354	–327, 643
Month 12	n	20	0	17	0
	Mean	2652	----	-50	----
	SD	381.78	----	307.30	----
	Median	2728	----	76.0	----
	Min, Max	1967, 3178	----	–666, 461	----

In the UVX-002 study, the following three instances were identified where the increases from baseline were greater than twice the SD:

1. Subject (b) (6) *in the UVX-002 CXL Group had a Baseline ECC reading of 2149 cells/mm2 and a Month 12 ECC reading of 3115 cells/mm^2, resulting in an increase from baseline of 966 cells/mm^2. Baseline and Month 12 values were verified against the source documentation which revealed a transcription error in the Baseline ECC (reading on printout is 2146 cells/mm^2).*

2. Subject (b) (6) *in the UVX-002 CXL Group had a Baseline ECC reading of 1387 cells/mm2 and a Month 3 ECC reading of 2370 cells/ mm^2, resulting in an increase from baseline of 983 cells/mm^2. Baseline and Month 3 values were verified against the source documentation.*

3. Subject (b) (6) *in the UVX-002 Control Group had a Baseline ECC reading of 1855 cells/mm^2 and a Month 3 reading of 2652 cells/mm^2, resulting in an increase from baseline of 797 cells/mm^2. Baseline and Month 3 values were verified against the source documentation.*

A revised table summarizing the ECC data for the ITT Keratoconus population correcting for the baseline ECC value for subject (b) (6) *in study UVX-002 is presented in Table 20.*

Table 20: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed Values (UVX-002, Safety Population)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline	
				CXL Group (N=73)	Control Group (N=74)
Baseline	n	68	66		
	Mean	2600	2627		
	SD	395.89	398.20		
	Median	2571	2692		
	Min, Max	1387, 3546	1186, 3407		
Month 3	n	60	62	58	58
	Mean	2486	2621	–88	–18
	SD	387.77	433.99	472.01	362.8
	Median	2467	2654	–67	–34
	Min, Max	1086, 3185	1052, 3472	–1820, 983	–872, 797
Month 12	n	60	1	58	1
	Mean	2615	2996	3.7	330
	SD	363.86		428.73	
	Median	2636	2996	67.5	330
	Min, Max	1529, 3322	2996, 2996	–1306, 969	330, 330

Avedro conducted a 100% review of the ECC data sets for study UVX-003 (corneal ectasia). Two increases from baseline were identified that were greater than 2X SD for the sample; both instances occurred in subject 03324 in the UVX-003 CXL Group. This subject had a Baseline ECC reading of 528 cells/mm^2 and a Month 3 ECC reading of 2169 cells/mm2, resulting in an increase from baseline of 1641 cells/mm^2 at Month 3. At Month 12, the ECC reading was 1613 cells/mm^2, which resulted in an increase from baseline of 1085 cells/ mm^2 at Month 12. Baseline, Month 3, and Month 12 values were reconfirmed against the source documentation.

A table summarizing the ECC data for the ITT ectasia population in study UVX-003 is presented in Table 21. Avedro believes that the variances observed in the ECC data sets for the UVX studies represent inherent errors of measurement of ECC in the keratoconus and corneal ectasia population.

Table 21: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed (UVX-003, ITT Population)

Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline	
				CXL Group (N=67)	Control Group (N=63)
Baseline	n	65	58		
	Mean	2518	2598		
	SD	578.76	417.76		
	Median	2525	2701		
	Min, Max	528, 5154	1629, 3592		
Month 3	n	57	55	57	51
	Mean	2447	2559	–45	–45
	SD	377.06	386.68	435.1	354.1
	Median	2467	2577	–51	–49
	Min, Max	1232, 3049	1706, 3412	–886, 1641	–857, 771
Month 12	n	49	2	49	2
	Mean	2380	2283	–124	–343
	SD	382.51	352.85	420.1	557.2
	Median	2392	2283	–129	–343
	Min, Max	1305, 3125	2033, 2532	–1220, 1085	–737, 51

This response is acceptable.

To resolve the above deficiencies, submit clinical data from adequate and well-controlled studies in the treatment of keratoconus and in which the datasets have been verified and the results meet their protocol-specified primary endpoint.

The submitted responses to 13 a-d and 14 a-d are acceptable.

6.1.5 BIORESEARCH MONITORING PROGRAM INSPECTION

During the recent inspection of your study monitoring practices conducted from February 3 -12, 2014, FDA field investigators observed inadequate documentation of study monitoring practices; specifically, for the period from June –September 2010, as specified in the Form FDA 483, initial and interim Monitoring Visit Reports, Data Entry Reports, and documentation of review of those reports is missing. To address gaps in study data monitoring for UVX-002 and UVX-003, we request an independent third party

assessment of data entry and monitoring practices at the top five enrolling sites for each of these two studies. We also request a similar independent reassessment for the conduct of Study UVX-001 at Dr. Stulting's site. We recommend that this reassessment take place at Emory University, the repository of the original source documentation for this study, unless it can be determined that the copies residing at Dr. Stulting's current site are certified true copies of the original documentation.

Avedro provided a response in the Type A Meeting Briefing Package, Section 3.18 (SN 0027, Module 1.6.2) where they submitted validated audit trail reports for UVX-002 andUVX-003 to address the gaps in study data monitoring for the period from June to September 2010.

An independent audit of Study UVX-001 was conducted on June 16-20 and July 14-18, 2014 at Emory University, the original site and repository for the original source documentation for the study. The audit focused on document review and evaluated GCP compliance, monitoring oversight, and accuracy of data entry. The audit consisted of a review of the regulatory binders, 100% of informed consent documents for all enrolled subjects, 100% of all critical data for all subjects, and enrollment eligibility and adverse event data for randomly selected subjects. The audit findings were submitted in a final audit report.

The third party audit report raised concerns about the adequacy or quality of adverse event reporting at the study site. Based on third party audit report, events on AE logs were entered by the study coordinator after Dr. Stulting (sponsor/investigator for this study) left Emory Vision. Information on the AE log includes the event, assessment of severity, and relatedness to epithelial defect, administration of riboflavin, and administration of UVA light.

The primary objective of an OSI follow-on inspection of Dr. Stulting at Emory Vision (located at Doctors Office Building #3, 5671 Peachtree Dunwoody Rd., Suite 400, Atlanta, GA 30342 since December 2014) was to resolve potentially discrepant observations related to AE reporting between the 2014 FDA inspection report (i.e., no discrepancies in AE reporting except for failure to report two SAEs "attempted suicide" for Subject (b) (6) *to the IRB) and applicant third party audit report (i.e., AEs may have been under- or mis-reported). During the follow-on OSI inspection, the original source documents (study worksheets and progress notes) were reviewed and findings were compared to AE data listings submitted to the NDA. The NDA AE data listing events include subject complaints, abnormal findings on physical examination (slit lamp exam), and significant medical diagnoses documented in the source documents; source document notations match data listings, but do not include assessment of relatedness or severity.*

There was no significant under-reporting of AEs (source documents for select subjects were scanned and events/reporting were discussed with review division during inspection). The discrepancies noted in the 3rd party audit pertained to events related to additional treatments which occurred in the fellow, untreated eyes.

The protocol for this study (as well as the other two studies being used to support this application) did not provide a definition of AE or how to assess relatedness to study procedure (creation of epithelial defect in cornea), followed by administration of study drug (riboflavin drops), and then followed by application of UV light. Regarding safety monitoring, the protocol indicates that complaints related to vision by a subject, as well as "any complications or AEs" that might have occurred would be documented along with slit lamp exam findings of operated eye, measured refraction, and measured visual acuity would be assessed. This may be the reason why the 3rd party audit identified items unrelated to the treatment procedures and identified them as unreported events.

The conclusion of that OSI follow-on inspection: Findings and events related to subject visual complaints, slit lamp findings, and significant interval diagnoses contained in the NDA submission AE data listings were verified and are consistent with those documented in original source worksheets and progress notes. Extraction of study data by site personnel and monitors contracted by the Applicant (Avedro), entry into an electronic CRF, and subsequent analyses of data contained in the NDA submission occurred after Dr. Stulting had left Emory Vision and notified FDA regarding closure of his IND.

This response is acceptable.

Summary Statement Regarding CR Approvability Issues

The applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 14, 2014, as approvability issues.

6.2 Additional Analyses

6.2.1 Mean Change from Baseline in Kmax for Progressive Keratoconus for and Corneal Ectasia

From the Biostatistics review dated 3/12/15:

A statistically significant difference in the mean change in Kmax from baseline between the CXL group and the control group was demonstrated at both Month 3 and Month 12 in UVX-001 and UVX-003, respectively, for corneal ectasia subjects (Biostatistics Table

1). Although the applicant's primary efficacy analysis at Month 12 resulted in statistically significant and clinically meaningful improvements in Kmax for keratoconus subjects, the efficacy of CXL treatment observed in keratoconus subjects was neither clinically meaningful nor statistically significant at Month 3 (Biostatistics Table 2). Furthermore, since most subjects in the control arm received CXL treatment at Month 3 or later, the analysis at Month 12 was complicated by the lack of sham data. In the applicant's analysis, the data at Month 3 or Month 6 was used to impute Month 12 data for control subjects receiving CXL treatment. This was analogous to last observation carried forward approach in the analysis.

Table 1: Analysis of the Mean Change from Baseline in Kmax for Corneal Ectasia Subjects (Studies UVX-001 and UVX-003, ITT, LOCF)

	UVX-001		UVX-002	
Visit/Category	CXL (N=24)	Sham (N=25)	CXL (N=67)	Sham (N=63)
Baseline (BL)	56.3 (6.3)	55.0 (5.5)	55.1 (7.1)	54.7 (6.8)
Month 3				
Change from BL	0.1 (1.3)	1.0 (1.7)	-0.2 (2.4)	0.6 (1.9)
Diff. (95% CI) [1]	-0.9 (-1.8, -0.1)		-0.8 (-1.6, -0.0)	
P-value [2]	0.0382		0.0386	
Month 12				
Change from BL	-1.0 (1.7)	1.0 (1.7)	-0.5 (2.2)	0.5 (2.3)
Diff. (95% CI) [1]	-2.0 (-3.0, -1.1)		-1.1 (-1.9, -0.3)	
P-value [2]	0.0001		0.0080	

[1] Difference = CXL – Sham.
[2] P-value on difference between CXL and Sham by t-test.

Table 2: Analysis of the Mean Change from Baseline in Kmax for Progressive Keratoconus Subjects (Studies UVX-001 and UVX-002, ITT, LOCF)

	UVX-001		UVX-002	
Visit/Category	CXL (N=29)	Sham (N=29)	CXL (N=73)	Sham (N=74)
Baseline (BL)	60.6 (7.3)	61.9 (8.3)	61.0 (9.8)	59.8 (9.2)
Month 3				
Change from BL	-0.3 (2.7)	0.1 (2.6)	-0.6 (4.4)	0.7 (5.6)
Diff. (95% CI) [1]	-0.5 (-1.9, 0.9)		-1.3 (-3.0, 0.3)	
P-value [2]	0.5085		0.1142	
Month 12				
Change from BL	-1.4 (2.8)	0.5 (3.0)	-1.7 (4.7)	1.2 (5.7)
Diff. (95% CI) [1]	-1.9 (-3.4, -0.3)		-2.9 (-4.6, -1.2)	
P-value [2]	0.0175		0.0010	

[1] Difference = CXL – Sham.
[2] P-value on difference between CXL and Sham by t-test.

6.2.2 Disposition Tables from Day 0 to Month 12

From the applicant's responses to the Complete Response letter located in SDN-033 (eCTD seq 0038) submitted 3/2/2014:

Updated subject disposition data are provided for keratoconus subjects in Table 1, and for corneal ectasia subjects in Table 2. For the purpose of these tables, study completers are defined as subjects who remained in the study for at least the start of the Month 12 visit window. 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 1).

Most subjects (90.2% CXL, 82.5% Control) completed the study, and 28 subjects (13.7%) discontinued. Reasons for discontinuation were administrative/other reasons (8.8%), voluntarily withdrawal (2.9%), and lost 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.

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 2). Most subjects (85.7% CXL, 81.8% Control) completed the study, and 29 subjects (16.2%) discontinued. Reasons for discontinuation were "administrative/other" (8.9%), lost to follow-up (6.1%), voluntarily withdrawal (1.1%). 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 1: Progressive Keratoconus Subject Disposition using Revised Definition for Study Completion

Category	UVX-001*		UVX-002		Pooled Studies	
	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)	20 (69.0)	72 (98.6)	65 (87.8)	92 (90.2)	85 (82.5)
Discontinued: n (%)	9 (31.0)	9 (31.0)	1 (1.4)	9 (12.2)	10 (9.8)	18 (17.5)
Administrative/other[a)]	9 (31.0)	9 (31.0)	0	0	9 (8.8)	9 (8.7)
Voluntary Withdrawal (unrelated to safety)	0	0	0	6 (8.1)	0	6 (5.8)
Lost to Follow-up	0	0	1 (1.4)	3 (4.1)	1 (1.0)	3 (2.9)
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
**Completers defined as those subjects who remained in the study for at least the start of the Month 12 visit window

Table 2: Corneal Ectasia Subject Disposition using Revised Definition for Study Completion

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)	17 (68.0)	58 (86.6)	55 (87.3)	78 (85.7)	72 (81.8)
Discontinued: n (%)	4 (16.7)	8 (32.0)	9 (13.4)	8 (12.7)	13 (14.3)	16 (18.2)
Administrative/Other[1)]	3 (12.5)	5 (20.0)	4 (6.0)	4 (6.3)	7 (7.7)	9 (10.2)
Lost to Follow-Up	1 (4.2)	3 (12.0)	5 (7.5)	2 (3.2)	6 (6.6)	5 (5.7)
Voluntary Withdrawal (unrelated to safety)	0	0	0	2 (3.2)	0	2 (2.3)
Adverse Event	0	0	0	0	0	0

[1)] 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
**Completers are defined as those subjects who remained in the study for at least the start of the Month 12 visit window

6.2.3 Corneal Thickness

The following tables summarize the observed results for corneal thickness at the apex and the thinnest location in the randomized eye at baseline and Month 1 to Month 12 in UVX-001, UVX-002, and UVX-003. The p-values should be interpreted with caution as they were not adjusted for multiplicity.

Table 65: Corneal Thickness (µm) at the Apex in the Randomized Eye – Observed Values (Keratoconus Subjects, UVX-001, ITT Population)

				Change from Baseline		
Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	Control Group (N=29)	p-value[a]
Baseline	n	29	29			
	Mean	461	450			
	SD	43.06	49.07			
	Median	462	454			
	Min, Max	358, 551	346, 535			
Month 1	n	29	28	29	28	
	Mean	436	449	–26	0.9	<0.0001
	SD	47.14	48.70	19.16	7.96	
	Median	442	455	–23	2.0	
	Min, Max	334, 523	340, 538	–76, 2	–17, 14	
Month 3	n	29	29	29	29	
	Mean	434	451	–27	1.1	<0.0001
	SD	47.63	48.41	17.21	10.05	
	Median	436	458	–33	4.0	
	Min, Max	325, 512	351, 539	–54, 5	–27, 22	
Month 6	n	28	18	28	18	
	Mean	455	444	–9.4	–1.9	0.1271
	SD	46.09	48.27	17.64	12.65	
	Median	445	442	–11	–1.5	
	Min, Max	350, 529	345, 533	–48, 25	–37, 14	
Month 12	n	20	0	20	0	
	Mean	466	----	–3.4	----	----
	SD	46.69	----	31.09	----	
	Median	457	----	–6.0	----	
	Min, Max	401, 567	----	–73, 84	----	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)

Source: SDN-011, UVX-001 Clinical Study Report, Table 65.

Table 71: Corneal Thickness (µm) at the Apex in the Randomized Eye – Observed Values (Corneal Ectasia Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline		p-value[a]
				CXL Group (N=24)	Control Group (N=25)	
Baseline	n	24	25			
	Mean	446	433			
	SD	64.36	42.41			
	Median	432	436			
	Min, Max	350, 611	357, 497			
Month 1	n	24	25	24	25	
	Mean	426	429	–19	–3.8	0.0173
	SD	68.97	44.52	30.36	9.00	
	Median	413	436	–24	–3.0	
	Min, Max	326, 568	340, 503	–53, 99	–25, 13	
Month 3	n	23	24	23	24	
	Mean	416	425	–32	–5.0	<0.0001
	SD	68.25	42.09	14.26	11.03	
	Median	401	428	–32	–3.5	
	Min, Max	322, 568	342, 491	–73, 3	–46, 8	
Month 6	n	22	13	22	13	
	Mean	440	423	–9.6	–6.8	0.6275
	SD	69.31	38.90	17.55	12.92	
	Median	423	425	–9.0	–2.0	
	Min, Max	334, 574	346, 490	–41, 21	–35, 7	
Month 12	n	20	0	20	0	
	Mean	447	----	–2.3	----	----
	SD	64.96	----	18.95	----	
	Median	441	----	–1.5	----	
	Min, Max	351, 583	----	–28, 41	----	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)

Source: SDN-011, UVX-001 Clinical Study Report, Table 71.

Table 38: Corneal Thickness (µm) at the Apex in the Randomized Eye – Observed Values (UVX-002, Safety Population)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline		p-value[a]
				CXL Group (N=73)	Control Group (N=74)	
Baseline	n	73	74			
	Mean	459	466			
	SD	44.36	43.04			
	Median	461	465			
	Min, Max	356, 586	353, 568			
Month 1	n	71	73	71	73	
	Mean	435	463	–24	–2.3	<0.0001
	SD	44.27	43.90	27.50	12.86	
	Median	436	464	–25	–2.0	
	Min, Max	319, 561	328, 555	–89, 120	–53, 25	
Month 3	n	68	66	68	66	
	Mean	430	467	–29	–0.0	<0.0001
	SD	43.68	43.07	19.24	11.05	
	Median	430	469	–28	0.0	
	Min, Max	340, 552	349, 561	–128, 19	–40, 26	
Month 6	n	68	20	68	20	
	Mean	442	469	–15	4.5	0.0064
	SD	41.65	54.96	24.97	33.54	
	Median	443	466	–17	–1.5	
	Min, Max	341, 554	376, 595	–120, 81	–32, 135	
Month 12	n	70	1	70	1	
	Mean	451	438	–7.1	–1.0	0.7432
	SD	43.14		18.37		
	Median	452	438	–5.5	–1.0	
	Min, Max	342, 559	438, 438	–98, 42	–1, –1	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)

Source: SDN-011, UVX-002 Clinical Study Report, Table 38.

Table 38: Corneal Thickness (µm) at the Apex in the Randomized Eye – Observed Values (UVX-003, ITT Population)

Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline		p-value[a]
				CXL Group (N=67)	Control Group (N=63)	
Baseline	n	64	63			
	Mean	446	454			
	SD	54.98	58.96			
	Median	449	454			
	Min, Max	310, 586	282, 590			
Month 1	n	64	61	61	61	
	Mean	418	457	–29	3.4	<0.0001
	SD	56.13	57.34	18.45	18.23	
	Median	418	452	–28	0.0	
	Min, Max	293, 554	324, 579	–69, 18	–23, 111	
Month 3	n	65	61	63	61	
	Mean	414	457	–29	2.9	<0.0001
	SD	60.97	54.34	20.35	18.92	
	Median	417	453	–29	2.0	
	Min, Max	269, 552	337, 578	–111, 18	–22, 108	
Month 6	n	62	19	60	19	
	Mean	429	478	–11	0.9	0.0404
	SD	55.98	46.61	22.60	21.30	
	Median	430	456	–13	–2.0	
	Min, Max	286, 551	425, 566	–91, 84	–31, 63	
Month 12	n	56	2	55	2	
	Mean	446	524	–0.9	37.5	0.0145
	SD	57.32	16.97	20.64	40.31	
	Median	449	524	0.0	37.5	
	Min, Max	293, 559	512, 536	–55, 50	9, 66	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)
Source: SDN-011, UVX-003 Clinical Study Report, Table 38.

7 REVIEW OF SAFETY

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following Phase 3 studies utilized to evaluate safety and efficacy are essentially identical in design:

1. UVX-001: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking In Eyes with **Corneal Ectasia** or **Progressive Keratoconus**

2. UVX-002: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with **Progressive Keratoconus**

3. UVX-003: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with **Corneal Ectasia after Refractive Surgery.**

7.1.2 Categorization of Adverse Events

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1. nomenclature.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See the original Medical Officer's review dated 3/7/2014.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

See the original Medical Officer's review dated 3/7/2014.

7.2.2 Explorations for Dose Response

See the original Medical Officer's review dated 3/7/2014.

7.2.3 Special Animal and/or In Vitro Testing

See the original Medical Officer's review dated 3/7/2014.

7.2.4 Routine Clinical Testing

See the original Medical Officer's review dated 3/7/2014.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the original Medical Officer's review dated 3/7/2014.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See the original Medical Officer's review dated 3/7/2014.

7.3 Major Safety Results

7.3.1 Deaths

See the original Medical Officer's review dated 3/7/2014.

7.3.2 Nonfatal Serious Adverse Events

See the original Medical Officer's review dated 3/7/2014.

7.3.3 Dropouts and/or Discontinuations

See the original Medical Officer's review dated 3/7/2014.

7.3.4 Significant Adverse Events

See the original Medical Officer's review dated 3/7/2014.

7.3.5 Submission Specific Primary Safety Concerns

See the original Medical Officer's review dated 3/7/2014.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Number of subjects with adverse events, reported by ≥2% of subjects, through Month 3 in UVX-001, UVX-002, and UVX-003

	Progressive Keratoconus		Cornea Ectasia	
	CXL	Control	CXL	Control
	N=102	N=103	N=91	N=88
Any AE	87	44	82	38
Ocular AE	86	40	82	33
Corneal opacity	58	4	62	7
Punctate keratitis	25	8	18	3
Corneal striae	24	12	8	6
Corneal epithelium defect	23	1	24	3
Eye pain	17	3	24	-
Vision blurred	16	2	15	4
Photophobia	11	-	17	-
Conjunctival hyperaemia	10	1	4	3
Eye irritation	10	1	8	1
Visual acuity reduced	10	9	10	1
Ocular discomfort	-	-	8	-
Eye oedema	7	-	-	-
Dry eye	6	2	13	4
Eyelid oedema	5	-	5	1
Foreign body sensation	5	-	5	1
Lacrimation increased	5	-	9	1
Anterior chamber flare	4	-	5	2
Glare	4	1	2	-
Ocular hyperaemia	4	1	3	1
Corneal disorder	3	1	3	-
Corneal oedema	3	-	3	-
Visual impairment	3	2	4	1
Keratitis	-	-	3	-
Meibomian gland dysfunction	-	-	3	2
Anterior chamber cell	2	-	2	1
Diplopia	2	1	-	-
Eye discharge	2	1	-	-
Eye pruritus	2	-	-	-
Vitreous detachment	2	-	-	-

	Progressive Keratoconus		Cornea Ectasia	
Corneal scar	7	5	3	1
Asthenopia	-	-	2	-
Eye complication assoc with device	2	-	-	-
Headache	4	-	7	3
Nasopharyngitis	2	1	-	-
Halo vision	-	-	2	-
Corneal abrasion	-	-	2	-
Dizziness	-	-	2	-

These are pooled common adverse event tables (i.e. UVX-001 and -002 for keratoconus and -001 and -003 for corneal ectasia). Note: subjects in the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed; subjects in the sham treatment group had topical anesthetic administered to the study eye but did not have the corneal epithelium removed.

The most common adverse events for either indication at ≥ 10% are corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following corneal epithelial debridement.

Ocular Adverse Events ≥5% in any CXL Eye at any time

	Keratoconus	Corneal Ectasia	Keratoconus	Corneal Ectasia
	UVX-001	UVX-001	UVX-002	UVX-003
	(N=74)	(N=57)	(N=219)	(N=162)
Corneal opacity	64	54	114	94
Corneal epithelium defect	40	20	29	33
Corneal striae	32	15	38	12
Punctate keratitis	27	24	35	27
Visual acuity reduced	17	12	31	25
Vision blurred	16	12	26	24
Corneal scar	12		10	4
Eye pain	10	11	48	32
Eye irritation	7		11	13
Lacrimation increased	7	6	11	14
Foreign body sensation	6	5		10
Photophobia	6	17	22	25

	Keratoconus	Corneal Ectasia	Keratoconus	Corneal Ectasia
	UVX-001	UVX-001	UVX-002	UVX-003
	(N=74)	(N=57)	(N=219)	(N=162)
Conjunctival hyperemia	5	3	14	13
Eye discharge	4			
Cornea disorder		5		
Ocular discomfort		5	6	14
Dry eye		4	15	23
Anterior chamber flare		3	6	6
Cornea edema		3		
Meibomian gland dysfunction		3		9
Ocular hyperemia		3		5
Ulcerative keratitis		3		
Eyelid edema			10	10
Corneal thinning			7	
Eye edema			6	
Glare			6	
Eye pruritis			5	
Visual impairment			5	9
Blepharitis				6
Halo vision				5
Corneal abrasion				4
Keratitis				4

The proportion of CXL eyes with a treatment emergent adverse event (at any time) was generally comparable to the incidence of treatment emergent adverse events from baseline to Month 3.

7.4.2 Laboratory Findings

See the original Medical Officer's review dated 3/7/2014.

7.4.3 Vital Signs

See the original Medical Officer's review dated 3/7/2014.

7.4.4 Electrocardiograms (ECGs)

See the original Medical Officer's review dated 3/7/2014.

7.4.5 Special Safety Studies/Clinical Trials

See the original Medical Officer's review dated 3/7/2014.

7.4.6 Immunogenicity

See the original Medical Officer's review dated 3/7/2014.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See the original Medical Officer's review dated 3/7/2014.

7.5.2 Time Dependency for Adverse Events

See the original Medical Officer's review dated 3/7/2014.

7.5.3 Drug-Demographic Interactions

See the original Medical Officer's review dated 3/7/2014.

7.5.4 Drug-Disease Interactions

See the original Medical Officer's review dated 3/7/2014.

7.5.5 Drug-Drug Interactions

See the original Medical Officer's review dated 3/7/2014.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the original Medical Officer's review dated 3/7/2014.

7.6.2 Human Reproduction and Pregnancy Data

See the original Medical Officer's review dated 3/7/2014.

7.6.3 Pediatrics and Assessment of Effects on Growth

Submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time.

A total of 33 pediatric subjects were enrolled in studies UVX-001 and UVX-002. No pediatric subjects were enrolled in UVX-003 and there were no pediatric ectasia subjects enrolled in UVX-001.

Pediatric Population

	UVX-001 (Keratoconus)		UVX-002	
	CXL Group	Sham Control Group	CXL Group	Sham Control Group
Age 14-18	0	1	7	3
Age 18-21	2	3	10	7

Progressive Keratoconus

In study UVX-001, one subject 14 – 18 years of age was randomized into the sham control group and remained in this group until the Month 6 visit, at which time the subject's sham eye was treated with CXL. The subject's fellow eye was also treated.

Five subjects 18 – 21 years of age were randomized to treatment: two in the CXL group and three in the sham control group. Of the two subjects randomized in the CXL group, one had their fellow eye treated. Of the three subjects randomized to the sham control group, two had their sham eye treated and one had their fellow eye treated.

In study UVX-002, ten (10) subjects 14 – 18 years of age were randomized to treatment: seven in the CXL group and three in the sham control group. Of the seven subjects randomized in the CXL group, five elected to have their fellow eye treated. Of the three subjects randomized to the sham control group, all had their sham eyes treated and two had their fellow eye treated.

Seventeen (17) subjects 18 – 21 years of age were randomized to treatment: ten in the CXL group and seven in the sham control group. Of the ten subjects randomized in the CXL group, five elected to have their fellow eye treated. Of the seven subjects randomized to the sham control group, all had their sham eyes treated and six had their fellow eye treated.

Mean Changes from Baseline Kmax in the Randomized Study Eye: Age 14-18 (UVX-001)					
				Change from Baseline	
		CXL Group	Sham Control Group	CXL Group	Sham Control Group
Visit	Statistic	(N=0)	(N=1)	(N=0)	(N=1)
Baseline	n	0	1		
	Mean		81.3		
	SD				
Month 3	n	0	1	0	1
Observed	Mean		87.4		6.1
	SD				
Month 6	n	0	1	0	1
Observed	Mean		84.1		2.8
	SD				
Month 12	n	0	1	0	1
LOCF	Mean		84.1		2.8
	SD				
Month 12	n	0	0	0	0
Observed	Mean				
	SD				

Mean Changes from Baseline Kmax in the Randomized Study Eye: Age 18-21 (UVX-001)					
		CXL	Sham Control	Change from Baseline	
		Group	Group	CXL Group	Sham Control Group
Visit	Statistic	(N=2)	(N=3)	(N=0)	(N=1)
Baseline	n	2	3		
	Mean	57.4	66.3		
	SD	6.86	10		
Month 3	n	2	3	2	3
Observed	Mean	57.8	67.1	0.4	0.8
	SD	7.6	9.5	0.7	3.4
Month 6	n	2	3	2	3
LOCF	Mean	57.7	67.1	0.3	0.8
	SD	8.3	9.5	1.5	3.4
Observed	n	2	0	2	0
	Mean	57.7		0.3	
	SD	8.3		1.5	
Month 12	n	2	3	2	3
LOCF	Mean	57.7	67.1	0.3	0.8
	SD	8.1	9.5	1.3	3.4
Month 12	n	2	0	2	0

Mean Changes from Baseline Kmax in the Randomized Study Eye: Age 18-21 (UVX-001)					
Observed	Mean	57.7		0.3	
	SD	8.1		1.3	

Mean Changes from Baseline Kmax in the Randomized Study Eye: Age 18-21 (UVX-002)					
				Change from Baseline	
		CXL Group	Sham Control Group	CXL Group	Sham Control Group
Visit	Statistic	(N=10)	(N=7)	(N=10)	(N=7)
Baseline	n	10	7		
	Mean	65.8	66		
	SD	13.1	10.3		
Month 3	n	9	7	9	7
Observed	Mean	64.8	66.5	-1.2	0.5
	SD	13	11.1	1.7	4.1
Month 6					
LOCF	n	10	7	10	7
	Mean	65.1	68.8	-0.8	2.8
	SD	12.7	13.6	2.2	3.5
Observed	n	8	2	8	2
	Mean	66.3	78.4	-1.2	5.7
	SD	13.7	13.7	2.2	1.8
Month 12					
LOCF	n	10	7	10	7
	Mean	62.6	68.8	-3.2	2.8
	SD	11.7	13.6	5.4	3.5
Observed	n	10	0	10	0
	Mean	62.6		-3.2	
	SD	11.7		5.4	

Table 29: Endothelial Cell Count (/mm^2) in the Randomized: Age 14-18 (UVX-001 and UVX-002 Pooled, Safety Population)

Visit	Statistic	CXL Group (N=7)	Control Group (N=4)	Change from Baseline	
				CXL Group (N=7)	Control Group (N=4)
Baseline	n	7	3		
	Mean	2761	2803		
	SD	250.11	420.88		
	Median	2717	2648		
	Min, Max	2484, 3190	2481, 3279		
Month 3	n	6	4	6	3
Observed	Mean	2789	2723	99.5	-50
	SD	253.46	431.38	300.3	121.8
	Median	2755	2557	32.0	-60
	Min, Max	2427, 3185	2421, 3356	-306, 511	-166, 77
Month 3	n	7	4	7	3
LOCF	Mean	2846	2723	85.3	-50
	SD	276.6	431.4	276.7	121.8
	Median	2793	2557	0.0	-60
	Min, Max	2427, 3190	2421, 3356	-306, 511	-166, 77
Month 12	n	6	0	6	0
Observed	Mean	2747	--	57.7	--
	SD	363.73	--	327.3	--
	Median	2887	--	85.0	--
	Min, Max	2151, 3096	--	-523, 447	--
Month 12	n	7	4	7	3
LOCF	Mean	2810	2723	49.4	-50
	SD	371.9	431.4	299.6	121.8
	Median	2976	2557	68.0	-60
	Min, Max	2151, 3190	2421, 3356	-523, 447	-166, 77

Table 30: Endothelial Cell Count (/mm^2) in the Randomized: Age 18-21 (UVX-001 and UVX-002 Pooled, Safety Population)

Visit	Statistic	CXL Group (N=12)	Control Group (N=10)	Change from Baseline	
				CXL Group (N=12)	Control Group (N=10)
Baseline	n	11	10		
	Mean	2840	2923		
	SD	348.14	239.98		
	Median	2874	2883		
	Min, Max	2352, 3425	2688, 3407		
Month 3	n	9	10	9	10
Observed	Mean	2559	2843	-331	-80
	SD	591.15	262.63	604.6	284.0
	Median	2646	2782	-295	-15
	Min, Max	1111, 3003	2525, 3438	-1769, 364	-548, 424
Month 3	n	11	10	11	10
LOCF	Mean	2569	2843	-271	-80
	SD	541.9	262.6	557.1	284.0
	Median	2646	2782	-218	-15
	Min, Max	1111, 3003	2525, 3438	-1769, 364	-548, 424
Month 12	n	10	0	10	0
Observed	Mean	2626	--	-263	--
	SD	515.76	--	476.0	--
	Median	2793	--	-96	--
	Min, Max	1574, 3322	--	-1306, 210	--
Month 12	n	11	10	11	10
LOCF	Mean	2601	2849	-239	-74
	SD	496.2	264.9	458.5	286.1
	Median	2747	2782	-84	9.4
	Min, Max	1574, 3322	2525, 3438	-1306, 210	-548, 424

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See the original Medical Officer's review dated 3/7/2014.

7.7 Additional Submissions / Safety Issues

No additional submissions are expected in this review cycle. UVX-001, -002, and-003 were competed prior to submission of the original NDA.

8 POSTMARKET EXPERIENCE

Photrexa Viscous and Photrexa are not presently marketed in any country. Therefore, there are no postmarketing reports for either Photexa formulations.

9 APPENDICES

9.1 Literature Review/References

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9.2 Advisory Committee Meeting

For a more detailed description of the Advisory Committee Meeting, the participants, and the discussions, see the Cross Discipline Team Leader Review for the resubmission.

A joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee (OP-MDAC) was held on February 24, 2015:

> When asked: Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for progressive keratoconus? Yes/No

The panel voted: **YES:** 10 **NO:** 4 **ABSTAIN:** 1

> When asked: Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for corneal ectasia following refractive surgery? Yes/No

The panel voted: **YES:** 6 **NO:** 4 **ABSTAIN:** 4 **NO VOTE:** 1

9.3 Labeling Recommendations

Following are reviewer's comments for the carton and container labeling and suggested revisions to the draft package insert.

Note: Photrexa Viscous (b) (4) and Photrexa (b) (4) are provided in a bulk pack of 10 (ten), single-use foil pouches. Each foil pouch contains a 3 mL glass syringe of Photrexa Viscous or Photrexa contained within a Tyvek pouch.

Carton Box

Reviewer's Comments:

The drug product names should be revised to read, (b) (4)

The established name on the carton label should be a font size that is at least half as large of that of the proprietary name with a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

[redacted] *should be revised to read, "For Single-Patient Use Only; For Ophthalmic Use."*

[redacted] *should be revised to read, "For Use with KXL System."*

You should add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

[redacted] *should be revised to read, "Storage: Store at 15◦ – 25◦ C (xx◦ – xx◦ F).*

Only one side of the box is presented. The other five sides of the box should be presented as well.

The statements [redacted] *re inadequate. The statements should be revised to include all ingredients, active and inactive.*

Container Label – Syringe

Reviewer's Comments:

The drug product names should be revised to read, (b) (4)

(b) (4) *should be revised to read,* (b) (4)

Pouch Label – Light Block Pouch (foil)

Reviewer's Comments:

The drug product names should be revised to read, (b) (4)

[redacted] (b) (4) *should be revised to read, "For Single-Patient Use Only; For Ophthalmic Use."*

[redacted] (b) (4) *should be revised to read, "For Use with KXL System."*

You should add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

"Pouch Contains…" should be revised to read, " Pouch Contains: Each foil pouch contains a 3 mL glass syringe of Photrexa Viscous contained within a Tyvek® pouch," or Pouch Contains: Each foil pouch contains a 3 mL glass syringe of Photrexa contained within a Tyvek® pouch."

The statements, [redacted] (b) (4) *re inadequate. The statements should be revised to include all ingredients, active and inactive.*

Pouch Label – Tyvek Pouch

Reviewer's Comments:

The drug product names should be revised to read, (b) (4)

(b) (4) *should be revised to read, "For Single-Patient Use Only; For Ophthalmic Use."*

(b) (4) *should be revised to read, "For Use with KXL System."*

You should add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

A statement should added, "Pouch Contains: Each Tyvek® pouch contains a 3 mL glass syringe of Photrexa Viscous," or "Pouch Contains: Each Tyvek® pouch contains a 3 mL glass syringe of Photrexa"

(b) (4) *should be revised to read, "Storage: Store at 15◦ – 25◦ C (xx◦ – xx◦ F) The statements,* (b) (4) *are inadequate. The statements should be revised to include all ingredients, active and inactive.*

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
03/24/2015

WILEY A CHAMBERS
03/24/2015

Cross-Discipline Team Leader Review

Date	March 7, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	203324
Applicant	Avedro, Inc.
Date of Submission	9/16/13
PDUFA Goal Date	3/16/14
505(b)(2)	Yes
Proprietary Name / Established (USAN) names	Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) and KXL System
Dosage forms / Strength	Topical ophthalmic solution, 0.1%
Proposed Indication(s)	(b) (4)
Recommended:	Not recommended for Approval

1. Introduction

Keratoconus is a naturally-occurring ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in corneal optical irregularities with increasing myopia, irregular astigmatism, and consequential loss of best corrected visual acuity (BCVA). The prevalence of keratoconus is often reported as 1 per 2000 people in the general population. Onset of keratoconus generally occurs during puberty or early adulthood and profoundly affects patients who develop the condition. If left untreated, patients experience progressive vision impairment, which may result in the need for corneal transplantation.

Corneal ectasia is a well-described complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy. It is a condition similar to keratoconus, but occurs postoperatively. Ectasia may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of both uncorrected visual acuity (UCVA) and BCVA.

There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery. For both keratoconus and corneal ectasia, early intervention usually involves 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 address the optical irregularity of the cornea. Surgically-implanted intrastromal ring segments may be used to improve contact lens wear in patients who are contact lens intolerant. These treatments do not halt the progression of keratoconus. Corneal transplantation is the only option available when functional vision can no longer be achieved.

Note: Throughout this review, the two formulations of riboflavin ophthalmic solution are referred to as Photrexa (contains dextran) and Photrexa (b) (4) (contains no dextran). The proprietary names for these two formations have not been designated in this review cycle.

2. Background

Avedro's riboflavin ophthalmic solution/UVA irradiation is a combination product consisting of a UVA 365 nm wavelength light source and riboflavin administered in conjunction with the UVA light as a photosensitizer.

This is a 505(b)(2) application. The applicant is not relying upon a listed product. A majority of the toxicological data for riboflavin was generated following oral administration because of its use in food or as a dietary supplement. Topical riboflavin with concurrent exposure to UV-A light has been used for the treatment of keratoconus and corneal ectasia and both in vitro and in vivo nonclinical studies have been conducted using this methodology. The applicant has conducted corneal crosslinking clinical trials utilizing the final formulations (s) of the to-be-marketed riboflavin.

In the clinical trials, the drug product was a sterile, phosphate-buffered saline solution for topical ophthalmic use containing 0.1% riboflavin (Vitamin B2) with and without 20% dextran (b) (4)

The UVA irradiation system is a portable electronic medical device. The device's light emitting diode (LED) is used to deliver a metered dose of UVA light to a targeted treatment area for illuminating the cornea during CXL.

The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for these combination products under RFD070013.

Avedro, Inc. opened IND 77,882 with a protocol submission dated November 7, 2007.

Avedro, Inc. submitted a request for orphan-drug designation dated May 26, 2011, for riboflavin ophthalmic solution and ultraviolet-A (LTVA) irradiation "for corneal cross-linking for the treatment of keratonus (sic)." The Office of Orphan Products Development granted orphan designation for treatment of keratonus (sic) on September 2, 2011.

Avedro, Inc. submitted a request for orphan-drug designation dated August 26, 2011, for riboflavin ophthalmic solution and ultraviolet-A irradiation for "treatment of corneal ectasia following refractive surgery." The Office of Orphan Products Development granted orphan designation for treatment of corneal ectasia following refractive surgery on December 2, 2011.

The primary original efficacy endpoint for the applicant's clinical trials was as the difference between the CXL group and the control group in maximum keratometry (Kmax) from baseline to Month 3. At the time the studies were initially planned, the Agency recommended a 12

month endpoint but the applicant believed that the primary efficacy endpoint could be analyzed at 3 months post-procedure based on their review of the existing literature. The applicant reviewed subsequent additional literature which suggested to them that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize.

A pre-NDA Meeting was held on September 21, 2011. CMC indicated that the briefing document was inadequate and requested additional information on the composition of the material used for the Phase 3 studies and the composition of the proposed commercial formulation. Clinical stated it was not possible to determine whether the clinical program will be sufficient to support approval based on the information previously submitted. Clinical would need to review the final study report for study UVX- 001, -002 and -003 to determine whether it is appropriate to combine patients from -001 into - 002 and -003. The lack of statistical significance between groups in the patients treated for keratoconus at Month 3 was noted as potentially problematic.

Avedro, Inc. submitted a New Drug Application (NDA) on March 8, 2012, for their riboflavin ophthalmic solution /KXL System. They received a refuse to file letter dated May 4, 2012. The application was not sufficiently complete to permit a substantive review. The Agency refused to file this application under 21 CFR 314.101(d).

A post "Refuse-to-File" meeting was held with Avedro, Inc. on May 31, 2012, to discuss the Agency's comments in the RTF letter dated May 4, 2012.

A CMC Type A meeting was held on August 15, 2012, where Avedro committed to revise the commercial formulation information proposed in the NDA to be consistent with the clinical formulations used in the clinical trials.

A general advice letter was send on October 19, 2012, in response to the September 24, 2012, submission seeking Agency advice on Avedros' plan for cGMP manufacturing of the drug substance, riboflavin 5'-phosphate sodium and drug product process validation and registration stability.

3. Product Quality

Photrexa (riboflavin ophthalmic solution) is a clear yellow solution containing 0.12% riboflavin 5'-phosphate sodium and 20% dextran in phosphate buffered saline.

Photrexa (b) (4) (riboflavin ophthalmic solution) is a clear yellow solution containing 0.12% riboflavin 5'-phosphate sodium in phosphate buffered saline. Photrexa (b) (4) does not contain dextran.

From the original Product Quality Review dated 2/20/14:

DRUG SUBSTANCE:
The drug substance riboflavin 5'-phosphate sodium is manufactured (b) (4) under DMF (b) (4) A Letter of Authorization to reference this DMF is provided. The acceptability of this material for use as a drug substance is based upon a satisfactory review of the DMF. At the current time this DMF has unresolved deficiencies.

Note: An information request was sent by the Agency on 2/7/14. The applicant responded in an Amendment dated 2/14/14. Although the applicant appears to have agreed to the proposed revisions to the drug substance specifications and stability protocol and appears to have replied to request for addition information regarding batch formulae and individual values for the monophosphates, diphosphates, etc. for validation lots, the Product Quality Review dated 2/20/14 states, "Outstanding issues still require resolution," for DMF (b) (4)

DRUG PRODUCT:
Quantitative Composition
As quoted in the original NDA the composition of the drug products is as follows:

Component	Function	Photrexa	Photrexa (b) (4)
Riboflavin 5'-phosphate sodium, USP	Active	0.12%	0.12%
Dextran 500 Sodium chloride, USP Sodium phosphate, monobasic, USP Sodium phosphate, dibasic, USP Sterile water for injection, USP	(b) (4)		

However, it would be more accurate to represent the formulations as follows:

Component	Function	Photrexa		Photrexa (b) (4)	
		Amount	mg/g	Amount	mg/g
Riboflavin*	Active	(b) (4)	1.20**	(b) (4)	1.20**
Dextran (b) (4)	(b) (4				(b) (4)
Sodium chloride, USP					
Sodium phosphate, monobasic, USP					
Sodium phosphate, dibasic, USP					
Sterile water for injection, USP					
Total					

*Present as riboflavin 5'-phosphate sodium
**Equivalent to 1.46 mg/g riboflavin phosphates

The average drop size for Photrexa is (b) (4) µL and for Photrexa (b) (4) it is (b) (4) µL.

The proposed marketing container-closure system is a 3 mL clear glass syringe fitted with a plunger with a rubber stopper and a plastic rigid tip cap. The syringe is packaged in a Tyvek pouch and this pouch is placed inside a foil pouch. The components are as follows:

Component	Description	Manufacturer	Specification Reference	DMF #
Syringe Barrel	(b) (4)			
Plunger Stopper				
Plunger Rod				
	(b) (4)			

REGULATORY SPECIFICATIONS:

In response to an Agency information request dated 11/13/13, the applicant r responded on 11/27/13 with the revised drug product specifications found below.

Table 4: Revised Drug Product Specifications

Test Description	Method	Acceptance Criteria
Appearance	Visual	A glass syringe containing a clear, yellow solution, no visible particulates, and no leakage
Identification	RP-HPLC	Retention time ((b) (4)%) and UV spectra conform
Assay	RP-HPLC	(b) (4)% of the label claim
Riboflavin 5'-monophosphate	RP-HPLC	Not less than (b) (4)% Relative Area
pH	USP <791>	(b) (4)
Sterility	USP <71>	No growth
Viscosity	USP <911>	Photrexa: (b) (4) cP Photrexa (b) (4) cP
Osmolality	USP <785>	Photrexa: (b) (4) mOsm/kg Photrexa (b) (4) mOsm/kg
Particulate Matter	USP <789>	(b) (4) particles/mL (b) (4) particles/mL particles/mL
Endotoxin	USP <85>	(b) (4) EU/mL
Degradants	RP-HPLC	Specified: (b) (4) NMT numerical value* (b) (4) NMT numerical value* Unspecified: NMT numerical value * Total: NMT numerical value *

*To be established during additional HPLC method validation.

Per the Product Quality reviewer, the drug product specification is not adequate. The drug product specification should include tests for degradants (specified, unspecified, and total) and appropriate acceptance criteria should be proposed.

INSPECTIONS:
An "Acceptable" site recommendation from the Office of Compliance has not been made. The District Office currently recommends Withhold for the drug product manufacturing site

In a memorandum dated 3/5/14, the Division of Good Manufacturing Practice Assessment Office of Manufacturing & Product Quality states,"

> The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection conducted by (b) (4) District ((b) (4) -DO) (b) (4) (b) (4) at the (b) (4) facility. This site is listed as the (b) (4) drug product manufacturer in support of this NDA. DGMPA has also reviewed the firm's (b) (4) written response to the 483 observations. This inspection was initiated by (b) (4) -DO to provide pre-approval coverage for NDA 203-324. According to (b) (4) -DO, the inspection was initially classified OAI for NDA specific coverage with a withhold recommendation. After an evaluation of the firm's response (b) (4) -DO re-affirmed their withhold recommendation.
>
> After review of the firm's response, DGMPA concurs with the (b) (4) -DO's withhold recommendation for the (b) (4) facility. (b) (4) -DO recommended withholding approval of this application due to product specific deficiencies. The FDA Form-483 included twelve observations with the first two to be the most significant, product specific observations. Since these are also reviewed in the application, the [Product Quality] reviewer was asked if such information has been received or reviewed.
>
> The reviewer confirmed that the information received so far is inadequate. More data are expected to come in an amendment by March 28, 2014. This is past the PDUFA date of March 16, 2014. Until the data are received and evaluated to be adequate, the deficiencies are still outstanding and impact application action.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 203324/000	**Action Goal:**	
Stamp Date:	08-MAR-2012	**District Goal:**	15-JAN-2014
Regulatory:	16-MAR-2014		
Applicant:	AVEDRO INC	**Brand Name:**	PHOTREXA/PHOTREXA (b) (4)
	230 3RD AVE 5TH FL	**Estab. Name:**	
	WALTHAM, MA 02451	**Generic Name:**	RIBOFLAVIN OPHTHALMIC SOLUTION
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	590	001; SOLUTION; RIBOFLAVIN; .12%	

Application Comment: NME (on 03-AUG-2012 by J. DAVID () 3017964247)

FDA Contacts:	M. ZHOU	Prod Qual Reviewer		3017962163
	D. MILLER	Micro Reviewer	(HFD-003)	3017963854
	N. BHANDARI	Product Quality PM		2404023815
	J. SMITH	Regulatory Project Mgr		3017961002
	B. SHANMUGAM	Team Leader		3017961457

Overall Recommendation:	PENDING	on 23-OCT-2013	by EES_PROD
	PENDING	on 02-OCT-2013	by EES_PROD
	PENDING	on 02-OCT-2013	by EES_PROD
	PENDING	on 02-OCT-2013	by EES_PROD
	PENDING	on 03-APR-2012	by EES_PROD

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, (b) (4) FINISHED DRUG PRODUCT TESTING AND STABILITY (on 25-SEP-2013 by N. BHANDARI () 2404023815)
MANUFACTURED (b) (4) (on 27-MAR-2012 by A. CUFF (HF-01) 3017964061)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-APR-2012				CUFFA
SUBMITTED TO DO	03-APR-2012	Product Specific and GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific and GMP Inspection			CEVERLY
INSPECTION SCHEDULED			(b) (4)		CEVERLY
REQUEST CANCELLED	02-MAY-2012				CUFFA
				REFUSE TO FILE	
SUBMITTED TO OC	02-OCT-2013				BHANDARIN
SUBMITTED TO DO	03-OCT-2013	Product Specific and GMP Inspection			WITTORFR
INSEPCTED PER FACTS (b) (4) NO PROFILE CODES LISTED.					
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific and GMP Inspection			CEVERLY
INSPECTION PERFORMED			(b) (4)		CLUNDI
INSPECTION SCHEDULED					CLUNDI
DO RECOMMENDATION	20-NOV-2013			WITHHOLD	CLUNDI
				(b) (4)	

Establishment: CFN: FEI: 3007851054
AVEDRO INC
230 3RD AVE
WALTHAM, MA 02451
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Establishment Comment: KXL DEVICE MANUFACTURER (on 23-OCT-2013 by N. BHANDARI () 2404023815)
Profile: NOT ELSEWHERE CLASSIFIED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	23-OCT-2013				BHANDARIN
OC RECOMMENDATION	06-FEB-2014			ACCEPTABLE	WILLIAMSJU
PLEASE REFER TO CONSULT MEMO IN DAARTS (MEMO SIGNED 2/4/14)				DISTRICT RECOMMENDATION	

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
Establishment Comment: DRUG SUBSTANCE MANUFACTURING, RELEASE TESTING, AND STABILITY (on 25-SEP-2013 by N. BHANDARI () 2404023815)
Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	02-OCT-2013				BHANDARIN
SUBMITTED TO DO	03-OCT-2013	Product Specific and GMP Inspection			WITTORFR
NME (b) (4)					
DO RECOMMENDATION	08-OCT-2013			ACCEPTABLE	AYOUNG
A ROUTINE CGMP INPSECTION WAS CONDUCTED AT THIS FIRM (b) (4) THE GMP COVERAGE INCLUDED THE REQUESTED PROFILE CLASS, (b) (4) (b) (4) THE INSPECTION RESULTED IN THE ISSUANCE OF A 1-ITEM FDA-483 FOR PROCEDURAL ISSUES (b) (4) THE FIRM AGREED TO ADDRESS THE OBSERVATION. BASED UPON THIS INSPECTION AND THE FIRM¿S PAST HISTORY, (b) (4) DO RECOMMENDS THEM AS ACCEPTABLE.				BASED ON FILE REVIEW	
DO RECOMMENDATION	08-OCT-2013			ACCEPTABLE	AYOUNG
A ROUTINE CGMP INPSECTION WAS CONDUCTED AT THIS FIRM (b) (4) THE GMP COVERAGE INCLUDED THE REQUESTED PROFILE CLASS, (b) (4) (b) (4) THE INSPECTION RESULTED IN THE ISSUANCE OF A 1-ITEM FDA-483 FOR PROCEDURAL ISSUES (b) (4) THE FIRM AGREED TO ADDRESS THE OBSERVATION. BASED UPON THIS INSPECTION AND THE FIRM¿S PAST HISTORY, (b) (4) DO RECOMMENDS THEM AS ACCEPTABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	08-OCT-2013			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: MANUFACTURING, RELEASE TESTING, PACKAGING AND STABILITY TESTING (on 27-MAR-2012 by A. CUFF (HF-01) 3017964061)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-APR-2012				CUFFA
SUBMITTED TO DO	03-APR-2012	Product Specific and GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific and GMP Inspection			BRYKMANR
REQUEST CANCELLED	02-MAY-2012			REFUSE TO FILE	CUFFA
SUBMITTED TO OC	02-OCT-2013				BHANDARIN
SUBMITTED TO DO	02-OCT-2013	Product Specific and GMP Inspection			WITTORFR
PDUFA 16-MAR-2014 AC 16-OCT-2012 FOR (b) (4)					
DO RECOMMENDATION	04-OCT-2013			ACCEPTABLE	MROSE
(b) (4) COVERED IN (b) (4) INSEPCTION FOUND ACCEPTABLE				BASED ON FILE REVIEW	
OC RECOMMENDATION	04-OCT-2013			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: CONTAINER CLOSURE INTEGRITY TESTING AND CONFIRMATORY TESTING OF IDENTIFICATION AND ASSAY (b) (4)
(b) (4) (on 27-MAR-2012 by A. CUFF (HF-01) 3017964061)
(b) (4) STABILITY TESTING (on 25-SEP-2013 by N. BHANDARI () 2404023815)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-APR-2012				CUFFA
OC RECOMMENDATION	03-APR-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	
REQUEST CANCELLED	02-MAY-2012				CUFFA
				REFUSE TO FILE	
SUBMITTED TO OC	02-OCT-2013				BHANDARIN
SUBMITTED TO DO	02-OCT-2013	Product Specific and GMP Inspection			WITTORFR
AC 17-MAY-2012 FOR CTL					
DO RECOMMENDATION	07-OCT-2013			ACCEPTABLE	VMATUSOV
PREVIOUS GMP/PAI EI DATED (b) (4) IS CLASSIFIED NAI. PROFILE CLASS CTL IS LISTED AS ACCEPTABLE. THERE ARE NO PENDING ENFORCEMENT ACTIONS THE WOULD IMPACT THIS RECOMMENDATION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	07-OCT-2013			ACCEPTABLE	SHARPT
NME				DISTRICT RECOMMENDATION	

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4) TESTING OF THE DRUG PRODUCT (on 03-APR-2012 by A. CUFF (HF-01) 3017964061)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-APR-2012				CUFFA
OC RECOMMENDATION	03-APR-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	
REQUEST CANCELLED	02-MAY-2012				CUFFA
				REFUSE TO FILE	
SUBMITTED TO OC	02-OCT-2013				BHANDARIN
SUBMITTED TO DO	03-OCT-2013	Product Specific and GMP Inspection			WITTORFR
NME AC 29-AUG-2013					
DO RECOMMENDATION	28-OCT-2013			ACCEPTABLE	CEVERLY
ALTHOUGH A (b) (4) INSPECTION WAS REQUESTED, (b) (4) DO DOES NOT FEEL THAT IT IS WARRANTED. THIS IS A NME AND FIRST APPLICATION FOR SPONSOR. CONTRACT LAB (b) (4) DISCUSSED THE FIRM'S HISTORY AND THE TESTING TO BE PERFORMED AND DETERMINED THAT WE ARE COMFORTABLE RECOMMENDING APPROVAL BASED ON FILE REVIEW. CARYN MCNAB, PRE-APPROVAL MANAGER				BASED ON FILE REVIEW	
OC RECOMMENDATION	29-OCT-2013			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: (b) (4) TESTING OF THE DRUG PRODUCT. (on 27-MAR-2012 by A. CUFF (HF-01) 3017964061)
(b) (4) FINSIHED DRUG PRODUCT TESTING, STABILITY TESTING (on 25-SEP-2013 by N. BHANDARI (2404023815)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-APR-2012				CUFFA
SUBMITTED TO DO	04-APR-2012	10-Day Letter			STOCKM
DO RECOMMENDATION	09-APR-2012			ACCEPTABLE	CLE
CGMP REGARDING STERILITY TESTING DURING PREVIOUS INSPECTIONS CLASSIFIED VAI (b) (4) AND NAI (b) (4) FOR PROFILE CTL. RECOMMEND APPROVAL BASED ON COMPLIANCE HX OF THE FIRM.				BASED ON FILE REVIEW	
OC RECOMMENDATION	09-APR-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	
REQUEST CANCELLED	02-MAY-2012				CUFFA
				REFUSE TO FILE	
REQUEST CANCELLED	02-MAY-2012				CUFFA
				REFUSE TO FILE	
SUBMITTED TO OC	02-OCT-2013				BHANDARIN
SUBMITTED TO DO	02-OCT-2013	Product Specific and GMP Inspection			WITTORFR
AC 09-MAR-2012 FOR CTL					
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific and GMP Inspection			EBUTLER
INSPECTION SCHEDULED	(b) (4)				EBUTLER
INSPECTION SCHEDULED					EBUTLER
INSPECTION PERFORMED					EBUTLER
DO RECOMMENDATION	22-JAN-2014			ACCEPTABLE	EBUTLER
INSPECTION CONDUCTED (b) (4) CLASSIFIED AS NAI. NO FDA 483 ISSUED. ALL PROFILE CLASSES FOUND ACCEPTABLE: (b) (4) CTL, (b) (4) PREVIOUS THREE INSPECTIONS WERE :2012 VAI, 2010 NAI, 2008 NAI.				INSPECTION	
OC RECOMMENDATION	28-JAN-2014			ACCEPTABLE	WILLIAMSJU
				DISTRICT RECOMMENDATION	

CMC DEFICIENCIES:
There are remaining outstanding deficiencies including:

- An Overall Recommendation of Acceptable has not been made by Compliance. The District Office currently recommends Withhold for the drug product manufacturing site.
- The validation of the HPLC method is not adequate
- The drug product specification is not adequate. The drug product specification should include tests for degradants (specified, unspecified, and total) and appropriate acceptance criteria should be proposed.
- The stability data cannot be evaluated without an appropriate drug product specification.
- DMF (b) (4) is currently inadequate. An official response to the Agency Deficiency letter dated 2/7/14 has not been received although the company has agreed to incorporate the Agency recommendations.

KXL System

The KXL System is an electronic medical device that delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of Photrexa or Photrexa (b) (4) (riboflavin ophthalmic solution). UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The figure below provides an illustration of the KXL System.

Figure 1: Overview Illustration of the KXL System

Source: 3.2.R Regional Information

The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient's cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

Table 1: KXL System Specifications

SPECIFICATION	DESCRIPTION
Electrical	Battery Powered: 12V 35 Ah SLA Line voltages 100-240 volts AC, (b) (4) Current (b) (4) Single Phase RMS, 50/60 Hz, (b) (4) Remote 2x AAA batteries
User accessible Fuses	250 V~ (b) (4)
Energy Delivery	UV Radiation 3 mW/cm^2 365 nm
External Interfaces	USB 2.0
Physical Dimensions	Length: (b) (4) cm Width: (b) (4) cm Height: (b) (4) cm (all dimensions with arm retracted)
Weight (crated system)	NW 45 Kg GW 120 Kg
Battery Life **(normal operating conditions)**	16 hours
Environmental Operating Conditions	The system operates under the following atmospheric conditions (no condensation).

Table 1: KXL System Specifications (Continued)

SPECIFICATION	DESCRIPTION
Ambient temperature	+10 to +40°C
Relative humidity	30% to 75%
Transport and Storage Conditions	The instrument withstands the following transport and storage conditions without damage or performance deterioration.
Ambient temperature	-15 to +70°C
Relative humidity	10% to 100% including condensation

The UV-X Illumination System was utilized during the Phase 3 clinical studies reported in the NDA. Avedro, Inc. believes that the KXL System for which commercial approval is being requested is equivalent to the UV-X Illumination System which was used during the Phase 3 clinical studies.

On October 7, 2013, the Division of Transplant and Ophthalmology requested that the Center for Devices and Radiologic Health (CDRH) review the device section of the application to address the following questions:

1. Can the proposed device component deliver the proposed amount of light (wavelength, power, time) described in the application?

2. Does CDRH have any recommended labeling changes to the KXL Operator's Manual?

On November 5, 2013, the Office of New Drug Quality Assessment (ONDQA) requested inspection of the KXL device manufacturing facility.

On February 10, 2014, a memorandum from CDRH was received. Within the CDRH, consult requests were made for various review areas including clinical, optical radiation hazard, electromagnetic compatibility and software.

For extensive details, see the Deputy Division Director's review dated 3/7/14.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology review dated 2/16/14:

The subject of this NDA application is Riboflavin Ophthalmic Solution 0.12% as a topical ophthalmic crosslinking agent for use in combination with the KXL System, an ultraviolet A (UVA) emitting device which facilitates crosslinking of corneal collagen upon irradiation.

The applicant has submitted NDA 203324 as a 505(b)(2) application and will rely on published nonclinical data to support this application. All nonclinical safety and pharmacology data cited in the NDA are from published, publicly available research articles.

Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photosensitizer.

The surface UVA dose proposed for human use, 3 mW/cm^2, resulted in an endothelial dose found to cause endothelial toxicity in the rabbit.[1] The applicant claims that the endothelial

[1] Wollensak, G. *et al*., 2003, "Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit", *J Cataract Refract Surg*, 29: 1786 – 1790.

dose resulting from this surface dose will not cause endothelial toxicity in humans, because the resultant endothelial dose is lower in the human than in rabbit. This difference in the calculated endothelial doses between humans and rabbits is presumably based on differences in the absorption coefficient of the riboflavin treated corneas of humans and rabbits. In an amendment dated 2-25-2014, the applicant explains that per the authors, the surface dose used in the rabbit study will produce a lower endothelial dose in humans of 0.18 mW/cm^2 (as opposed to 0.36 mW/cm^2 in rabbits). Therefore, it was concluded by the applicant that the surface dose resulting in toxicity in rabbits is safe in humans (3 mW/cm^2). The difference in calculated endothelial doses between rabbits and humans following a 3 mW/cm^2 surface dose appears to be based on different corneal absorption coefficients between rabbits and humans.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review dated 1/17/14:

NDA 203-324 has been reviewed by the Clinical Pharmacology review team for Photrexa and Photrexa-(b) (4) (riboflavin ophthalmic solutions). From the perspective of Clinical Pharmacology, it is recommended that this NDA be approved, provided that satisfactory agreement is reached between the sponsor and FDA regarding the FDA revisions to the language in the package insert.

Riboflavin is used in corneal crosslinking as a photosensitizer, allowing the cornea to absorb a greater amount of the UV irradiation. The oxygen free radicals produced induces the formation of intra- and inter- collagen fibril covalent bonds, leading to biomechanical stabilization of the cornea.

There were no pharmacokinetic studies conducted to determine the actual systemic exposures to riboflavin following topical ocular instillation of the 0.12% riboflavin ophthalmic solutions during one-time corneal collagen crosslinking treatment.

Assuming 100% bioavailability of riboflavin following topical ocular instillation of the proposed 0.12% riboflavin eyedrops, the average systemic exposure to riboflavin during one-time CCXL treatment of one eye in the 12-month UVX trials would not exceed (b) (4) mg, which is below the Joint FAO/WHO Expert Committee on Food Additives upper limit of acceptable oral daily intake of riboflavin (35 mg for a 70 kg person).

6. Sterility Assurance

From the original drug substance Product Quality Microbiology Review dated 2/18/14:

NDA 203324 is recommended for approval from the standpoint of product quality microbiology.

Container-Closure Integrity (CCI) testing was performed (b) (4) The test is a (b) (4) method (b) (4) The method was validated for both the Photrexa and Photrexa (b) (4) drug product (ReportNS-06986134). The CCI testing was performed on stability lots, and testing met the acceptance criteria. The drug products are (b) (4) filled into single use syringes for topical ophthalmic application. (b) (4) Both Photrexa and Photrexa (b) (4) studies met the acceptance criteria for the (b) (4) manufacturing process.

No product quality microbiology deficiencies were identified based upon the information provided.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 3/7/14:

The clinical development program of riboflavin ophthalmic solution/UVA irradiation in the treatment of keratoconus involved 2 studies, UVX-001 and UVX-002. The clinical development program of riboflavin ophthalmic solution/UVA irradiation in the treatment of corneal ectasia following refractive surgery involved 2 studies, UVX-001 and UVX-003.

The studies were nearly identical in design and conduct. However, UVX-001 had a mixed population of subjects with corneal ectasia and keratoconus, whereas only corneal ectasia subjects were enrolled in UVX-003. Further, UVX-001 was a single-center study, and UVX-003 involved 9 sites. All sites were located in the US.

In response to potential review issue #2 from the RTF letter dated May 4, 2012[2], the CSRs for UVX-001, UVX-002 and UVX-003 were revised by Avedro, Inc. to describe each individual trial without pooling (Module 5.3.5.1). As secondary, supportive information, pooled keratoconus results (UVX-001 keratoconus data and UVX-002 data) and pooled ectasia results (UVX-001 ectasia data and UVX-003 data) were submitted for the primary efficacy parameter.

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 (Kmax), quantifies the pathognomonic feature of keratoconus and corneal ectasia. Based on the etiology and manifestation of keratoconus and corneal ectasia, Kmax was

[2] "The Clinical Study Reports (CSRs) for UVX-002 and UVX-003 do not contain unpooled demographic or adverse event data. The CSRs should be revised to contain both pooled and unpooled demographic and adverse event data. These CSRs should be separate, independent documents which adequately describe each individual trial without pooling. It is acceptable to include pooled efficacy data as secondary, supportive analyses in the CSRs."

accepted by the Agency as a clinically meaningful and reproducible endpoint to be measured in these patient populations. For each study, the primary efficacy endpoint was corneal curvature, as measured by Kmax.

The intent-to-treat (ITT) population consisted of all treated subjects, analyzed according to the randomized treatment. All safety and efficacy analyses were performed using the ITT population. All subjects received the appropriate randomized treatment; therefore, the ITT and safety populations are the same.

The per protocol (PP) set was to consist of all ITT subjects in whom there were no major protocol deviations, as defined at end of study. Per the SAP, all efficacy analyses of the Kmax endpoint were to be conducted on the PP population. However, no per protocol population was defined, and no analyses were performed.

Analysis of Primary Endpoint(s)

UVX-001 Keratoconus

Table 25: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF) - (Keratoconus Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline: CXL Group (N=29)	Change from Baseline: Control Group (N=29)	P-value[a]
Baseline	n	29	29			
	Mean	60.6	61.9			
	SD	7.34	8.32			
	Median	59.2	62.0			
	Min, Max	50, 79	48, 81			
Month 1	n	29	29	29	29	
	Mean	62.0	58.9	1.4	–2.9	0.0563
	SD	8.41	14.07	2.68	11.66	
	Median	60.1	58.9	0.9	–0.3	
	Min, Max	52, 89	–0, 79	–1, 14	–62, 5	
Month 3	n	29	29	29	29	
	Mean	60.3	62.0	–0.3	0.1	0.5085
	SD	8.23	9.38	2.68	2.61	
	Median	58.3	60.8	–0.7	–0.1	
	Min, Max	48, 86	48, 87	–5, 11	–7, 7	
Month 6	n	29	29	29	29	
	Mean	59.7	62.3	–0.9	0.5	0.0674
	SD	8.10	9.52	2.61	2.99	
	Median	57.7	60.8	–1.1	0.0	
	Min, Max	48, 83	48, 84	–5, 7	–7, 8	
Month 12	n	29	29	29	29	
	Mean	59.2	62.3	–1.4	0.5	0.0175
	SD	7.82	9.52	2.84	2.99	
	Median	58.4	60.8	–1.0	0.0	
	Min, Max	49, 83	48, 84	–8, 7	–7, 8	

[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)

Source: Table 14.2.1.1.2 (Section 14.2.1)

The applicant's dataset contains errors. For example, Kmax cannot be zero (Control Group, Month 1); change from baseline cannot be -62 (Control Group, Month 1). This analysis will need to be re-run after non-physiological values are removed.

Based on the dataset provided, the difference between the CXL and control groups in mean change from baseline in Kmax progressively increased, in favor of CXL, from Month 3 through Month 12 for keratoconus subjects. The difference between treatment groups was < 1.0 D at Month 3 (–0.3 D vs. 0.1 D) and exceeded 1.0 D at Month 6 (–0.9 D vs. 0.5 D) and Month 12 (–1.4 D vs. 0.5 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant at Month 12 (p=0.0175).

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

UVX-001 Corneal Ectasia

Table 38: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF) - (Corneal Ectasia Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline		P-value[a]
				CXL Group (N=24)	Control Group (N=25)	
Baseline	n	24	25			
	Mean	56.3	55.0			
	SD	6.26	5.45			
	Median	56.2	55.2			
	Min, Max	47, 72	47, 68			
Month 1	n	24	25	24	25	
	Mean	57.4	55.8	1.1	0.8	0.6408
	SD	7.59	5.96	2.06	1.73	
	Median	57.2	55.5	0.9	0.5	
	Min, Max	43, 77	48, 67	–5, 6	–3, 7	
Month 3	n	24	25	24	25	
	Mean	56.4	56.0	0.1	1.0	0.0382
	SD	7.02	6.40	1.26	1.68	
	Median	55.1	56.0	0.0	0.7	
	Min, Max	48, 74	48, 70	–3, 3	–1, 7	
Month 6	n	24	25	24	25	
	Mean	55.7	56.0	–0.6	1.0	0.0010
	SD	6.60	6.19	1.61	1.69	
	Median	53.2	56.6	–0.8	0.6	
	Min, Max	48, 70	48, 70	–5, 3	–1, 7	
Month 12	n	24	25	24	25	
	Mean	55.3	56.0	–1.0	1.0	0.0001
	SD	6.62	6.19	1.68	1.69	
	Median	53.3	56.6	–0.9	0.6	
	Min, Max	47, 71	48, 70	–5, 3	–1, 7	

[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)
Source: Table 14.2.1.1.2 (Section 14.2.2)

The difference between the CXL and control groups in mean change from baseline Kmax progressively increased, 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 (0.1 D vs. 1.0 D) and exceeded 1.0 D at Month 6 (–0.6 D vs. 1.0 D) and Month 12 (–1.0 D vs. 1.0 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant at Month 12 (p=0.0001).

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

UVX-002 Keratoconus

Table 15: Mean Changes from Baseline K_{max} in the Randomized Study Eye: LOCF (UVX-002, ITT Population)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline: CXL Group (N=73)	Change from Baseline: Control Group (N=74)	P-value[a]
Baseline	n	73	74			
	Mean	61.0	59.8			
	SD	9.81	9.16			
	Median	58.0	57.5			
	Min, Max	48, 96	48, 90			
Month 1	n	73	74	73	74	
	Mean	62.2	59.3	1.2	–0.5	0.0678
	SD	9.37	11.91	3.36	7.18	
	Median	59.4	57.3	1.0	–0.0	
	Min, Max	49, 94	0, 91	–17, 8	–58, 8	
Month 3	n	73	74	73	74	
	Mean	60.4	60.5	–0.6	0.7	0.1142
	SD	8.92	10.91	4.44	5.58	
	Median	58.4	57.8	0.0	–0.1	
	Min, Max	48, 90	49, 108	–33, 6	–9, 44	
Month 6	n	73	74	73	74	
	Mean	59.9	61.0	–1.1	1.2	0.0129
	SD	8.34	11.25	5.06	5.71	
	Median	57.9	58.0	–0.5	–0.1	
	Min, Max	47, 88	49, 108	–36, 12	–9, 44	
Month 12	n	73	74	73	74	
	Mean	59.3	61.0	–1.7	1.2	0.0010
	SD	8.50	11.25	4.69	5.70	
	Median	58.0	58.0	–1.0	–0.1	
	Min, Max	47, 91	49, 108	–32, 7	–9, 44	

[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).

Source: Table 14.2.1.1.3 (Section 14.2.1)

The applicant's dataset contains errors. For example, Kmax cannot be zero (Control Group, Month 1); change from baseline cannot be -58 (Control Group, Month 1). This analysis will need to be re-run after non-physiological values are removed.

Based on the dataset provided, the difference between the CXL and control groups in mean change from baseline Kmax progressively increased, in favor of CXL, from Month 3 through Month 12. The difference between treatment groups exceeded 1.0 D at Month 3 (–0.6 D vs. 0.7 D), Month 6 (–1.1 D vs. 1.2 D), and Month 12 (–1.7 D vs. 1.2 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant at Month 12 (p=0.0010).

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

UVX-003 Corneal Ectasia

Table 15: Mean Changes from Baseline K_{max} in the Randomized Study Eye: LOCF (UVX-003, ITT Population)

Visit	Statistic	CXL Group (N=67)[a]	Control Group (N=63)	Change from Baseline: CXL Group (N=67)[a]	Change from Baseline: Control Group (N=63)	P-value[b]
Baseline	n	63	63			
	Mean	55.1	54.7			
	SD	7.09	6.77			
	Median	53.9	52.9			
	Min, Max	45, 75	43, 76			
Month 1	n	67	63	63	63	
	Mean	56.0	54.7	1.0	0.0	0.0005
	SD	7.04	6.67	1.84	1.10	
	Median	55.7	53.4	0.6	0.1	
	Min, Max	45, 76	43, 75	–3, 6	–2, 2	
Month 3	n	67	63	63	63	
	Mean	54.9	55.3	–0.2	0.6	0.0386
	SD	6.99	6.81	2.38	1.88	
	Median	53.4	53.8	0.1	0.5	
	Min, Max	45, 77	43, 78	–9, 7	–3, 12	
Month 6	n	67	63	63	63	
	Mean	54.6	55.2	–0.5	0.5	0.0084
	SD	6.64	6.96	1.95	2.28	
	Median	53.3	53.8	–0.2	0.5	
	Min, Max	45, 71	43, 78	–8, 3	–9, 12	
Month 12	n	67	63	63	63	
	Mean	54.5	55.2	–0.5	0.5	0.0080
	SD	6.85	6.97	2.21	2.26	
	Median	53.5	54.1	–0.3	0.5	
	Min, Max	45, 74	43, 78	–10, 4	–9, 12	

[a] Four subjects did not have a K_{max} measurement at baseline.
[b] 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).
Source: Table 14.2.1.1.3 (Section 14.2.1)

The difference between the CXL and control groups in mean change from baseline Kmax favored CXL from Month 3 through Month 12. The difference between treatment groups was less than 1.0 D at Month 3 (–0.2 D vs. 0.6 D) and reached 1.0 D at Month 6 (–0.5 D vs. 0.5 D) and Month 12 (–0.5 D vs. 0.5 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant (p=0.0080) at Month 12.

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

Summary Efficacy Statement

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for the corneal ectasia indication. The datasets for the keratoconus indication from UVX-001 and UVX-002 contain errors (i.e., non-physiologic values). The applicant will be expected to reanalyze their keratoconus Kmax efficacy data from UVX-001 and -002 after non physiologic values are removed

8. Safety

From the original Medical Officer Review dated 3/7/2014:

All CXL-treated eyes received the same UVA irradiation treatment (365 nm at an irradiance of 3 mW/cm^2 for 30 minutes). Sham-treated eyes underwent the same UV irradiation procedure except the UVA light source was not illuminated during the procedure. For both indications, the mean number of drops of riboflavin with dextran administered prior to the UVA procedure (or mock procedure in sham eyes) and during the UVA procedure (or mock procedure in sham eyes) was approximately 16 and 15 drops, respectively. CXL-treated eyes that did not meet the requirement for corneal thickness ≥ 400 microns after UVA pre-treatment with riboflavin plus dextran received a second solution of riboflavin without dextran. No subjects received CXL treatment more than once in the same eye. Subjects who received CXL in untreated fellow eyes (from CXL group) and untreated sham eye and untreated fellow eye (from control group) received CXL at least 3 months after the initial randomized treatment. The Table below summarizes the number of eyes treated with any CXL in the pooled keratoconus and corneal ectasia studies (i.e., primary study eyes randomized to CXL, primary study eyes randomized to control which subsequently received CXL, and fellow eyes in either treatment group which received CXL).

Table 3: Treatments Administered in the Pooled Keratoconus and Corneal Ectasia Studies: Primary (Study) Eyes and Secondary Eyes (Safety Population)

Randomization:	Primary (Study Eye)		Secondary Eyes			Total
	CXL n (%)	Sham n (%)	Fellow Eye CXL n (%)	None n (%)	Sham Eye CXL n (%)	
SUBJECTS WITH KERATOCONUS						
Subjects Randomized to CXL (N=102)	102 (100.0)	---	56 (54.9)	46 (45.1)	---	---
Subjects Randomized to Sham (N=103)	---	103 (100.0)	41 (39.8)	9 (8.7)	94 (91.3)	---
Total CXL (N=293)	102 (34.8)	---	97 (33.1)	---	94 (32.1)	293 (100.0)
SUBJECTS WITH CORNEAL ECTASIA						
Subjects Randomized to CXL (N=91)	91 (100.0)	---	26 (28.6)	65 (71.4)	---	---
Subjects Randomized to Sham (N=88)	---	88 (100.0)	22 (25.0)	8 (9.1)	80 (90.9)	---
Total CXL (N=219)	91 (41.6)	---	48 (21.9)	---	80 (36.5)	219 (100.0)

Source: 2.5 Clinical Overview Section 4.2.3

Disposition of Subjects

UVX-001 Keratoconus

Table 7: Subject Disposition (Keratoconus Subjects, UVX-001, ITT Population)

Category	CXL Group (N=29)	Control Group (N=29)	Total (N=58)
Received Randomized Treatment (CXL or Sham) (N)	29	29	58
Completed study (n, %)	20 (69.0%)	12 (41.4%)	32 (55.2%)
Discontinued study (n, %)	9 (31.0%)	17 (58.6%)	26 (44.8%)
Administrative[a]	9 (31.0%)	17 (58.6%)	26 (44.8%)

[a] The investigator left the site and the study was terminated by the Sponsor.
Source: Table 14.1.1 (Section 14.1.1)

Table 14.1.1
Subject Disposition
(ITT Population)

		CXL Group (N=29)	Control Group (N=29)	Total (N=58)
Reason for Study Exit	n	29	29	58
	Completed Study	20(69.0%)	12(41.4%)	32(55.2%)
	Voluntary Withdrawal	0	0	0
	Administrative	9(31.0%)	17(58.6%)	26(44.8%)
	Lost to Follow-Up	0	0	0

The ITT population consisted of 58 keratoconus subjects, with 29 subjects randomized to each of the 2 treatment groups.

As shown in the table above, more than half of the keratoconus subjects (55%) completed the study, with more subjects completing in the CXL group (69%) compared with the control group (41%). The proportion of subjects who discontinued the study was 31% and 59% in the CXL and control groups, respectively. All subjects who discontinued prematurely did so because the investigator left the site and the study was terminated by the Sponsor. None of the subjects discontinued due to an AE.

UVX-001 Corneal Ectasia

Table 8: Subject Disposition (Corneal Ectasia Subjects, UVX-001, ITT Population)

Category	CXL Group (N=24)	Control Group (N=25)	Total (N=49)
Received Randomized Treatment (CXL or Sham) (N)	24	25	49
Completed study (n, %)	20 (83.3%)	11 (44.0%)	31 (63.3%)
Discontinued study (n, %)	4 (16.7%)	14 (56.0%)	18 (36.7%)
Other[a]	3 (12.5%)	10 (40.0%)	13 (26.5%)
Lost to Follow-Up	1 (4.2%)	3 (12.0%)	4 (8.2%)
Administrative	0	1 (4.0%)	1 (2.0%)

[a] The investigator left the site and the study was terminated by the Sponsor.
Source: Table 14.1.1 (Section 14.1.2)

Table 14.1.1
Subject Disposition
(ITT Population)

		CXL Group (N=24)	Control Group (N=25)	Total (N=49)
Reason for Study Exit	n	24	25	49
	Completed Study	20(83.3%)	11(44.0%)	31(63.3%)
	Voluntary Withdrawal	0	0	0
	Administrative	0	1(4.0%)	1(2.0%)
	Lost to Follow-Up	1(4.2%)	3(12.0%)	4(8.2%)
	Other	3(12.5%)	10(40.0%)	13(26.5%)

The ITT population consisted of 49 corneal ectasia subjects, with 24 subjects randomized the CXL group and 25 randomized to the control group.

As shown in the table above, the majority of corneal ectasia subjects (63%) completed the study, with more subjects completing in the CXL group (83%) compared with the control group (44%). The proportion of subjects who discontinued the study was 17% and 56% in the CXL and control groups, respectively. The majority of subjects who discontinued prematurely did so because the investigator left the site and the study was terminated by the Sponsor.

UVX-002 Keratoconus

Table 6: Subject Disposition (UVX-002, ITT Population)

	CXL Group (N=73)	Control Group (N=74)	Total (N=147)
Received Randomized Treatment (CXL or Sham) (N)	73	74	147
Completed study (n, %)	65 (89.0%)	62 (83.8%)	127 (86.4%)
Discontinued study (n, %)	8 (11.0%)	12 (16.2%)	20 (13.6%)
Voluntary withdrawal (unrelated to safety)	3 (4.1%)	8 (10.8%)	11 (7.5%)
Lost to follow-up	5 (6.8%)	4 (5.4%)	9 (6.1%)

Source: Table 14.1.1 (Section 14.1)

14.1.1 Subject Disposition
(ITT Population)

		CXL Group (N=73)	Control Group (N=74)	Total (N=147)
Reason for Study Exit	n	73	74	147
	Completed Study	65(89.0%)	62(83.8%)	127(86.4%)
	Voluntary Withdrawal	3(4.1%)	8(10.8%)	11(7.5%)
	Administrative	0	0	0
	Lost to Follow-Up	5(6.8%)	4(5.4%)	9(6.1%)

A total of 147 subjects were randomized into the study (73, CXL group; 74, control [sham] group) (Table 6). Most subjects (86%) completed the study. The proportion of subjects who discontinued the study was 11% and 16% in the CXL and control groups, respectively. Reasons for discontinuation were voluntary withdrawal (unrelated to safety) and lost to follow-up.

UVX-003 Corneal Ectasia

Table 6: Subject Disposition (UVX-003, ITT Population)

	CXL Group (N=67)	Control Group (N=63)	Total (N=130)
Received Randomized Treatment (CXL or Sham) (N)	67	63	130
Completed study (n, %)	56 (83.6%)	48 (76.2%)	104 (80.0%)
Discontinued study (n, %)	11 (16.4%)	15 (23.8%)	26 (20.0%)
Other	5 (7.5%)	7 (11.1%)	12 (9.2%)
Lost to Follow-Up	6 (9.0%)	3 (4.8%)	9 (6.9%)
Voluntary Withdrawal (unrelated to safety)	0	5 (7.9%)	5 (3.8%)

Source: Table 14.1.1 (Section 14.1)

14.1.1 Subject Disposition (ITT Population)

		CXL Group (N=67)	Control Group (N=63)	Total (N=130)
Reason for Study Exit	n	67	63	130
	Completed Study	56(83.6%)	48(76.2%)	104(80.0%)
	Voluntary Withdrawal	0	5(7.9%)	5(3.8%)
	Administrative	0	0	0
	Lost to Follow-Up	6(9.0%)	3(4.8%)	9(6.9%)
	Other	5(7.5%)	7(11.1%)	12(9.2%)

The ITT population consisted of 130 subjects, with 67 subjects randomized to the CXL group and 63 subjects randomized to the control group.

As shown in the table above, most subjects (80%) completed the study. The proportion of subjects who discontinued the study was 16% and 24% in the CXL and control groups, respectively. Reasons for discontinuation were "other" (9%), lost to follow-up (7%), and voluntarily withdrawal (unrelated to safety) (4%).

Deaths

There were no subject deaths in any treatment group in any trial.

Common Adverse Events

UVX-001 and-002 for Keratoconus

Table 7: Summary of Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Keratoconus)

MedDRA System Organ Class/ Preferred Term	CXL Group (N=102)	Control Group (N=103)
Number (%) of Subjects Reporting Any AEs[a]	336:87 (85.3%)	75:44 (42.7%)
Eye Disorders	304:86 (84.3%)	59:40 (38.8%)
Corneal opacity	73:58 (56.9%)	4:4 (3.9%)
Punctate keratitis	28:25 (24.5%)	8:8 (7.8%)
Corneal striae	25:24 (23.5%)	12:12 (11.7%)
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%)
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%)
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
Other Ocular TEAEs		
Corneal scar	9:7 (6.9%)	5:5 (4.9%)
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%)

[a] 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.
Source: Table 14.3.1.2.1, Section 8.1

Table 16: Summary of Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Corneal Ectasia)

MedDRA System Organ Class/ Preferred Term	CXL Group (N=91)	Control Group (N=88)
Number (%) of Subjects Reporting Any AEs	328:82 (90.1%)	66:38 (43.2%)
Ocular TEAEs	296:82 (90.1%)	53:33 (37.5%)
Corneal opacity	74:62 (68.1%)	7:7 (8.0%)
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%)
Photophobia	18:17 (18.7%)	0
Vision blurred	15:15 (16.5%)	4:4 (4.5%)
Dry eye	14:13 (14.3%)	4:4 (4.5%)
Visual acuity reduced	10:10 (11.0%)	1:1 (1.1%)
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 dysfunction	4:3 (3.3%)	2:2 (2.3%)
Ocular hyperaemia	3:3 (3.3%)	1:1 (1.1%)
Corneal scar	3:3 (3.3%)	1:1 (1.1%)
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

Note: Ocular events in the fellow eye are excluded.
Source: Table 14.3.1.2.1, Section 8.2

These are pooled common adverse event tables (i.e. UVX-001 and -002 for keratoconus and -001 and -003 for corneal ectasia). Note: subjects in the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed; subjects in the sham treatment group had topical anesthetic administered to the study eye but did not have the corneal epithelium removed.

The most common adverse events for either indication at ≥ 10% are corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following corneal epithelial debridement.

These adverse event tables only represent reported events through Month 3. . 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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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.

By the last study visit, 165/248 (66.5%) eye disorders resolved. The percentage of events that resolved (resolved events/total number of events) by the last study visit was 9798% for vision blurred 93% for corneal epithelium defect, 90% for punctate keratitis, and 83% for corneal opacity (haze).[3]

By the last study visit for corneal ectasia subjects, 118/190 (63%) eye disorders resolved. The percentage of events that resolved (resolved events/total number of events) by the last study visit was 90% for punctate keratitis, 89% for vision blurred, 89% for corneal epithelium defect, and 80% for corneal opacity (haze).[4]

Serious Adverse Events

UVX-001

In the CXL group, no keratoconus or corneal ectasia subjects experienced a serious adverse event during the study. Two subjects in the control group (1, keratoconus; 1, corneal ectasia) experienced a serious adverse event. Subject (b) (6) (keratoconus) had serious adverse events of two suicide attempts from baseline to Month 3. Subject (b) (6) (corneal ectasia) had a serious adverse event of head injury from baseline to Month 3.

Subject (b) (6) (keratoconus subject, control group) was a 20-year-old Caucasian, non-Hispanic female who received control treatment OD on (b) (6) (Day 26) and again on (b) (6) (Day 72), the subject attempted suicide, resulting in hospitalization on each occasion. Treatment included 1 liter IV N-acetylcysteine, 50g PO charcoal, and PO Mucomyst (dose unknown) for the first suicide attempt and 1 liter IV N-acetylcysteine and 50g PO charcoal for the second attempt. Outcome was reported as resolved (same day as onset). The subject remained in the study and received CXL treatment OD (crossover from sham) (b) (6) She completed the study and attended all follow-up visits through Month 12 (except for Month 1, which was missed due to the attempted suicide).

Subject (b) (6) (corneal ectasia subject, control group) was a 50-year-old Caucasian, non-Hispanic male who received control treatment OS on (b) (6) (Day 34),

[3] Table 14.3.5.14
[4] Table 14.3.5.14

the subject experienced severe head injury and was hospitalized. The event was considered by the investigator to be unrelated to riboflavin, UVA light, and epithelial defect. Outcome was reported as resolved (date not reported). The subject received CXL treatment OS (crossover from sham) (b) (6) The subject's last evaluation was at Month 3; thereafter, the subject was lost to follow-up and was discontinued from the study.

UVX-002
None of the subjects in the keratoconus CXL group and 3 subjects in the control group experienced a serious adverse event during the study. In the control group, serious adverse events were corneal ulcer following CXL in the sham eye (Subject (b) (6)); appendicitis requiring appendectomy (Subject (b) (6)); and an infectious cat bite requiring hospitalization (Subject (b) (6)). Each of these events occurred after Month 3.

Subject (b) (6) (control group) was a 19-year-old Caucasian, non-Hispanic male who received sham treatment OS (b) (6) and subsequently received CXL treatment OU at the Month 6 follow-up visit (b) (6) He developed a corneal ulcer (OS) with onset 3 days after receiving CXL treatment. The corneal ulcer 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 corneal ulcer resolved (b) (6)

Subject (b) (6) was originally a control patient OD and received CXL treatment OS at the six month OD follow-up. This adverse event appears directly related to the planned corneal epithelial debridement for CXL treatment.

Subject (b) (6) (control group) was a 35-year-old, Caucasian (ethnicity not reported) female who developed appendicitis approximately 5 months after baseline. She was hospitalized and had an appendectomy. Outcome was reported as resolved.

Subject (b) (6) (control group) was a 52-year-old, Caucasian, non-Hispanic female who was hospitalized for treatment of an infectious cat bite approximately 9 months after baseline. Outcome was reported as resolved.

UVX-003
One subject in the corneal ectasia CXL group and no subjects in the control group experienced a serious adverse vent during the study.

Subject (b) (6) (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. The Lasik flap was lifted to remove the epithelial growth. The corneal epithelium defect resolved on Day 43.

Safety Summary Statement

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications to support safety.

The most common adverse events for both the keratoconus and corneal ectasia indications occurring at 10% to 92% in UVX-001, -002, and -003 were corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following the corneal epithelial debridement which accompanied the procedure.

The clinical trials performed by the applicant followed these criteria for clinical application of crosslinking:

- corneal epithelium removed to facilitate diffusion of riboflavin throughout the corneal stroma
- 0.1% riboflavin ophthalmic solution be applied for at least 30 minutes before the UV exposure
- UV irradiance of 3 m W/cm^2 and a wavelength of 370 nm must be homogenous
- cornea to be X-linked must have a minimal thickness of 400 µm to protect the endothelium (Spoerl *et al* 2007).

Any potential damage to the corneal endothelium, the lens or the retina is expected to be minimized when these criteria are fulfilled (Spoerl *et al* 2007).

A 120-Day Safety Update was submitted on February 19, 2014. Per the update, the Phase 3 studies in support of the original NDA were completed with the final study reports submitted in the original NDA. Per the applicant, there are no additional safety data from these studies. The applicant markets the similar product, VibeX, in Europe. The applicant will be expected to submit any postmarketing data on the VibeX product(s) which could be relevant for the safety profit for Photrexa.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The safety and effectiveness of corneal collagen cross-linking has not been established in patients less than 14 years of age. In the Phase 3 studies, there were 16 patients between 14-18 years of age.

Submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 2/28/14:

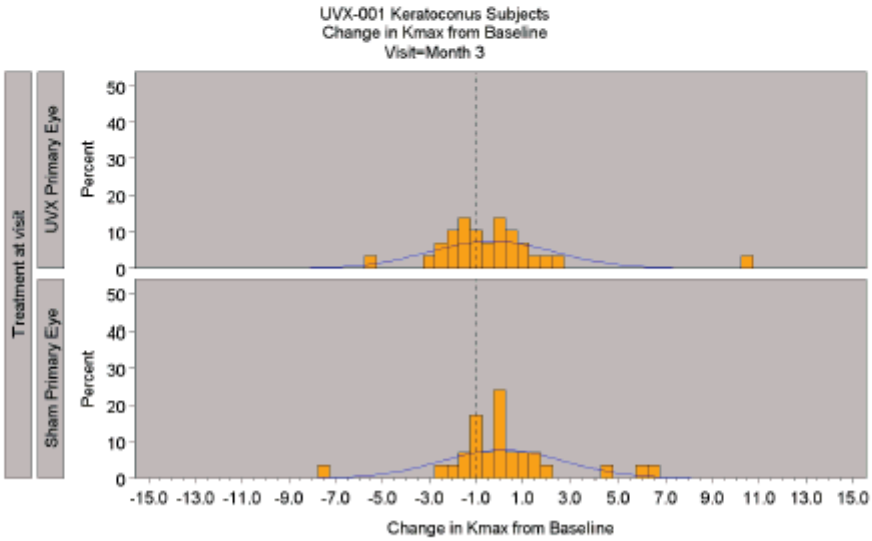
The primary efficacy evaluation was based on the change from baseline in the maximum corneal curvature as measured by the maximum keratometry (Kmax, in the unit of diopter [D]). When the statistical evaluation of the efficacy was based on data at Month 3 as originally planned in the protocols, a statistically significant difference in the mean change in Kmax from baseline to Month 3 between the CXL group and the control group was observed in UVX-001 and UVX- 003, respectively, for corneal ectasia subjects. The difference observed in both studies (0.9 D and 0.8 D for UVX-001 and UVX-003, respectively) was close to 1.0 D, a threshold considered to be a clinical success. However, the efficacy of CXL treatment observed in keratoconus subjects was neither clinically meaningful nor statistically significant. A difference of 0.5 D and 1.3 D in the mean change in Kmax from baseline to Month 3 between the CXL group and the control group was reported in UVX-001 and UVX-002, respectively. The difference observed in UVX-001 was less than 1.0 D, the threshold for clinical success. The difference observed in UVX-002 was greater than 1.0 D, but the difference is not statistically significant. The observed difference of 1.3 D was likely driven by one large decrease in Kmax experienced by one subject in the CXL group and one large increase in Kmax experienced by one subject in the control group. These two groups were not differentiable in terms of the median (0 vs -0.1 D).

The Applicant extended the time-point of the primary efficacy analysis from Month 3 to

Months 12 after the studies were completed. Their analysis indicated that CXL treatment resulted in statistically significant and clinically meaningful improvements in Kmax for both indications in all three studies. This was concluded from an analysis that included a significant amount of imputed data at Month 12 for the control group. The study design allowed the subjects in the control group to cross over to receive the CXL treatment in the study eyes after Month 3. As a result, no subjects or only two subjects in the control groups for the respective studies remained in the assigned treatment (i.e., control) and had efficacy data at Month 12. Therefore, a direct comparison of treatment effect at Month 12 cannot be made. In the Applicant's primary efficacy analysis, the efficacy data at Month 3 or Month 6 prior to cross-over was carried forward to Month 12; the treatment comparison at Month 12 was essentially a comparison of CXL at Month 12 with the control at Month 3 and Month 6. The estimate of the treatment effect could be unreliable if the efficacy data at Month 3 and Month 6 is not representative of the efficacy data at Month 12.

Table 6: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-001, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline CXL (N=29)	Change from Baseline Control (N=29)	Difference[1]	p-value [2]
Baseline	Mean (SD)	60.6 (7.3)	61.9 (8.3)				
	Median	59.2	62.0				
	Min, Max	49.5, 79.2	47.7, 81.3				
Month 1	Mean (SD)	62.0 (8.4)	58.9 (14.1)	1.4 (2.7)	-2.9 (11.7)	----	0.0002 *
	Median	60.1	58.9	0.9	-0.3	4.3 (-0.1,8.8)	0.0563 **
	Min, Max	51.5, 89.4	-0.3, 78.6	-1.4, 13.9	-62.3, 4.8	4.3 (-0.2,8.9)	0.0587 ***
Month 3	**Mean (SD)**	**60.3 (8.2)**	**62.0 (9.4)**	**-0.3 (2.7)**	**0.1 (2.6)**	----	**0.2048 ***
	Median	**58.3**	**60.8**	**-0.7**	**-0.1**	**-0.5 (-1.9,0.9)**	**0.5085 ****
	Min, Max	**48.0, 86.2**	**47.5, 87.4**	**-5.4, 10.7**	**-7.4, 6.6**	**-0.4 (-1.7,1.0)**	**0.5918 *****
Month 6	Mean (SD)	59.7 (8.1)	62.3 (9.5)	-0.9 (2.6)	0.5 (3.0)	----	0.0557 *
	Median	57.7	60.8	-1.1	0	-1.4 (-2.9,0.1)	0.0674 **
	Min, Max	48.0, 82.6	47.5, 84.1	-5.2, 7.1	-6.8, 7.6	-1.3 (-2.8,0.2)	0.0838 ***
Month 12	Mean (SD)	59.2 (7.8)	62.3 (9.5)	-1.4 (2.8)	0.5 (3.0)	----	0.0170 *
	Median	58.4	60.8	-1.0	0	-1.9 (-3.4,-0.3)	0.0175 **
	Min, Max	48.6, 82.6	47.5, 84.1	-7.8, 7.1	-6.8, 7.6	-1.8 (-3.4,-0.3)	0.0217 ***

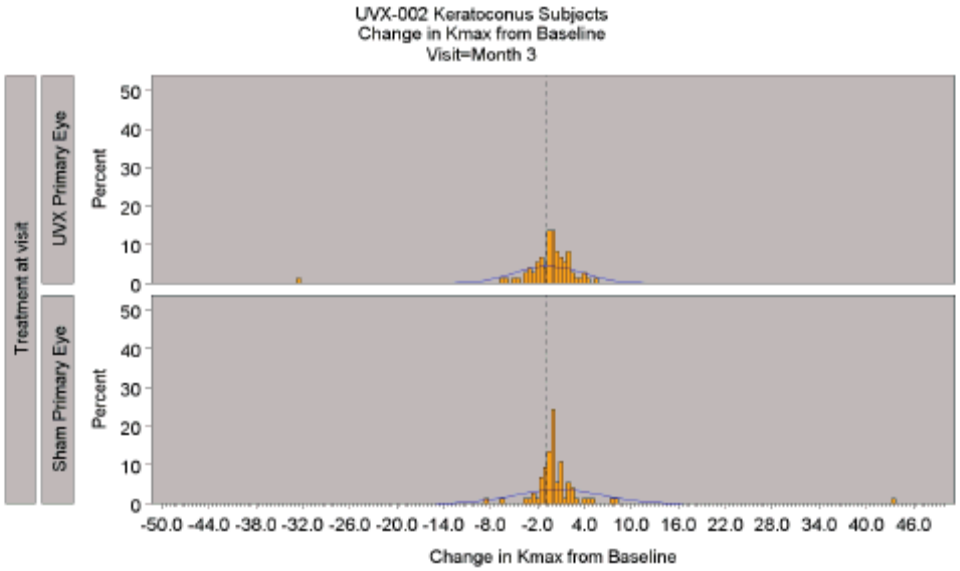


[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-001 CSR Table 14.2.1.1.2 and Reviewer's analysis.

Table 7: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-002, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline CXL (N=73)	Change from Baseline Control (N=74)	Difference[1]	p-value [2]
Baseline	Mean (SD)	61.0 (9.8)	59.8 (9.2)				
	Median	58.0	57.5				
	Min, Max	47.8, 96.4	48.3, 90.3				
Month 1	Mean (SD)	62.2 (9.4)	59.3 (11.9)	1.2 (3.4)	-0.5 (7.2)	----	0.0009 *
	Median	59.4	57.3	1.0	-0.1	1.7 (-0.1,3.5)	0.0678 **
	Min, Max	49.3, 93.8	0, 91.3	-16.8, 8.1	-58.4, 8.0	1.7 (-0.1,3.6)	0.0622 ***
Month 3	**Mean (SD)**	**60.4 (8.9)**	**60.5 (10.9)**	**-0.6 (4.4)**	**0.7 (5.6)**	----	**0.5076 ***
	Median	**58.4**	**57.8**	**0**	**-0.1**	**-1.3 (-3.0,0.3)**	**0.1142 ****
	Min, Max	**47.8, 89.5**	**48.8, 108.0**	**-32.7, 5.5**	**-8.5, 43.6**	**-1.2 (-2.8,0.4)**	**0.1426 *****
Month 6	Mean (SD)	59.9 (8.3)	61.0 (11.3)	-1.1 (5.1)	1.2 (5.7)	----	0.0059 *
	Median	57.9	58.0	-0.5	-0.1	-2.2 (-4.0,-0.5)	0.0129 **
	Min, Max	47.3, 87.5	49.4, 108.0	-36.2, 11.6	-8.5, 43.6	-2.1 (-3.8,-0.4)	0.0177 ***
Month 12	Mean (SD)	59.3 (8.5)	61.0 (11.3)	-1.7 (4.7)	1.2 (5.7)	----	≤0.0001*
	Median	58.0	58.0	-1.0	-0.1	-2.9 (-4.6,-1.2)	0.0010 **
	Min, Max	46.6, 90.9	49.4, 108.0	-31.6, 7.3	-8.5, 43.6	-2.8 (-4.5,-1.1)	0.0015 ***

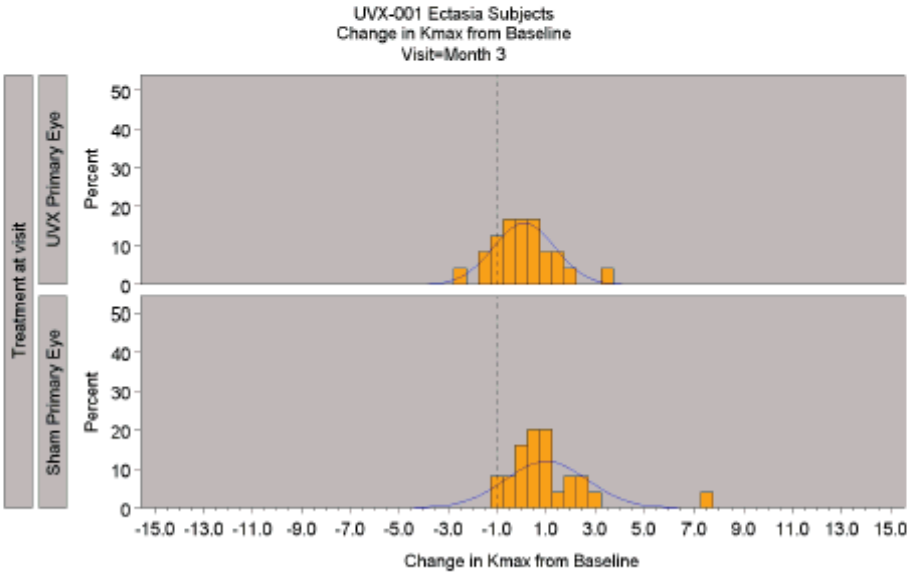


[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-002 CSR Table 14.2.1.1.3 and Reviewer's analysis.

Table 8: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-001, ITT Population; LOCF)

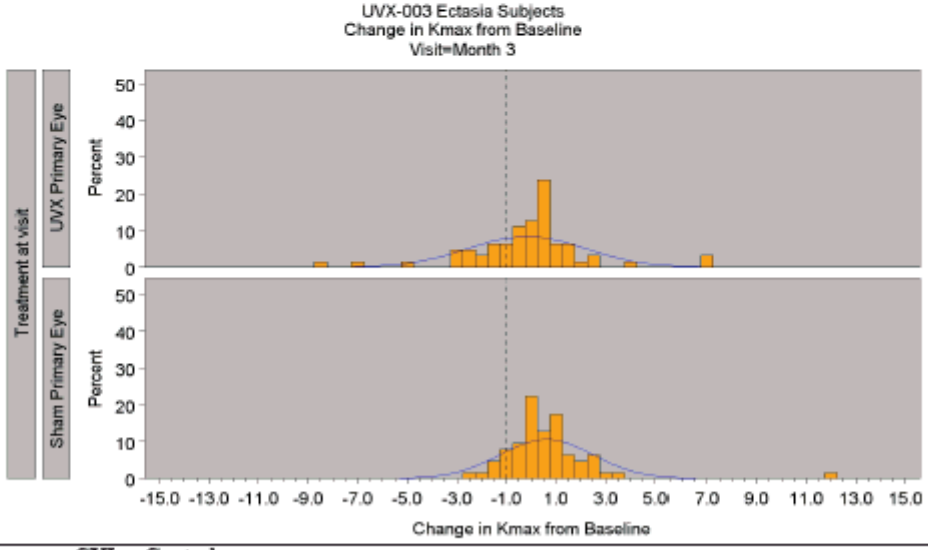
Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline: CXL (N=24)	Change from Baseline: Control (N=25)	Difference 95% CI [1]	p-value [2]
Baseline	Mean (SD)	56.3 (6.3)	55.0 (5.5)				
	Median	56.2	55.2				
	Min, Max	47.4, 71.6	47.0, 68.2				
Month 1	Mean (SD)	57.4 (7.6)	55.8 (6.0)	1.1 (2.1)	0.8 (1.7)	----	0.1966 *
	Median	57.2	55.5	0.9	0.5	0.3 (-0.8,1.3)	0.6408 **
	Min, Max	42.9, 77.0	47.7, 67.1	-4.5, 6.0	-3.0, 6.5	0.1 (-0.9,1.1)	0.8622 ***
Month 3	**Mean (SD)**	**56.4 (7.0)**	**56.0 (6.4)**	**0.1 (1.3)**	**1.0 (1.7)**	**----**	**0.0374 ***
	Median	**55.1**	**56.0**	**0.0**	**0.7**	**-0.9 (-1.8,-0.1)**	**0.0382 ****
	Min, Max	**47.6, 73.8**	**47.6, 70.4**	**-2.5, 3.3**	**-1.0, 7.3**	**-1.1 (-1.8,-0.3)**	**0.0068 *****
Month 6	Mean (SD)	55.7 (6.6)	56.0 (6.2)	-0.6 (1.6)	1.0 (1.7)	----	0.0010 *
	Median	53.2	56.6	-0.8	0.6	-1.7 (-2.6,-0.7)	0.0010 **
	Min, Max	47.7, 70.4	47.6, 70.0	-4.5, 3.3	-1.0, 6.9	-1.7 (-2.7,-0.8)	0.0006 ***
Month 12	Mean (SD)	55.3 (6.6)	56.0 (6.2)	-1.0 (1.7)	1.0 (1.7)	----	<0.0001 *
	Median	53.3	56.6	-0.9	0.6	-2.0 (-3.0,-1.1)	0.0001 **
	Min, Max	47.0, 71.4	47.6, 70.0	-4.6, 3.3	-1.0, 6.9	-2.1 (-3.1,-1.2)	<.0001 ***



[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.
Source: UVX-001 CSR Table 14.2.1.1.2 and Reviewer's analysis.

Table 9: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-003, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline CXL (N=67)	Change from Baseline Control (N=63)	Difference[1]	p-value [2]
Baseline [3]	Mean (SD)	55.1 (7.1)	54.7 (6.8)				
	Median	53.9	52.9				
	Min, Max	44.9, 74.5	42.9, 76.3				
Month 1	Mean (SD)	56.0 (7.0)	54.7 (6.7)	1.0 (1.8)	0.0 (1.1)	----	0.0019 *
	Median	55.7	53.4	0.6	0.1	1.0 (0.4,1.5)	0.0005 **
	Min, Max	45.2, 75.8	43.4, 75.1	-3.1, 5.8	-2.2, 2.4	1.0 (0.4,1.5)	0.0004 ***
Month 3	**Mean (SD)**	**54.9 (7.0)**	**55.3 (6.8)**	**-0.2 (2.4)**	**0.6 (1.9)**	**----**	**0.0418 ***
	Median	**53.4**	**53.8**	**0.1**	**0.5**	**-0.8 (-1.6,-0.0)**	**0.0386 ****
	Min, Max	**44.8, 77.3**	**43.4, 77.6**	**-8.6, 6.8**	**-2.7, 11.9**	**-0.8 (-1.5,-0.0)**	**0.0417 *****
Month 6	Mean (SD)	54.6 (6.6)	55.2 (7.0)	-0.5 (2.0)	0.5 (2.3)	----	0.0045 *
	Median	53.3	53.8	-0.2	0.5	-1.0 (-1.8,-0.3)	0.0084 **
	Min, Max	45.0, 71.4	43.3, 77.6	-8.4, 2.6	-8.6, 11.9	-1.0 -1.7,-0.3)	0.0086 ***
Month 12	Mean (SD)	54.5 (6.8)	55.2 (7.0)	-0.5 (2.2)	0.5 (2.3)	----	0.0017 *
	Median	53.5	54.1	-0.3	0.5	-1.1 (-1.9,-0.3)	0.0080 **
	Min, Max	44.9, 74.3	43.3, 77.6	-10.2, 3.8	-8.6, 11.9	-1.1 (-1.8,-0.3)	0.0087 ***



[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.
[3] **Four subjects in CXL group did not have a K_{max} measurement at baseline.**
Source: UVX-003 CSR Table 14.2.1.1.3 and Reviewer's analysis.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review (dated 12/19/13) of the product labeling based on the applicant's 9/16/13 submission.

DMEPA has not reviewed the substantially complete draft label in this review cycle.

In a 5/22/13 teleconference between representatives from DMPEA and the applicant, DMEPA expressed look-alike and sound-alike concerns with the currently marketed products (b) (4) The applicant was presented with two options:

> 1) Submit the proposed name (b) (4) under the IND and wait for DMEPA to complete their proprietary name review (b) (4) by the IND PDUFA goal date to receive a denial letter
>
> or
>
> 2) Submit a new proposed proprietary name for review under the IND application or when a response is submitted to the "Refusal to File" letter.

In a 2/18/14 teleconference between representatives from DMPEA and the applicant, DMEPA inform the applicant of its safety concerns with the proposed proprietary name Photrexa (b) (4). DMEPA emphasized that the root name "Photrexa" was acceptable (b) (4) The applicant stated that it wished to withdraw the proposed proprietary name request for the "Photrexa" and "Photrexa (b) (4)". DMEPA stated that due to the approaching OND PDUFA date, we are willing to look at two to three names in terms of preliminary safety evaluation submitted via email prior to the official submission to the Agency.

In a 2/18/14 teleconference between representatives from DMPEA and the applicant, DMEPA suggested the modifier "Viscous" as a possible alternative (b) (4) The applicant explained that they had met with their senior management and the thought process was that other chemicals add viscosity to the product and that "Viscous "was too broad" of a term. DMEPA strongly suggested Photrexa Viscous as being the best option at this time with limited naming options.

In a 3/3/15 submission, the applicant submitted the names Photrexa and Photrexa Viscous.

The review Division does not agree that the name "Photrexa Viscous" is appropriate or accurate for the 20% dextran product. The applicant is correct; "viscous does represent 'too broad a term.'"

FINANCIAL DISCLOSURE
Financial disclosure information has been provided by the applicant for the covered clinical studies in this application.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators.* Study designs *were* randomized with predominately objective endpoints; With the exception of Hersch MD, the clinical investigators identified in Form 3455 provided minimal contribution to study data.

After the clinical portion of the application was preliminarily reviewed; an inspection was requested for the following 5 sites:

UVX-001	Stulting, M.D.	107 total patients
UVX-002/003	Hersh, M.D.	84 total patients
UVX-002/003	Price, M.D.	47 total patients
UVX-002/003	Hardten, M.D.	31 total patients
UVX-002/003	Donnenfeld, M.D.	30 total patients

Each of these 5 sites has a potentially significant impact on the study results (see below).

OSI
A routine Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated 2/22/14:

The clinical site of Drs. Stulting, Price, Hardten, Hersh, and Donnenfeld were selected for inspection. The sites above were selected because all enrolled relatively large numbers of subjects and each of the five sites had significant impact on study results. Please note that a large number of subjects discontinued the UXV-001study prematurely because the investigator (Dr. Stulting) left the site; the study was then terminated by the IRB. The proportion of subjects who discontinued the study was 17% and 56% in the treatment and control groups, respectively. Also, the same panel of principal investigators was utilized in both UVX-002 and UVX-003. UVX-002 evaluated keratoconus subjects; UVX-003 evaluated corneal ectasia subjects.

Name of CI, Location	Protocol #/ Site #/ # of primary eyes	Inspection Dates	Final Classification
Francis Price, Jr., M.D. Price Vision Group and Cornea Research Foundation of America 9002 N. Meridian St., Suite 100 Indianapolis, IN 46260	UVX-002/ Site #04/ 26 primary eyes UVX-003/ Site #04/ 21 primary eyes	8-17 Jan 2014	VAI.
David Hardten, M.D., FACS Minnesota Eye Consultants, P.A. 710 E. 24th St., Suite 100 Minneapolis, MN 55404	UVX-002/ Site #10/ 16 primary eyes UVX-003/ Site #10/ 15 primary eyes	14-27 Jan 2014	VAI. Pending final classification.
Peter Hersh, M.D. Cornea and Laser Eye Institute 300 Frank W. Burr Blvd., Suite 71 Teaneck, NJ 07666	UVX-002/ Site #03/ 54 primary eyes UVX-003/ Site #03/ 30 primary eyes	6-16 Jan 2014	NAI. Pending final classification.
Eric D. Donnenfeld, M.D. Ophthalmic Consultants of Long Island 2000 North Village Ave., Suite 402 Rockville Centre, NY 11570	UVX-002/ Site # 02/ 11 primary eyes UVX-003/ Site #02/ 19 primary eyes	21 -29 Jan 2014	VAI. Pending final classification.
Avedro Inc. (sponsor) 230 Third Avenue Waltham MA 02451	UVX-001 UVX-002 UVX-003	3-12 Feb 2014	VAI. Pending final classification.
R. Doyle Stulting, M.D. Current contact information: Woolfson Eye Institute At Emory University: Study Coordinator: Kristin West	UVX-001/ Site # 01/ 107 primary eyes	Ongoing	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

Inspection of Dr. Stulting's clinical investigator site is ongoing. Drs. Price, Hardten, and Donnenfeld, and the sponsor were issued Form FDA 483s. The preliminary classification for all of these inspections is Voluntary Action Indicated (VAI) based on preliminary communications with the field investigators.

Observations were made regarding missing monitoring reports or documentation of review of those reports at the sponsor; however, there does not appear to have been an impact on collection of efficacy or safety data at the clinical sites. Otherwise, based on the inspection

findings available at this time, the studies appear to have been conducted adequately, and the data submitted by this applicant appear acceptable in support of the respective indication.

12. Labeling

NDA 203324, Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) and KXL System, is not recommended for approval for the treatment of corneal ectasia until chemistry and manufacturing inspectional issues are resolved.

NDA 203324, Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) and KXL System, is not recommended for approval (b) (4) There is insufficient data from adequate and well controlled trials to establish the efficacy. The datasets provided for UVX-01 and UVX-002 for the keratoconus indication contain errors. The keratoconus Kmax efficacy data from UVX-001 and -002 should be re-analyzed after non physiologic values are removed. An explanation for the non physiologic values found in the datasets should be provided.

Incomplete, draft labeling is located in this review; additional requests for clinical information will necessitate revision to this labeling. CDRH recommend labeling for the device portion of this application has not been provided in this review cycle.

An edited version of the package insert submitted by the applicant on 9/16/13 is found in the Appendix of this review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 203324, Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) and KXL System, is not recommended for approval for the treatment of corneal ectasia. Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

NDA 203324, Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) and KXL System, is not recommended for approval (b) (4) There is insufficient data from adequate and well controlled trials to establish the efficacy. The datasets provided for UVX-01 and UVX-002 for the keratoconus indication contain errors. The keratoconus Kmax efficacy data from UVX-001 and -002 should be re-analyzed after non physiologic values are removed. An explanation for the non physiologic values found in the datasets should be provided.

RISK BENEFIT ASSESSMENT:
There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery. For both keratoconus and corneal ectasia, early intervention usually involves 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 address the optical irregularity of the cornea. Surgically-implanted intrastromal ring segments may be used to improve contact lens wear in patients who are contact lens intolerant. These treatments do not halt the progression of keratoconus. Corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal transplantation is not without risk – postoperative complications include transplant failure, rejection, secondary cataract, secondary glaucoma, and recurrence of keratoconus in the transplanted graft (Raiskup-Wolf *et al* 2008).

The goal of corneal collagen cross-linking (CXL) is to biomechanically stabilize the weak cornea in keratoconus and postoperative corneal ectasia and decrease the clinical progression of these diseases. In the crosslinking procedure, riboflavin is administered topically to the eye (typically one drop every 2 minutes for 30 minutes). After riboflavin saturation into the corneal stroma, exposure to ultraviolet A (UVA) light (365 nm; 3 mW/cm^2 irradiation; 30 minutes' duration) induces crosslinking.

Normally riboflavin ophthalmic solution containing 20% dextran is used. However, if corneal thickness is < 400 μm riboflavin ophthalmic solution containing no dextran is used until the corneal thickness is 400 μm.

The primary original efficacy endpoint for the applicant's clinical trials was as the difference between the CXL group and the control group in maximum keratometry (Kmax) from baseline to Month 3. At the time the studies were initially planned, the Agency recommended a 12 month endpoint but the applicant believed that the primary efficacy endpoint could be analyzed at 3 months post-procedure based on their review of the existing literature. The applicant reviewed subsequent additional literature which suggested to them that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize.

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for the corneal ectasia indication. The datasets for the keratoconus indication from UVX-001 and UVX-002 contain errors (i.e., non-physiologic values). The applicant will be expected to reanalyze their keratoconus Kmax efficacy data from UVX-001 and -002 after non physiologic values are removed.

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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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. The loss of control subjects makes the analysis of observed data challenging to interpret due to the decreasing sample size at later time points.

The most common adverse events for both the keratoconus and corneal ectasia indications occurring at 10% to 92% in UVX-001, -002, and -003 were corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following the corneal epithelial debridement which accompanied the procedure.

The benefits of the CXL procedure are considered to outweigh the risks for the corneal ectasia indication. The clinical trials performed by the applicant followed these criteria for clinical application of crosslinking:

- corneal epithelium removed to facilitate diffusion of riboflavin throughout the corneal stroma
- 0.1% riboflavin ophthalmic solution be applied for at least 30 minutes before the UV exposure
- UV irradiance of 3 m W/cm^2 and a wavelength of 370 nm must be homogenous
- cornea to be X-linked must have a minimal thickness of 400 μm to protect the endothelium (Spoerl *et al* 2007).

Any potential damage to the corneal endothelium, the lens or the retina is expected to be minimized when these criteria are fulfilled (Spoerl *et al* 2007).

Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology and have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
03/10/2014

WILEY A CHAMBERS
03/10/2014

Deputy Division Director Review of NDA 203324

Date	March 7, 2014
NDA	203324
Applicant	Avedro, Inc.
Date of Submission	September 16, 2013
Established (USAN) name	Riboflavin ophthalmic solution and KXL System
Dosage forms / Strength	Topical ophthalmic solution, 0.1%
Proposed Indication(s)	(b) (4)
Recommended Action:	Not recommended for Approval

1. Introduction

Keratoconus is an ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in corneal optical irregularities. The prevalence of keratoconus is often reported as 1 per 2000 people in the general population. Onset of keratoconus generally occurs during puberty or early adulthood and profoundly affects patients who develop the condition. If left untreated, many patients experience progressive vision impairment, which may result in the need for corneal transplantation.

Corneal ectasia is a well-described complication of refractive surgery. It is a condition similar to keratoconus, but occurs post-operatively. Ectasia may result from unrecognized preoperative keratoconus or from the surgery itself. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities.

There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery. The system or earlier versions proposed in this application have been marketed in other parts of the world for many years, particularly in Europe and South America. In Europe, the product is regulated as a device requiring only a CE mark.

2. Background

Avedro's riboflavin ophthalmic solution/UVA irradiation is a combination product consisting of a UVA 365 nm wavelength light source and riboflavin administered in conjunction with the UVA light as a photosensitizer.

This is a 505(b)(2) application. The applicant is not relying upon literature information concerning the systemic use of riboflavin but not a particular "listed product." A majority of the toxicological data for riboflavin was generated following oral administration because of its use in food or as a dietary supplement. The published literature includes many clinical and non-clinical studies (frequently uncontrolled) using riboflavin and a UV light source. UV light systems marketed for dermatology use have frequently been used. The applicant has conducted corneal crosslinking clinical trials utilizing the final formulations(s) of the to-be-marketed riboflavin.

For this application, the drug product was a sterile, phosphate-buffered saline solution for topical ophthalmic use containing 0.1% riboflavin (Vitamin B2) with and without 20% dextran (b) (4) (b) (4) The UVA irradiation system is a portable electronic medical device. The device's light emitting diode (LED) is used to deliver a metered dose of UVA light to a targeted treatment area for illuminating the

cornea during CXL. The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for these combination products under RFD070013.

Avedro, Inc. opened IND 77,882 with a protocol submission dated November 7, 2007. Avedro, Inc. submitted a request for orphan-drug designation dated May 26, 2011, for riboflavin ophthalmic solution and ultraviolet-A (LTVA) irradiation for corneal cross-linking for the treatment of keratoconus. The Office of Orphan Products Development granted orphan designation for treatment of keratoconus on September 2, 2011.

Avedro, Inc. submitted a request for orphan-drug designation dated August 26, 2011, for riboflavin ophthalmic solution and ultraviolet-A irradiation for "treatment of corneal ectasia following refractive surgery." The Office of Orphan Products Development granted orphan designation for treatment of corneal ectasia following refractive surgery on December 2, 2011.

The primary original efficacy endpoint for the applicant's clinical trials was the difference between the CXL group and the control group in maximum keratometry (Kmax) from baseline to Month 3. At the time the studies were initially planned, the Agency recommended a 12 month endpoint but the applicant believed that the primary efficacy endpoint could be analyzed at 3 months post-procedure based on their review of the existing literature. The applicant reviewed subsequent additional literature which suggested to them that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize.

Avedro, Inc. submitted a New Drug Application (NDA) on March 8, 2012, for their riboflavin ophthalmic solution /KXL System. They received a refuse to file letter dated May 4, 2012. The application was not sufficiently complete to permit a substantive review for reasons which included a proposed formulation which differed from the formulations used in the clinical studies. The Agency refused to file this application under 21 CFR 314.101(d). A post "Refuse-to-File" meeting was held with Avedro, Inc. on May 31, 2012, to discuss the Agency's comments in the RTF letter dated May 4, 2012.

A CMC Type A meeting was held on August 15, 2012, where Avedro committed to revise the commercial formulation information proposed in the NDA to be consistent with the clinical formulations used in the clinical trials. A general advice letter was send on October 19, 2012, in response to the September 24, 2012, submission seeking Agency advice on Avedro's plan for cGMP manufacturing of the drug substance, riboflavin 5'-phosphate sodium and drug product process validation and registration stability.

There are multiple literature articles describing clinical trials of riboflavin and UVA light exposure. They include studies demonstrating the safety and efficacy after 5 years in 40 eyes (Hashemi et al. Corneal Collagen Cross-linking with Riboflavin and Ultraviolet A Irradiation for Keratoconus. Ophthalmology 2013;120:1515–1520.) The safety and efficacy after 4 years in 400 eyes including pediatric patients (Vinciguerra et al. Corneal Cross-Linking as a Treatment for Keratoconus Four-Year Morphologic and Clinical Outcomes with Respect to Patient Age. *Ophthalmology* 2013;120:908–916.) The safety and efficacy after 1-5 years in 26 patients (Richoz et al. Corneal Collagen Cross-Linking for Ectasia after LASIK and Photorefractive Keratectomy Long-Term Results. *Ophthalmology* 2013;120:1354–135.) The safety and efficacy in a three year controlled clinical trial (Wittig-Silva et al. A Randomized, Controlled

Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus Three-Year Results [In Press: *Ophthalmology* 2014]). The safety and efficacy of higher irradiance levels (Chow et al. Intraoperative pachymetry using spectral-domain optical coherence tomography during accelerated corneal collagen crosslinking. *Biomed Research International*. Volume 2013, Article ID 848363, 6 pages. http://dx.doi.org/10.1155/2013/848363.)

3. Product Quality

Two riboflavin ophthalmic solutions have been proposed for marketing. Riboflavin ophthalmic solution is a clear yellow solution containing 0.12% riboflavin 5'-phosphate sodium and 20% dextran in phosphate buffered saline. A second riboflavin solution without dextran was also used in the clinical trials.

The drug substance riboflavin 5'-phosphate sodium is manufactured (b) (4) under DMF (b) (4) A Letter of Authorization to reference this DMF is provided. At the current time this DMF has unresolved deficiencies.

Drug Product Quantitative Composition

Component	Function	Photrexa		Photrexa ZD	
		Amount	mg/g	Amount	mg/g
Riboflavin*	Active	(b) (4)	1.20**	(b) (4)	1.20**
Dextran 500					(b) (4)
Sodium chloride, USP					
Sodium phosphate, monobasic, USP					
Sodium phosphate, dibasic, USP					
Sterile water for injection, USP					
Total					

*Present as riboflavin 5'-phosphate sodium
**Equivalent to 1.46 mg/g riboflavin phosphates

The average drop size for riboflavin drops with dextran is (b) (4) µL and for riboflavin drops without dextran is (b) (4) µL. The proposed marketing container-closure system is a 3 mL clear glass syringe fitted with a plunger with a rubber stopper and a plastic rigid tip cap. The syringe is packaged in a Tyvek pouch and this pouch is placed inside a foil pouch.

As described in the Product Quality review, the drug product specification are not adequate because they do not include tests for degradants (specified, unspecified, and total) and do not include an acceptance criteria for the degradants.

Container-Closure Integrity (CCI) testing was performed (b) (4)
The test is a (b) (4) method (b) (4) The method was validated for both drug products (ReportNS-06986134). The CCI testing was performed on stability lots, and testing met the

acceptance criteria. The drug products are [redacted] filled into single use syringes for topical ophthalmic application. [redacted] Both studies met the acceptance criteria for the [redacted] manufacturing process. No product quality microbiology deficiencies were identified based upon the information provided.

The District Office currently recommends Withhold for the drug product manufacturing site. In a memorandum dated 3/5/14, the Division of Good Manufacturing Practice Assessment Office of Manufacturing & Product Quality states that The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection conducted by [redacted] District ([redacted]-DO) from [redacted] at the [redacted] facility. This site is listed as the [redacted] drug product manufacturer in support of this NDA. DGMPA has also reviewed the firm's [redacted] written response to the 483 observations. According to [redacted]-DO, the inspection was initially classified OAI for NDA specific coverage with a withhold recommendation. After an evaluation of the firm's response [redacted]-DO re-affirmed their withhold recommendation. DGMPA concurred with the [redacted]-DO's withhold recommendation for the [redacted] facility. The FDA Form-483 included twelve observations with the first two to be the most significant, product specific observations. More data are expected to come in an amendment by March 28, 2014. Until the data are received and evaluated to be adequate, the deficiencies are still outstanding and impact application action.

4. Nonclinical Pharmacology/Toxicology

All nonclinical safety and pharmacology data cited in the NDA are from published, publicly available research articles. The surface UVA dose proposed for human use, 3 mW/cm^2, was reported to result in endothelial toxicity in the rabbit. The applicant however responded that the endothelial dose resulting from this surface dose would not cause endothelial toxicity in humans, because the resultant endothelial dose is lower in humans than in rabbit. This difference in the calculated endothelial doses between humans and rabbits is based on differences in the absorption coefficient of the riboflavin treated corneas of humans and rabbits.

5. Clinical Pharmacology/Biopharmaceutics

There were no pharmacokinetic studies conducted to determine the actual systemic exposures to riboflavin following topical ocular instillation of the 0.12% riboflavin ophthalmic solutions during one-time corneal collagen crosslinking treatment. Assuming 100% bioavailability of riboflavin following topical ocular instillation of the proposed 0.12% riboflavin eyedrops, the average systemic exposure to riboflavin during one-time CCXL treatment of one eye in the 12-month UVX trials would not exceed [redacted] mg, which is below the Joint FAO/WHO Expert Committee on Food Additives upper limit of acceptable oral daily intake of riboflavin (35 mg for a 70 kg person).

6. Clinical/Statistical - Efficacy

The clinical development program of riboflavin ophthalmic solution/UVA irradiation in the treatment of keratoconus involved 2 studies, UVX-001 and UVX-002. The clinical development program of riboflavin

ophthalmic solution/UVA irradiation in the treatment of corneal ectasia following refractive surgery involved 2 studies, UVX-001 and UVX-003.

The studies were nearly identical in design and conduct. However, UVX-001 had a mixed population of subjects with corneal ectasia and keratoconus, whereas only corneal ectasia subjects were enrolled in UVX-003. Further, UVX-001 was a single-center study, and UVX-003 involved 9 sites. All sites were located in the US.

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 (Kmax), quantifies the pathognomonic feature of keratoconus and corneal ectasia. Based on the etiology and manifestation of keratoconus and corneal ectasia, Kmax was accepted by the Agency as a clinically meaningful and reproducible endpoint to be measured in these patient populations. For each study, the primary efficacy endpoint was corneal curvature, as measured by Kmax.

The intent-to-treat (ITT) population consisted of all treated subjects, analyzed according to the randomized treatment. All safety and efficacy analyses were performed using the ITT population. All subjects received the appropriate randomized treatment; therefore, the ITT and safety populations are the same.
The applicant's dataset contains errors. For example, Kmax cannot be zero (Control Group, Month 1); change from baseline cannot be -62 (Control Group, Month 1). This is just one of the errors where non-physiological values have been included. As seen in the graphs provided below, there are "outliers" which have a significant effect on the reported results. If the values are typographical errors, they will need to be re-entered and the analysis re-run. If they represent variability in the measurement such that an accurate assessment of the corneal curvature cannot be obtained by this method, additional data will need to be obtained.

Analysis of Primary Endpoint(s)
UVX-001 Keratoconus

Table 25: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF) - (Keratoconus Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline: CXL Group (N=29)	Change from Baseline: Control Group (N=29)	P-value[a]
Baseline	n	29	29			
	Mean	60.6	61.9			
	SD	7.34	8.32			
	Median	59.2	62.0			
	Min, Max	50, 79	48, 81			
Month 1	n	29	29	29	29	
	Mean	62.0	58.9	1.4	−2.9	0.0563
	SD	8.41	14.07	2.68	11.66	
	Median	60.1	58.9	0.9	−0.3	
	Min, Max	52, 89	−0, 79	−1, 14	−62, 5	
Month 3	n	29	29	29	29	
	Mean	60.3	62.0	−0.3	0.1	0.5085
	SD	8.23	9.38	2.68	2.61	
	Median	58.3	60.8	−0.7	−0.1	
	Min, Max	48, 86	48, 87	−5, 11	−7, 7	
Month 6	n	29	29	29	29	
	Mean	59.7	62.3	−0.9	0.5	0.0674
	SD	8.10	9.52	2.61	2.99	
	Median	57.7	60.8	−1.1	0.0	
	Min, Max	48, 83	48, 84	−5, 7	−7, 8	
Month 12	n	29	29	29	29	
	Mean	59.2	62.3	−1.4	0.5	0.0175
	SD	7.82	9.52	2.84	2.99	
	Median	58.4	60.8	−1.0	0.0	
	Min, Max	49, 83	48, 84	−8, 7	−7, 8	

[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)
Source: Table 14.2.1.1.2 (Section 14.2.1)

UVX-001 Corneal Ectasia

Table 38: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF) - (Corneal Ectasia Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline: CXL Group (N=24)	Change from Baseline: Control Group (N=25)	P-value[a]
Baseline	n	24	25			
	Mean	56.3	55.0			
	SD	6.26	5.45			
	Median	56.2	55.2			
	Min, Max	47, 72	47, 68			
Month 1	n	24	25	24	25	
	Mean	57.4	55.8	1.1	0.8	0.6408
	SD	7.59	5.96	2.06	1.73	
	Median	57.2	55.5	0.9	0.5	
	Min, Max	43, 77	48, 67	–5, 6	–3, 7	
Month 3	n	24	25	24	25	
	Mean	56.4	56.0	0.1	1.0	0.0382
	SD	7.02	6.40	1.26	1.68	
	Median	55.1	56.0	0.0	0.7	
	Min, Max	48, 74	48, 70	–3, 3	–1, 7	
Month 6	n	24	25	24	25	
	Mean	55.7	56.0	–0.6	1.0	0.0010
	SD	6.60	6.19	1.61	1.69	
	Median	53.2	56.6	–0.8	0.6	
	Min, Max	48, 70	48, 70	–5, 3	–1, 7	
Month 12	n	24	25	24	25	
	Mean	55.3	56.0	–1.0	1.0	0.0001
	SD	6.62	6.19	1.68	1.69	
	Median	53.3	56.6	–0.9	0.6	
	Min, Max	47, 71	48, 70	–5, 3	–1, 7	

[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)
Source: Table 14.2.1.1.2 (Section 14.2.2)

UVX-002 Keratoconus

Table 15: Mean Changes from Baseline K_{max} in the Randomized Study Eye: LOCF (UVX-002, ITT Population)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline: CXL Group (N=73)	Change from Baseline: Control Group (N=74)	P-value[a]
Baseline	n	73	74			
	Mean	61.0	59.8			
	SD	9.81	9.16			
	Median	58.0	57.5			
	Min, Max	48, 96	48, 90			
Month 1	n	73	74	73	74	
	Mean	62.2	59.3	1.2	–0.5	0.0678
	SD	9.37	11.91	3.36	7.18	
	Median	59.4	57.3	1.0	–0.0	
	Min, Max	49, 94	0, 91	–17, 8	–58, 8	
Month 3	n	73	74	73	74	
	Mean	60.4	60.5	–0.6	0.7	0.1142
	SD	8.92	10.91	4.44	5.58	
	Median	58.4	57.8	0.0	–0.1	
	Min, Max	48, 90	49, 108	–33, 6	–9, 44	
Month 6	n	73	74	73	74	
	Mean	59.9	61.0	–1.1	1.2	0.0129
	SD	8.34	11.25	5.06	5.71	
	Median	57.9	58.0	–0.5	–0.1	
	Min, Max	47, 88	49, 108	–36, 12	–9, 44	
Month 12	n	73	74	73	74	
	Mean	59.3	61.0	–1.7	1.2	0.0010
	SD	8.50	11.25	4.69	5.70	
	Median	58.0	58.0	–1.0	–0.1	
	Min, Max	47, 91	49, 108	–32, 7	–9, 44	

[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).
Source: Table 14.2.1.1.3 (Section 14.2.1)

UVX-003 Corneal Ectasia

Table 15: Mean Changes from Baseline K_{max} in the Randomized Study Eye: LOCF (UVX-003, ITT Population)

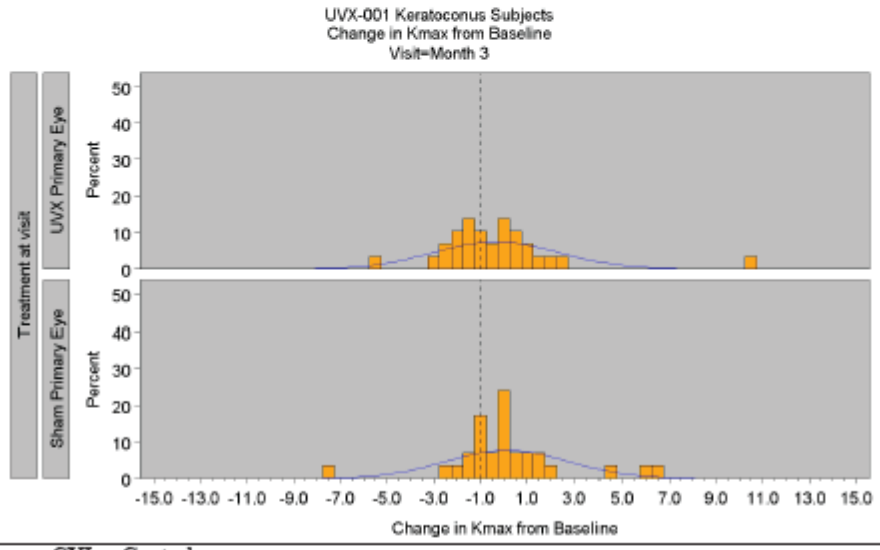
Visit	Statistic	CXL Group (N=67)[a]	Control Group (N=63)	Change from Baseline: CXL Group (N=67)[a]	Change from Baseline: Control Group (N=63)	P-value[b]
Baseline	n	63	63			
	Mean	55.1	54.7			
	SD	7.09	6.77			
	Median	53.9	52.9			
	Min, Max	45, 75	43, 76			
Month 1	n	67	63	63	63	
	Mean	56.0	54.7	1.0	0.0	0.0005
	SD	7.04	6.67	1.84	1.10	
	Median	55.7	53.4	0.6	0.1	
	Min, Max	45, 76	43, 75	–3, 6	–2, 2	
Month 3	n	67	63	63	63	
	Mean	54.9	55.3	–0.2	0.6	0.0386
	SD	6.99	6.81	2.38	1.88	
	Median	53.4	53.8	0.1	0.5	
	Min, Max	45, 77	43, 78	–9, 7	–3, 12	
Month 6	n	67	63	63	63	
	Mean	54.6	55.2	–0.5	0.5	0.0084
	SD	6.64	6.96	1.95	2.28	
	Median	53.3	53.8	–0.2	0.5	
	Min, Max	45, 71	43, 78	–8, 3	–9, 12	
Month 12	n	67	63	63	63	
	Mean	54.5	55.2	–0.5	0.5	0.0080
	SD	6.85	6.97	2.21	2.26	
	Median	53.5	54.1	–0.3	0.5	
	Min, Max	45, 74	43, 78	–10, 4	–9, 12	

[a] Four subjects did not have a K_{max} measurement at baseline.
[b] 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).
Source: Table 14.2.1.1.3 (Section 14.2.1)

Tables 6-9 from the Statistical Review:

Table 6: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-001, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline CXL (N=29)	Change from Baseline Control (N=29)	Difference[1]	p-value [2]
Baseline	Mean (SD)	60.6 (7.3)	61.9 (8.3)				
	Median	59.2	62.0				
	Min, Max	49.5, 79.2	47.7, 81.3				
Month 1	Mean (SD)	62.0 (8.4)	58.9 (14.1)	1.4 (2.7)	-2.9 (11.7)	----	0.0002 *
	Median	60.1	58.9	0.9	-0.3	4.3 (-0.1,8.8)	0.0563 **
	Min, Max	51.5, 89.4	-0.3, 78.6	-1.4, 13.9	-62.3, 4.8	4.3 (-0.2,8.9)	0.0587 ***
Month 3	**Mean (SD)**	**60.3 (8.2)**	**62.0 (9.4)**	**-0.3 (2.7)**	**0.1 (2.6)**	----	**0.2048 ***
	Median	**58.3**	**60.8**	**-0.7**	**-0.1**	**-0.5 (-1.9,0.9)**	**0.5085 ****
	Min, Max	**48.0, 86.2**	**47.5, 87.4**	**-5.4, 10.7**	**-7.4, 6.6**	**-0.4 (-1.7,1.0)**	**0.5918 *****
Month 6	Mean (SD)	59.7 (8.1)	62.3 (9.5)	-0.9 (2.6)	0.5 (3.0)	----	0.0557 *
	Median	57.7	60.8	-1.1	0	-1.4 (-2.9,0.1)	0.0674 **
	Min, Max	48.0, 82.6	47.5, 84.1	-5.2, 7.1	-6.8, 7.6	-1.3 (-2.8,0.2)	0.0838 ***
Month 12	Mean (SD)	59.2 (7.8)	62.3 (9.5)	-1.4 (2.8)	0.5 (3.0)	----	0.0170 *
	Median	58.4	60.8	-1.0	0	-1.9 (-3.4,-0.3)	0.0175 **
	Min, Max	48.6, 82.6	47.5, 84.1	-7.8, 7.1	-6.8, 7.6	-1.8 (-3.4,-0.3)	0.0217 ***

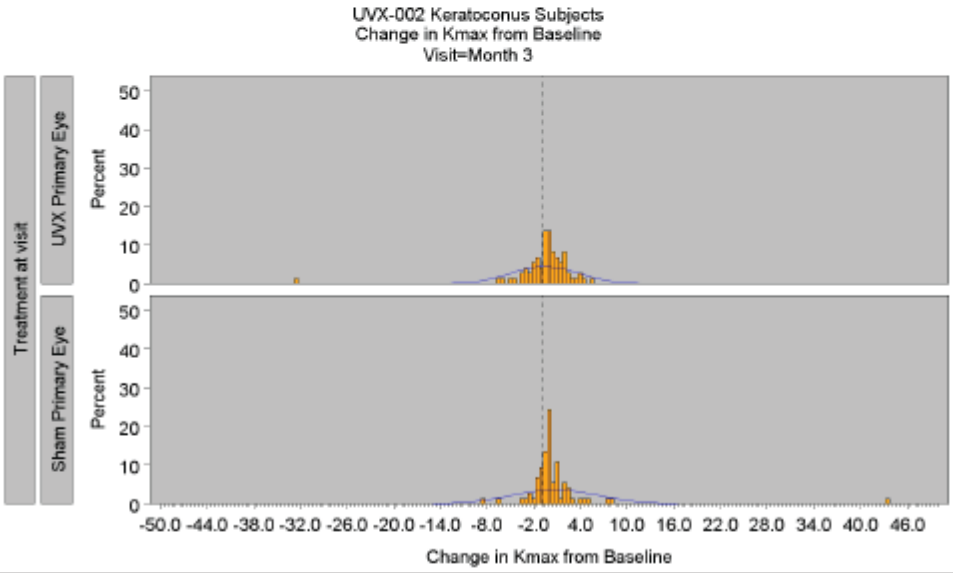


[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-001 CSR Table 14.2.1.1.2 and Reviewer's analysis.

Table 7: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-002, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline CXL (N=73)	Change from Baseline Control (N=74)	Difference[1]	p-value [2]
Baseline	Mean (SD)	61.0 (9.8)	59.8 (9.2)				
	Median	58.0	57.5				
	Min, Max	47.8, 96.4	48.3, 90.3				
Month 1	Mean (SD)	62.2 (9.4)	59.3 (11.9)	1.2 (3.4)	-0.5 (7.2)	----	0.0009 *
	Median	59.4	57.3	1.0	-0.1	1.7 (-0.1,3.5)	0.0678 **
	Min, Max	49.3, 93.8	0, 91.3	-16.8, 8.1	-58.4, 8.0	1.7 (-0.1,3.6)	0.0622 ***
Month 3	**Mean (SD)**	**60.4 (8.9)**	**60.5 (10.9)**	**-0.6 (4.4)**	**0.7 (5.6)**	----	**0.5076 ***
	Median	**58.4**	**57.8**	**0**	**-0.1**	**-1.3 (-3.0,0.3)**	**0.1142 ****
	Min, Max	**47.8, 89.5**	**48.8, 108.0**	**-32.7, 5.5**	**-8.5, 43.6**	**-1.2 (-2.8,0.4)**	**0.1426 *****
Month 6	Mean (SD)	59.9 (8.3)	61.0 (11.3)	-1.1 (5.1)	1.2 (5.7)	----	0.0059 *
	Median	57.9	58.0	-0.5	-0.1	-2.2 (-4.0,-0.5)	0.0129 **
	Min, Max	47.3, 87.5	49.4, 108.0	-36.2, 11.6	-8.5, 43.6	-2.1 (-3.8,-0.4)	0.0177 ***
Month 12	Mean (SD)	59.3 (8.5)	61.0 (11.3)	-1.7 (4.7)	1.2 (5.7)	----	<0.0001*
	Median	58.0	58.0	-1.0	-0.1	-2.9 (-4.6,-1.2)	0.0010 **
	Min, Max	46.6, 90.9	49.4, 108.0	-31.6, 7.3	-8.5, 43.6	-2.8 (-4.5,-1.1)	0.0015 ***

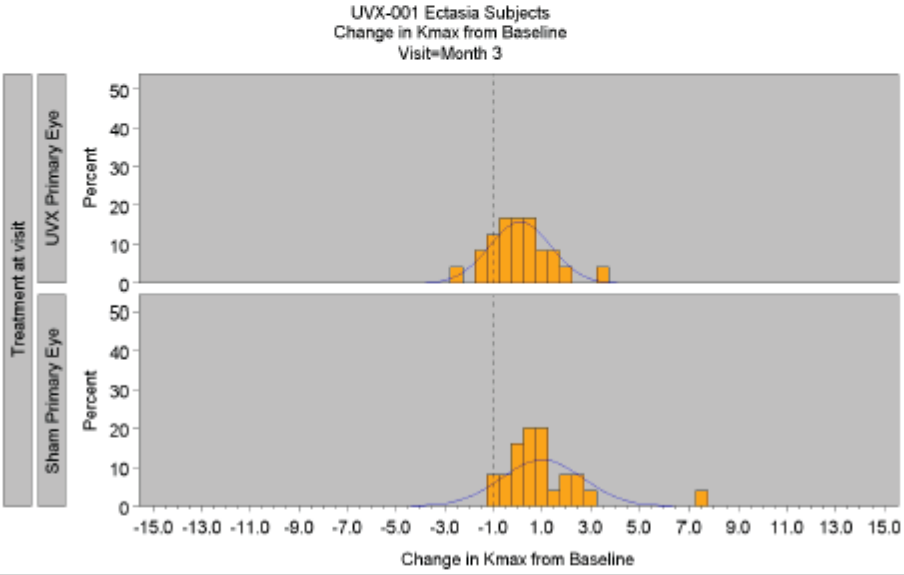


[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-002 CSR Table 14.2.1.1.3 and Reviewer's analysis.

Table 8: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-001, ITT Population; LOCF)

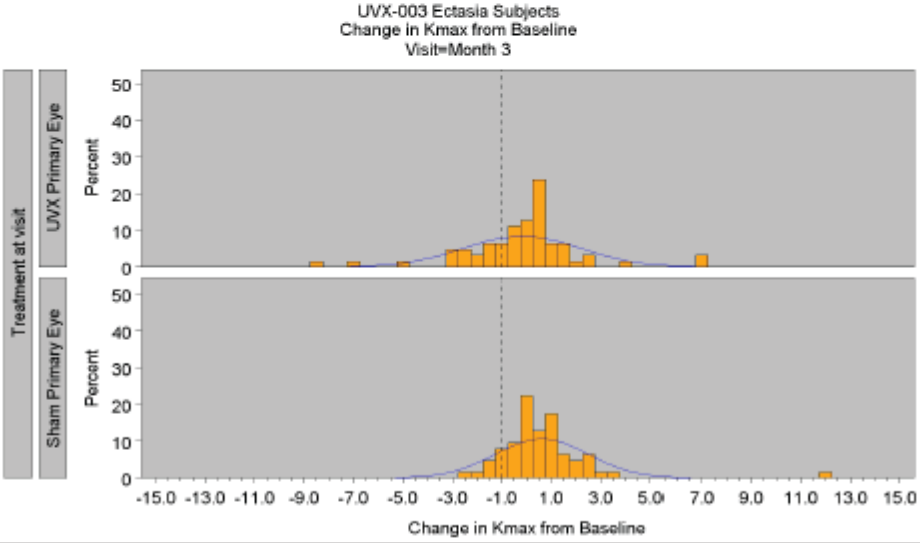
Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline CXL (N=24)	Change from Baseline Control (N=25)	Difference 95% CI [1]	p-value [2]
Baseline	Mean (SD)	56.3 (6.3)	55.0 (5.5)				
	Median	56.2	55.2				
	Min, Max	47.4, 71.6	47.0, 68.2				
Month 1	Mean (SD)	57.4 (7.6)	55.8 (6.0)	1.1 (2.1)	0.8 (1.7)	----	0.1966 *
	Median	57.2	55.5	0.9	0.5	0.3 (-0.8,1.3)	0.6408 **
	Min, Max	42.9, 77.0	47.7, 67.1	-4.5, 6.0	-3.0, 6.5	0.1 (-0.9,1.1)	0.8622 ***
Month 3	**Mean (SD)**	**56.4 (7.0)**	**56.0 (6.4)**	**0.1 (1.3)**	**1.0 (1.7)**	----	**0.0374 ***
	Median	**55.1**	**56.0**	**0.0**	**0.7**	**-0.9 (-1.8,-0.1)**	**0.0382 ****
	Min, Max	**47.6, 73.8**	**47.6, 70.4**	**-2.5, 3.3**	**-1.0, 7.3**	**-1.1 (-1.8,-0.3)**	**0.0068 *****
Month 6	Mean (SD)	55.7 (6.6)	56.0 (6.2)	-0.6 (1.6)	1.0 (1.7)	----	0.0010 *
	Median	53.2	56.6	-0.8	0.6	-1.7 (-2.6,-0.7)	0.0010 **
	Min, Max	47.7, 70.4	47.6, 70.0	-4.5, 3.3	-1.0, 6.9	-1.7 (-2.7,-0.8)	0.0006 ***
Month 12	Mean (SD)	55.3 (6.6)	56.0 (6.2)	-1.0 (1.7)	1.0 (1.7)	----	<0.0001 *
	Median	53.3	56.6	-0.9	0.6	-2.0 (-3.0,-1.1)	0.0001 **
	Min, Max	47.0, 71.4	47.6, 70.0	-4.6, 3.3	-1.0, 6.9	-2.1 (-3.1,-1.2)	<.0001 ***



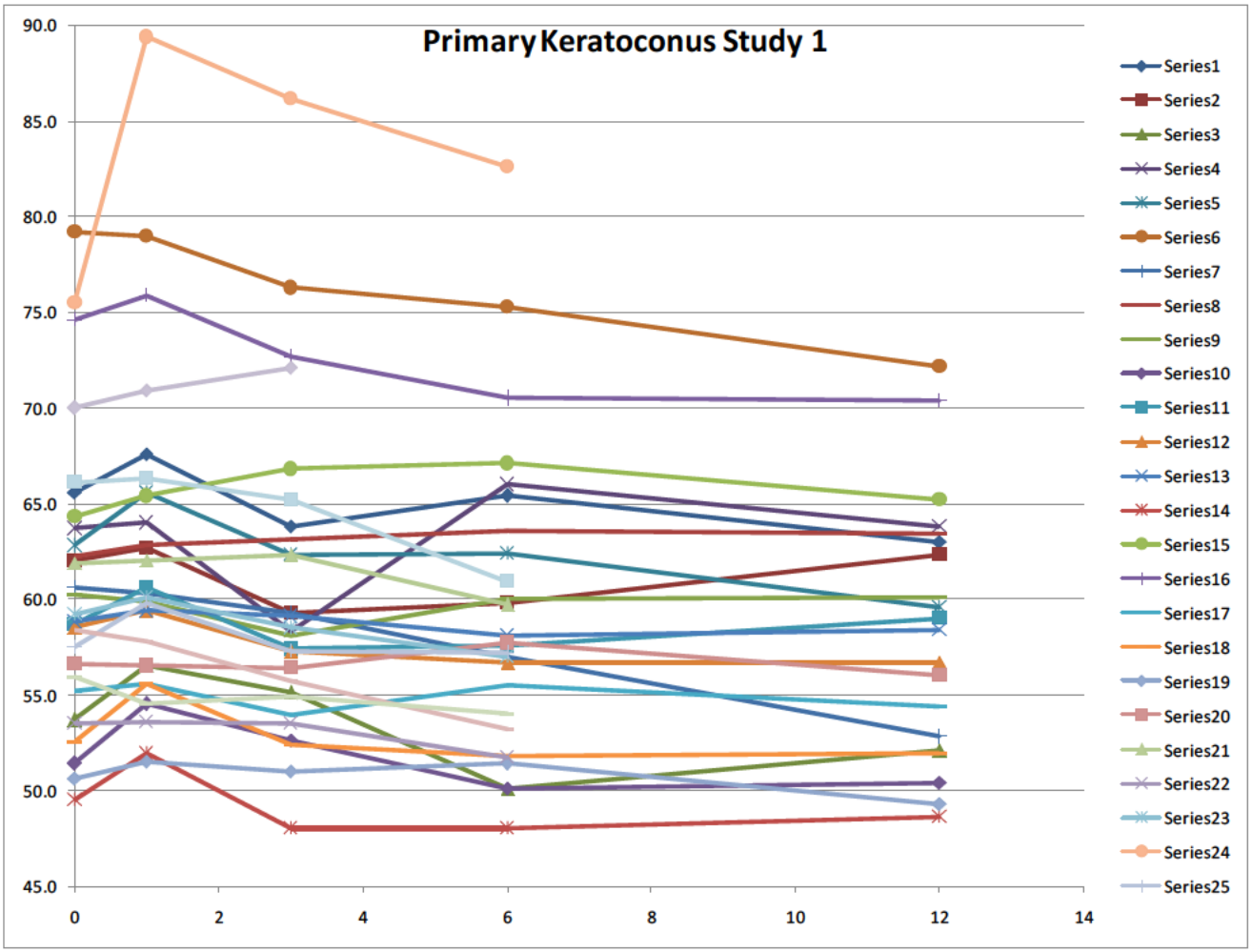
[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.
Source: UVX-001 CSR Table 14.2.1.1.2 and Reviewer's analysis.

Table 9: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-003, ITT Population; LOCF)

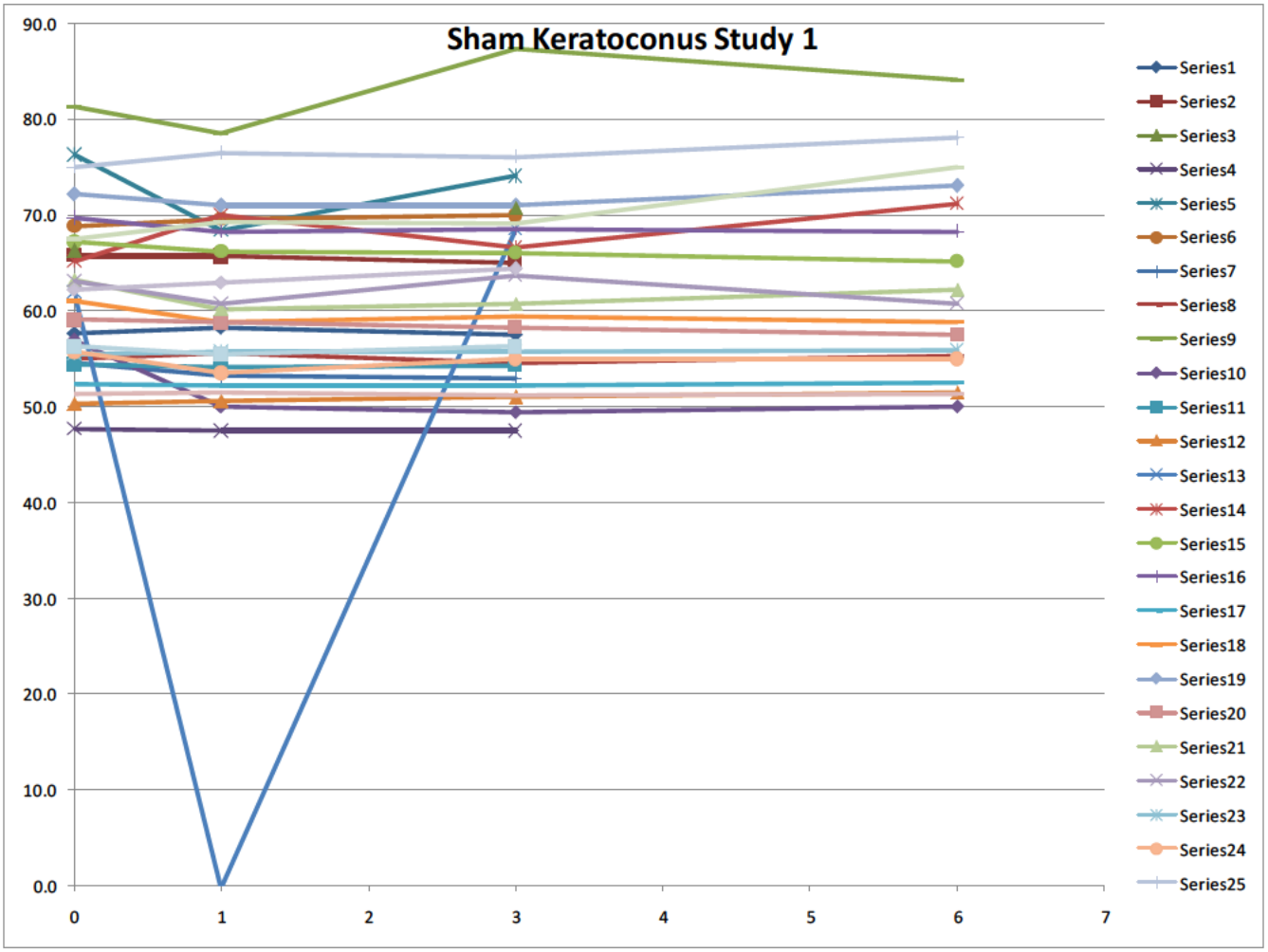
Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline CXL (N=67)	Change from Baseline Control (N=63)	Difference[1]	p-value [2]
Baseline [3]	Mean (SD)	55.1 (7.1)	54.7 (6.8)				
	Median	53.9	52.9				
	Min, Max	44.9, 74.5	42.9, 76.3				
Month 1	Mean (SD)	56.0 (7.0)	54.7 (6.7)	1.0 (1.8)	0.0 (1.1)	----	0.0019 *
	Median	55.7	53.4	0.6	0.1	1.0 (0.4,1.5)	0.0005 **
	Min, Max	45.2, 75.8	43.4, 75.1	-3.1, 5.8	-2.2, 2.4	1.0 (0.4,1.5)	0.0004 ***
Month 3	**Mean (SD)**	**54.9 (7.0)**	**55.3 (6.8)**	**-0.2 (2.4)**	**0.6 (1.9)**	----	**0.0418 ***
	Median	**53.4**	**53.8**	**0.1**	**0.5**	**-0.8 (-1.6,-0.0)**	**0.0386 ****
	Min, Max	**44.8, 77.3**	**43.4, 77.6**	**-8.6, 6.8**	**-2.7, 11.9**	**-0.8 (-1.5,-0.0)**	**0.0417 *****
Month 6	Mean (SD)	54.6 (6.6)	55.2 (7.0)	-0.5 (2.0)	0.5 (2.3)	----	0.0045 *
	Median	53.3	53.8	-0.2	0.5	-1.0 (-1.8,-0.3)	0.0084 **
	Min, Max	45.0, 71.4	43.3, 77.6	-8.4, 2.6	-8.6, 11.9	-1.0 -1.7,-0.3)	0.0086 ***
Month 12	Mean (SD)	54.5 (6.8)	55.2 (7.0)	-0.5 (2.2)	0.5 (2.3)	----	0.0017 *
	Median	53.5	54.1	-0.3	0.5	-1.1 (-1.9,-0.3)	0.0080 **
	Min, Max	44.9, 74.3	43.3, 77.6	-10.2, 3.8	-8.6, 11.9	-1.1 (-1.8,-0.3)	0.0087 ***



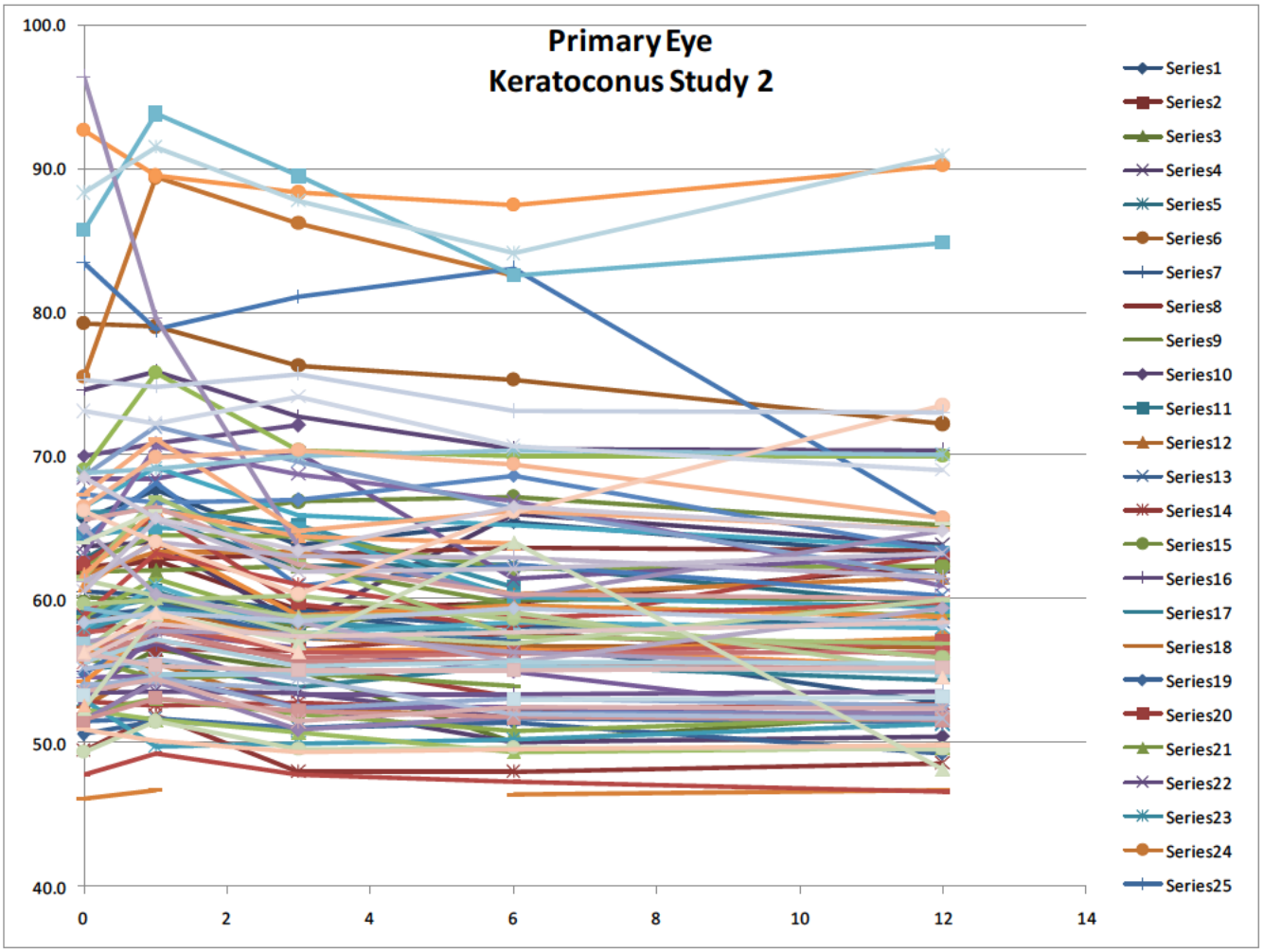
[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.
[3] **Four subjects in CXL group did not have a K_{max} measurement at baseline.**
Source: UVX-003 CSR Table 14.2.1.1.3 and Reviewer's analysis.



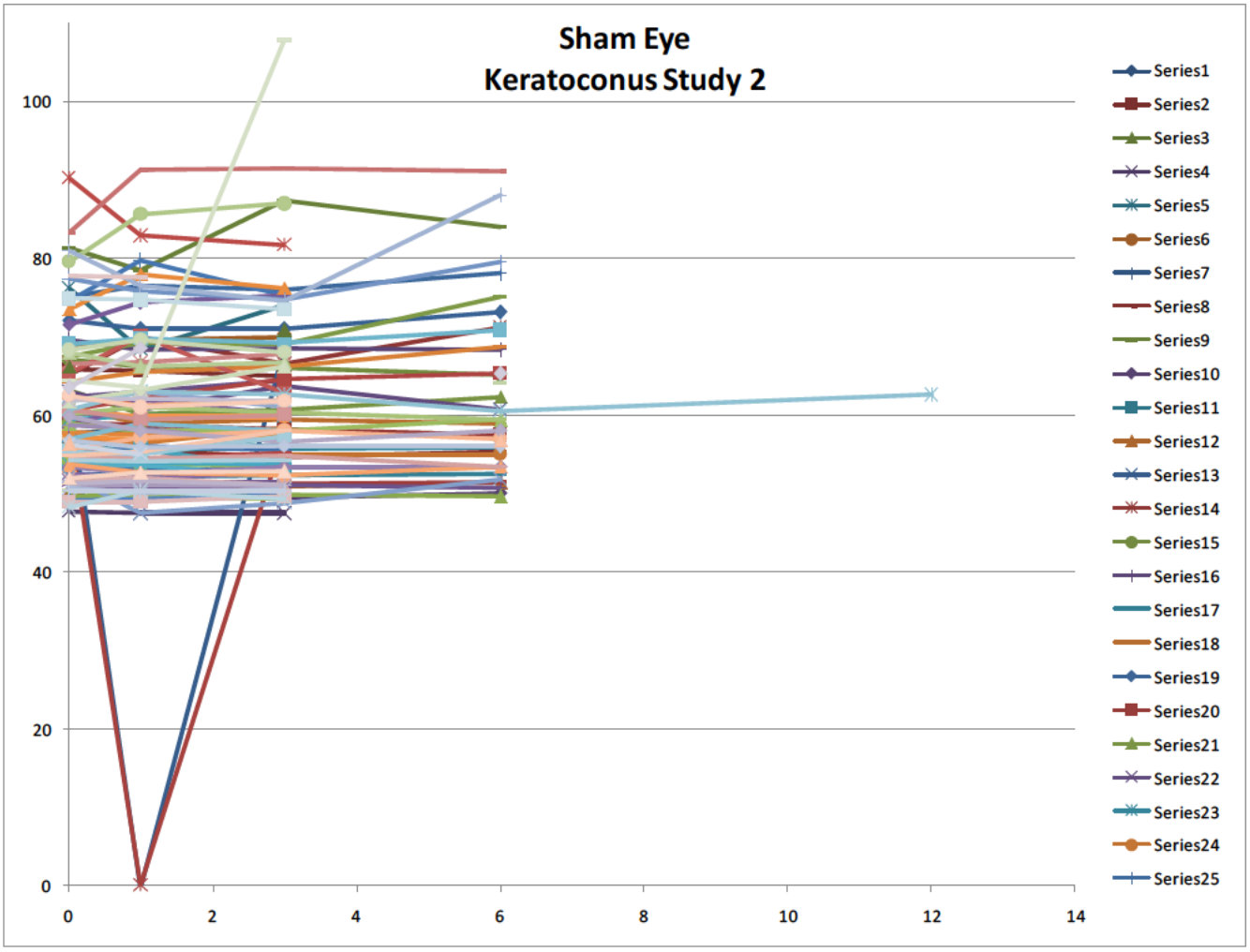
This graph demonstrates an increase in Kmax at the first month, followed by a progressive decrease in Kmax in a significant number of patients between Months 3 and 12. The decrease in Kmax is considered a clinically significant effect.



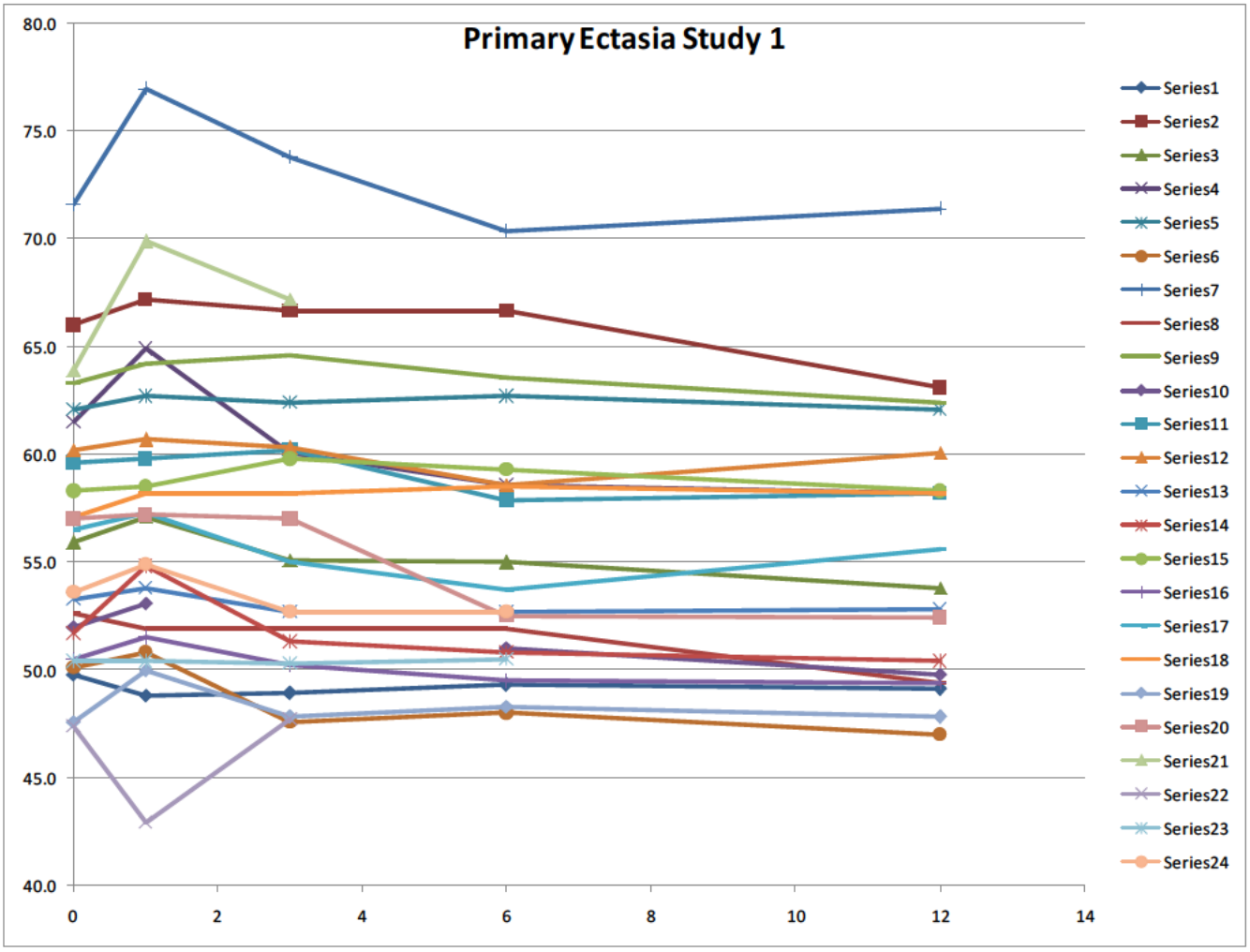
This graph demonstrates a gradual increase in Kmax however it also shows a non-physiologic value.



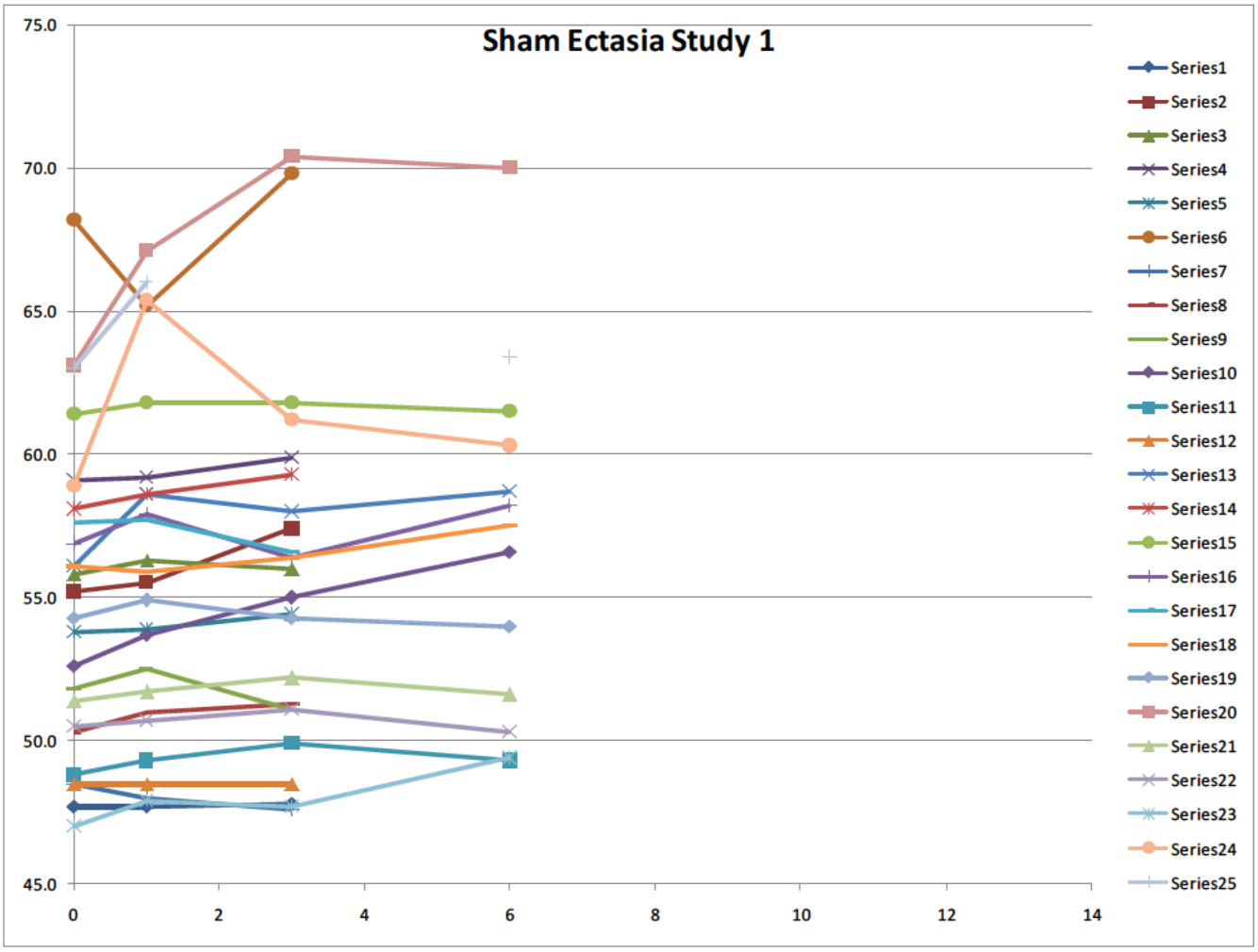
This graph demonstrates an increase in Kmax at the first month, followed by a progressive decrease in Kmax in a significant number of patients between Months 3 and 12. However, there are a number of outliers which raise questions about the validity of the data.



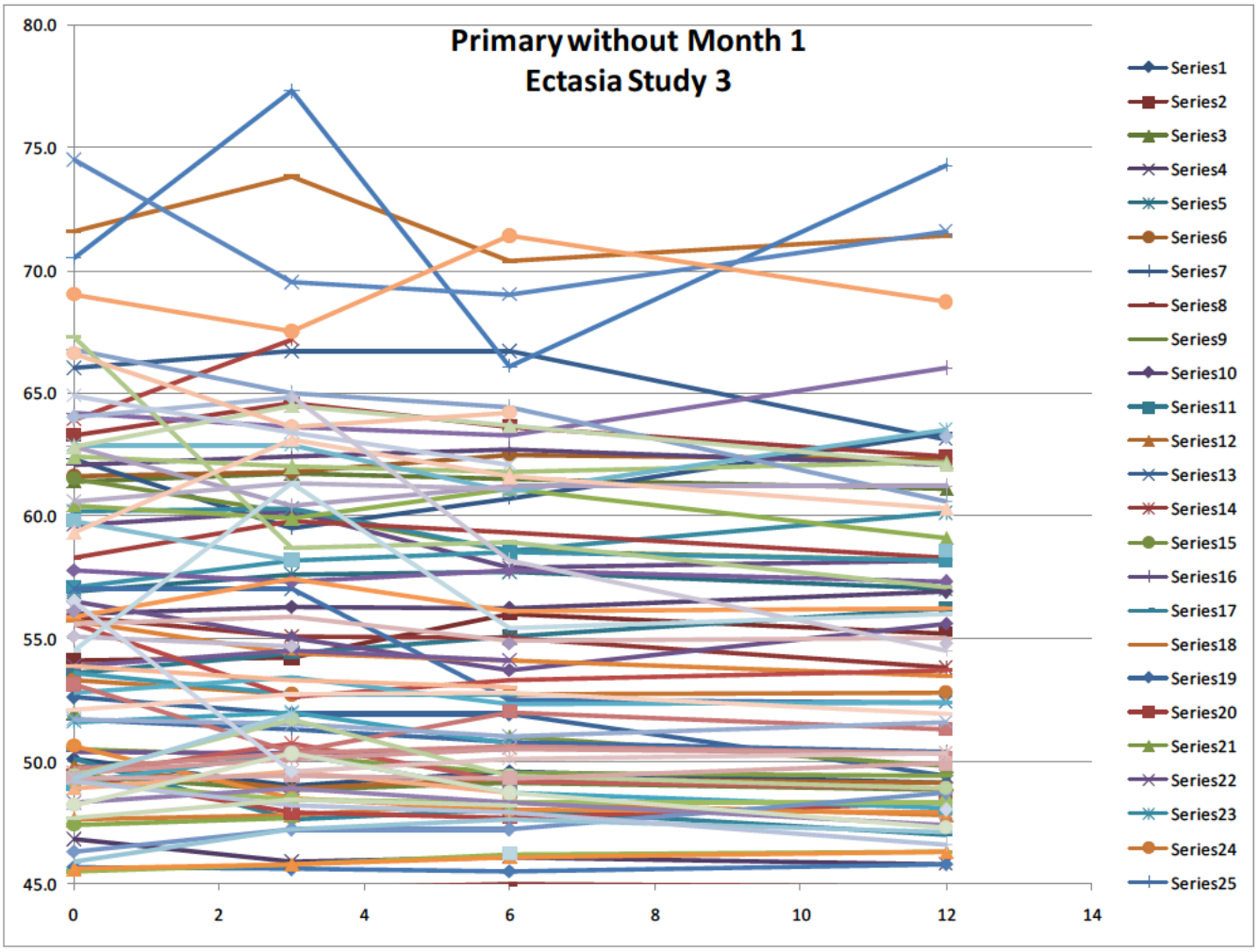
This graph demonstrates a gradual increase in Kmax however it also shows a non-physiologic value.



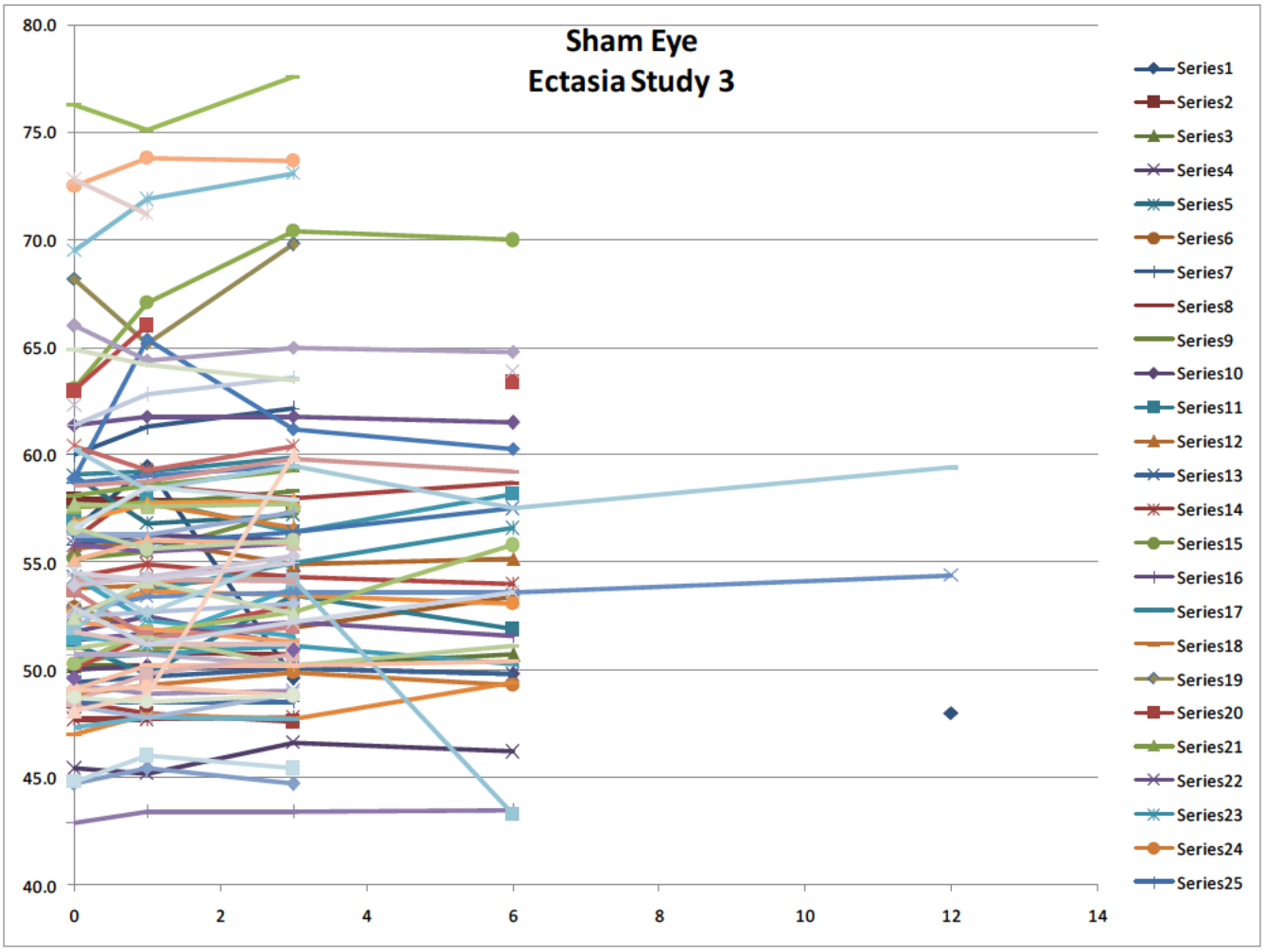
This graph demonstrates an increase in Kmax at the first month, followed by a progressive decrease in Kmax in a significant number of patients between Months 3 and 12. The decrease in Kmax is considered a clinically significant effect.



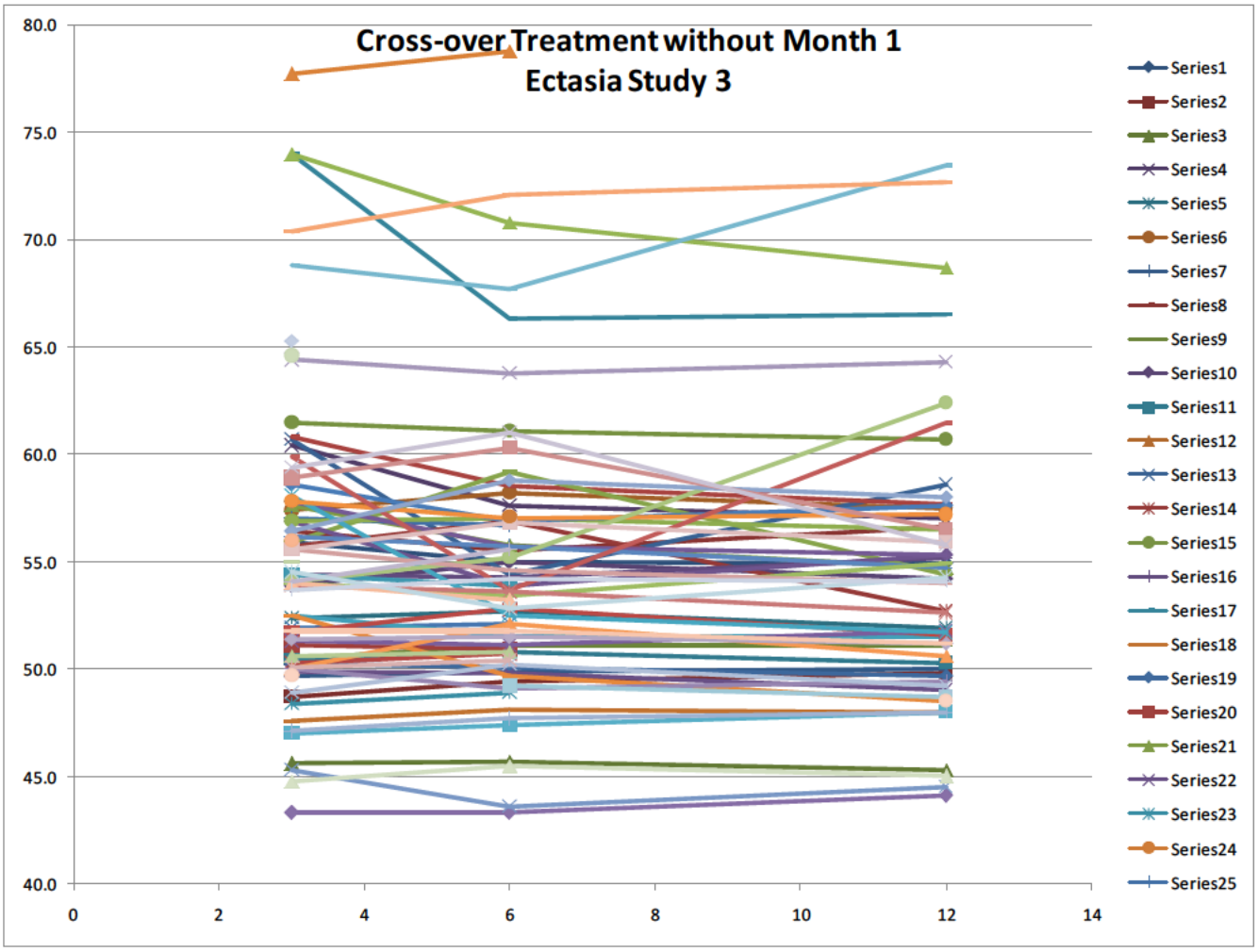
This graph demonstrates a gradual increase in Kmax.



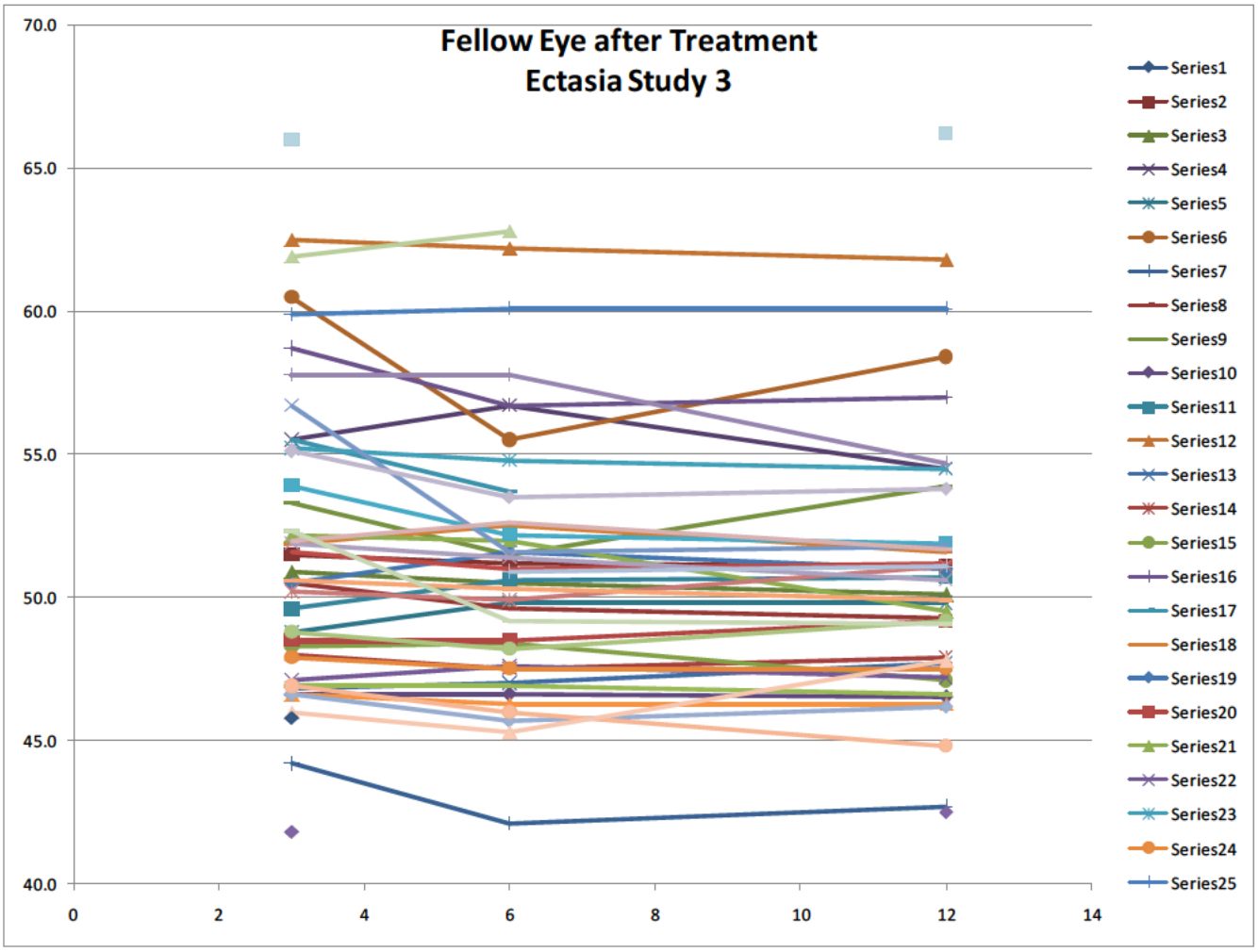
This graph demonstrates a decrease in Kmax in a significant number of patients between Months 3 and 12. An increase was observed during the first month, but is not included in this graph to improve readability. The decrease in Kmax is considered a clinically significant effect.



This graph demonstrates a gradual increase in Kmax in multiple patients.



Eyes treated with Sham were allowed to be crossed over to treatment. Shown above is the follow-up after cross-over treatment.



The fellow eye of a treated eye was allowed to be treated three to six months after the primary eye had been treated. The follow-up of these eyes is shown above. Many eyes had a decrease in Kmax.

Summary Efficacy Statement

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for the corneal ectasia indication. The datasets for the keratoconus indication from UVX-001 and UVX-002 contain errors (i.e., non-physiologic values) and the results are driven by "outliers." The applicant will be expected to reanalyze their keratoconus Kmax efficacy data from UVX-001 and -002 after non physiologic values are removed and account for the impact of the outliers.

7. Safety

All CXL-treated eyes received the same UVA irradiation treatment (365 nm at an irradiance of 3 mW/cm^2 for 30 minutes). Sham-treated eyes underwent the same UV irradiation procedure except the UVA light source was not illuminated during the procedure. For both indications, the mean number of drops of riboflavin with dextran administered prior to the UVA procedure (or mock procedure in sham eyes) and during the UVA procedure (or mock procedure in sham eyes) was approximately 16 and 15 drops, respectively. CXL-treated eyes that did not meet the requirement for corneal thickness ≥ 400 microns after UVA pre-treatment with riboflavin plus dextran received a second solution of riboflavin without dextran. No subjects received CXL treatment more than once in the same eye. Subjects who received CXL in untreated fellow eyes (from CXL group) and untreated sham eye and untreated fellow eye (from control group) received CXL at least 3 months after the initial randomized treatment. The Table below summarizes the number of eyes treated with any CXL in the pooled keratoconus and corneal ectasia studies (i.e., primary study eyes randomized to CXL, primary study eyes randomized to control which subsequently received CXL, and fellow eyes in either treatment group which received CXL).

Common Adverse Events UVX-001 and-002 for Keratoconus

Table 7: Summary of Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Keratoconus)

MedDRA System Organ Class/ Preferred Term	CXL Group (N=102)	Control Group (N=103)
Number (%) of Subjects Reporting Any AEs[a]	336:87 (85.3%)	75:44 (42.7%)
Eye Disorders	304:86 (84.3%)	59:40 (38.8%)
Corneal opacity	73:58 (56.9%)	4:4 (3.9%)
Punctate keratitis	28:25 (24.5%)	8:8 (7.8%)
Corneal striae	25:24 (23.5%)	12:12 (11.7%)
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%)
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%)
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
Other Ocular TEAEs		
Corneal scar	9:7 (6.9%)	5:5 (4.9%)
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%)

[a] 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.
Source: Table 14.3.1.2.1, Section 8.1

Table 16: Summary of Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Corneal Ectasia)

MedDRA System Organ Class/ Preferred Term	CXL Group (N=91)	Control Group (N=88)
Number (%) of Subjects Reporting Any AEs	328:82 (90.1%)	66:38 (43.2%)
Ocular TEAEs	296:82 (90.1%)	53:33 (37.5%)
Corneal opacity	74:62 (68.1%)	7:7 (8.0%)
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%)
Photophobia	18:17 (18.7%)	0
Vision blurred	15:15 (16.5%)	4:4 (4.5%)
Dry eye	14:13 (14.3%)	4:4 (4.5%)
Visual acuity reduced	10:10 (11.0%)	1:1 (1.1%)
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 dysfunction	4:3 (3.3%)	2:2 (2.3%)
Ocular hyperaemia	3:3 (3.3%)	1:1 (1.1%)
Corneal scar	3:3 (3.3%)	1:1 (1.1%)
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

Note: Ocular events in the fellow eye are excluded.
Source: Table 14.3.1.2.1, Section 8.2

These are pooled common adverse event tables (i.e. UVX-001 and 002 for keratoconus and 001 and 003 for corneal ectasia). Note: subjects in the CXL group had topical anesthetic administered to the study eye, and the corneal epithelium was removed; subjects in the sham treatment group had topical anesthetic administered to the study eye but did not have the corneal epithelium removed.

The most common adverse events for either indication at ≥ 10% are corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequalae following corneal epithelial debridement.

Safety Summary Statement

The most common adverse events for both the keratoconus and corneal ectasia indications occurring at 10% to 92% in UVX-001, -002, and -003 were corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequalae following the corneal epithelial debridement which accompanied the procedure.

A 120-Day Safety Update was submitted on February 19, 2014. Per the update, the Phase 3 studies in support of the original NDA were completed with the final study reports submitted in the original NDA. Per the applicant, there are no additional safety data from these studies. The applicant markets the similar product, VibeX, in Europe. The applicant will be expected to submit any postmarketing data on the VibeX product(s) which could be relevant for the safety profit for Photrexa.

8. Advisory Committee Meeting

No Advisory Committee Meeting was held. Riboflavin is a well known compound with a well established safety profile. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9. Pediatrics

The safety and effectiveness of corneal collagen cross-linking has not been established in patients less than 14 years of age. The disease exists in the adolescent population. In the Phase 3 studies, there were 16 patients between 14-18 years of age. Submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time.

10. Other Relevant Regulatory Issues

A routine Office of Scientific Investigations (OSI) audit was requested. The clinical site of Drs. Stulting, Price, Hardten, Hersh, and Donnenfeld were selected for inspection. The sites above were selected because all enrolled relatively large numbers of subjects and each of the five sites had significant impact on study results. Please note that a large number of subjects discontinued the UXV-001study prematurely because the investigator (Dr. Stulting) left the site; the study was then terminated by the IRB. The proportion of subjects who discontinued the study was 17% and 56% in the treatment and control groups, respectively. Also, the same panel of principal investigators was utilized in both UVX-002 and UVX-003. UVX-002 evaluated keratoconus subjects; UVX-003 evaluated corneal ectasia subjects.

Name of CI, Location	Protocol #/ Site #/ # of primary eyes	Inspection Dates	Final Classification
Francis Price, Jr., M.D. Price Vision Group and Cornea Research Foundation of America 9002 N. Meridian St., Suite 100 Indianapolis, IN 46260	UVX-002/ Site #04/ 26 primary eyes UVX-003/ Site #04/ 21 primary eyes	8-17 Jan 2014	VAI.
David Hardten, M.D., FACS Minnesota Eye Consultants, P.A. 710 E. 24th St., Suite 100 Minneapolis, MN 55404	UVX-002/ Site #10/ 16 primary eyes UVX-003/ Site #10/ 15 primary eyes	14-27 Jan 2014	VAI. Pending final classification.
Peter Hersh, M.D. Cornea and Laser Eye Institute 300 Frank W. Burr Blvd., Suite 71 Teaneck, NJ 07666	UVX-002/ Site #03/ 54 primary eyes UVX-003/ Site #03/ 30 primary eyes	6-16 Jan 2014	NAI. Pending final classification.
Eric D. Donnenfeld, M.D. Ophthalmic Consultants of Long Island 2000 North Village Ave., Suite 402 Rockville Centre, NY 11570	UVX-002/ Site # 02/ 11 primary eyes UVX-003/ Site #02/ 19 primary eyes	21 -29 Jan 2014	VAI. Pending final classification.
Avedro Inc. (sponsor) 230 Third Avenue Waltham MA 02451	UVX-001 UVX-002 UVX-003	3-12 Feb 2014	VAI. Pending final classification.
R. Doyle Stulting, M.D. Current contact information: Woolfson Eye Institute At Emory University: Study Coordinator: Kristin West	UVX-001/ Site # 01/ 107 primary eyes	Ongoing	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

Inspection of Dr. Stulting's clinical investigator site is ongoing. Drs. Price, Hardten, and Donnenfeld, and the sponsor were issued Form FDA 483s. The preliminary classification for all of these inspections is Voluntary Action Indicated (VAI) based on preliminary communications with the field investigators.

Observations were made regarding missing monitoring reports or documentation of review of those reports at the sponsor; however, there does not appear to have been an impact on collection of efficacy or safety data at the clinical sites. Otherwise, based on the inspection findings available at this time, the studies appear to have been conducted adequately, and the data submitted by this applicant appear acceptable in support of the respective indication.

CDRH Consult Review

On October 7, 2013, the Division of Transplant and Ophthalmology requested that the Center for Devices and Radiologic Health (CDRH) review the device section of the application to address the following questions:

1. Can the proposed device component deliver the proposed amount of light (wavelength, power, time) described in the application?

2. Does CDRH have any recommended labeling changes to the KXL Operator's Manual?

On November 5, 2013, the Office of New Drug Quality Assessment (ONDQA) requested inspection of the KXL device manufacturing facility.

On February 10, 2014, a memorandum from CDRH was received. Within the CDRH, consult requests were made for various review areas including clinical, optical radiation hazard, electromagnetic compatibility and software.

Below is a brief summary from the consult memo:

1. **Clinical**

"There are some major concerns regarding this "first of a kind" medical product. The device used in the clinical trials is not identical to the device proposed for approval. One major concern relates to differences observed between the two device proposed for marketing and the device used in the clinical trial. Differences include a fixed illumination diameter in the device proposed for marketing approval (9mm) and a variable illumination diameter in the device used in the trial (7, 9, 11 mm). With regard to the indication for keratoconus, the orphan designation is for keratoconus. However, the clinical studies enrolled subjects with progressive keratoconus. We believe there may be differences in the risk/benefit considerations between these two populations since some keratoconus patients remain stable for years and some progress.

Regarding the mechanics of the clinical trial, due to the potential for subject crossover from the control arm to the treatment arm at 3 months, a variety of concerns arise including reduced accountability beyond the 3 month visit for the control arm and concern regarding the use of last observation carried forward (LOCF) analyses to supplement the month 12 data. However, we note that using the 3 month visit data without LOCF analyses (as initially intended based on the study design), the applicant does not meet pre-specified effectiveness endpoint targets for all indications. Regardless, we strongly believe that long-term data would be valuable for this technology. Also, three separate clinical studies are reported and the pool ability across studies has not been established. Therefore, there are concerns regarding the limited sample size for each treatment group. [The planned sample size was 160 subjects (80 eyes per treatment group) for 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 applicant also included pediatric patients in their study. However, we do not believe sufficient data is available from this study to support labeled use for pediatric patients (there were 16 patients between 14-18 years of age).

We believe that the approval of this combination product would represent a major milestone in ophthalmic patient care. Thus, we strongly believe that the clinical concerns raised by the CDRH warrant, at minimum, an advisory committee meeting."

I have reviewed the issues raised in this section and do not believe that they represent concerns sufficient to withhold approval of this application for the following reasons:

a. The applicant provided the diameter setting for each treatment in the original submitted datasets. Less than 1% of the treatments were conducted with the 7 mm diameter. Eighty-eight percent of treatments were with the 9 mm diameter and approximately 11% used the 11 mm. For ectasia, approximately 1% of the treatments were conducted with the 7 mm diameter, 88% of treatment with the 9 mm diameter and approximately 10% with the 11 mm diameter. The subsets of patients with 7mm and 11mm are too small to provide meaningful analyses. The selection of the 9 mm diameter should be considered reasonable since the safety and efficacy data was derived primarily from the 9 mm diameter.

b. Keratoconus is a progressive disease. While the rate of progression may vary at different points during life, progressive keratoconus is not a separate condition from keratoconus. All keratoconus is progressive at some point in the disease.

c. The Agency recommended a 12 month endpoint instead of the 3 month endpoint. The applicant was concerned that irreversible harm might occur to these patients if they waited too long before treatment. The eyes which were "crossed-over" were the "sham" eyes. Additional safety information was not needed from this control group and these eyes continued to be followed after they received treatment. Patients treated with riboflavin were followed for 12 months.

d. The assumption used in the LOCF method is that the disease will not spontaneously regress on its own. Keratoconus and corneal ectasia are not known to spontaneously regress. While the rate of progression might vary, the assumption that the Kmax will not improve on its own without intervention is accurate. The only variability excluding progression that is expected to occur is in the accuracy of the measurement.

e. The primary endpoint was met for each indication. The 12 month data point was specified as the primary endpoint in the revised statistical plan prepared prior to the data analysis.

f. The study results were not pooled. Each indication was supported by two clinical studies.

g. The conditions studied in this application occur in pediatric patients. The results of pediatric patients treated were consistent with the data from the adult patients treated.

h. Intacs received a Humanitarian Device Exemption (H040002), intended to be used for the reduction or elimination of myopia and astigmatism in patients with keratoconus, who are no longer able to achieve adequate vision with their contact lenses or spectacles. It is noted that the device for this indication was not the subject of an Advisory Panel Meeting. Riboflavin is a well known and established

compound. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

2. Electromagnetic Compatibility

"Because this device will be used in close proximity to other electronic devices, it is important to evaluate the electromagnetic compatibility (EMC) of this device, as well as the immunity of this device to electromagnetic interference.

The applicant claims conformity to EN 60601-1-2 as well as to IEC 60601-1-2. However, the EMC test reports do not cite IEC 60601-1-2 and this standard represents FDA's most current thinking and "best practices" for electromagnetic compatibility considerations.

While there are concerns regarding test reports and labeling, there are also larger concerns that result in the collection of additional testing information."

The deficiencies noted in this section represent requests to verify that statements made in the application or requests to add statements to the labeling. These deficiencies have been conveyed to the applicant and a response was provided. A review of this response by CDRH has not been completed as of this date.

3. Software

"This software contained in this medical product represents a major level of concern (LOC) as any malfunction could result in major injury to a patient. Therefore, the we reviewed the software documentation submitted by the applicant in-depth in areas including the device hazard analysis, software requirements specifications, software design specifications, software development environment and verification and validation activities.

In general, the software documentation was satisfactorily completed. However, there are concerns regarding cyber security and run-time error detection, which are important to device functionality and patient information. Thus, there is additional information needed to complete our review."

The deficiencies noted in this section represent requests for additional clarification of information provided in the application. These deficiencies have been conveyed to the applicant and a response was provided. A review of this response by CDRH has not been completed as of this date.

4. Optical Radiation Hazard analysis

The power settings for the UV-light delivery may be hazardous to the eye. The total energy output for the device was not reviewed during the IND; neither were the irradiance levels. There have not been limitations set for the output levels by neither software nor hardware controls. The only mitigation proposed by the company was to make treatment cards available for purchase that limit the output; the cards available for purchase *in* the US would limit the device to settings used in the study. While this proposal would "limit" the device output, it does not sufficiently limit the possibility of raising the power beyond the levels in the investigational studies. At minimum, we would expect a software lockout, as we require in refractive laser devices (i.e., LASIK). However, please note that the lockouts used for refractive

> lasers are *only treatment-range lockouts, not lockouts for power settings.* Therefore, it does not completely eliminate the possibility of emission of excessive power levels. Thus, the most appropriate mitigation is a hardware modification that limits power output to ensure safer levels of energy.
>
> The applicant appears to contend their device is a "Class 1 laser device." However, it is not clear whether they mean a group 1 laser per ISO 15004-2 or whether they believe they are a class 1 laser per 21 CFR 1040. In either event, based on their assessment, they believe they are a low-risk laser device, which is not correct based on our initial evaluation of the laser output specifications.

The summary conclusions in this section are theoretical and not supported by the literature. Higher power settings have been studied and reported in the literature to be safe. The use of RFID cards for the commercial use is an acceptable method of limiting the use. No justification has been provided for requiring duplicative methods.

> **"Recommendation**
> We have identified several areas of deficiency within the application. While the reviews for clinical and optical radiation hazard remain ongoing, we do have deficiencies to immediately convey interactively to the applicant for response. In addition to the deficiencies identified below, we believe that because this device/drug combination product is a first-of-a-kind, many of these issues should be presented to an ophthalmic advisory committee of experts. This advisory committee consultation would serve to help define the regulatory path moving forward with regards to clinical study design, device issues and post-approval study considerations."

As noted above, the deficiencies identified by CDRH have been conveyed to the applicant and the applicant has responded to those deficiencies. The "regulatory path" for this combination product was set by the Office of Combination Products.

11. Labeling

Labeling has been deferred because the application is not being recommended for approval at this time and the deficiencies may affect the proposed labeling. NDA 203324, riboflavin ophthalmic solution and KXL System, is not recommended for approval for the treatment of corneal ectasia until chemistry and manufacturing inspectional issues are resolved. It is also not recommended for approval (b) (4) There is insufficient data from adequate and well controlled trials to establish the efficacy. The datasets provided for UVX-01 and UVX-002 for the keratoconus indication contain errors. The keratoconus Kmax efficacy data from UVX-001 and -002 should be re-analyzed after non physiologic values are removed. An explanation for the non-physiologic values found in the datasets should be provided.

12. Recommendations

NDA 203324, riboflavin ophthalmic solution and KXL System, is not recommended for approval for the treatment of corneal ectasia. Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

NDA 203324, riboflavin ophthalmic solution and KXL System, is not recommended for approval (b) (4) There is insufficient data from adequate and well controlled trials to establish the efficacy. The datasets provided for UVX-01 and UVX-002 for the keratoconus indication contain errors. The keratoconus Kmax efficacy data from UVX-001 and -002 should be re-analyzed after non physiologic values are removed. An explanation for the non physiologic values found in the datasets should be provided.

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
03/07/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203324
Priority or Standard	Priority
Submit Date(s)	9/16/2013
Received Date(s)	9/16/2013
PDUFA Goal Date	3/16/2014
Division / Office	Division of Transplant and Ophthalmology Products/Office of Antimicrobial Products
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	3/6/2014
Established Name	riboflavin ophthalmic solution and KXL System
(Proposed) Trade Name	Photrexa and Photrexa (b) (4)
Therapeutic Class	photoenhancer
Applicant	Avedro, Inc.
Formulation(s)	ophthalmic solution
Dosing Regimen	1 drop of topically on the eye every 2 minutes for 30 minutes
Proposed Indication(s)	(b) (4)

Intended Population(s)	keratoconus and corneal ectasia following refractive surgery

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 203324, Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) and KXL System, is recommended for approval for the treatment of corneal ectasia once chemistry and manufacturing inspectional issues are resolved. Incomplete, draft labeling is located in this review, but additional requests for clinical information will necessitate revision to this labeling.

1.2 Risk Benefit Assessment

Keratoconus is a naturally-occurring ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in corneal optical irregularities with increasing myopia, irregular astigmatism, and consequential loss of best corrected visual acuity (BCVA). The prevalence of keratoconus is often reported as 1 per 2000 people in the general population. Onset of keratoconus generally occurs during puberty or early adulthood and profoundly affects patients who develop the condition. If left untreated, patients experience progressive vision impairment, which may result in the need for corneal transplantation.

Corneal ectasia is a well-described complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy. It is a condition similar to keratoconus, but occurs postoperatively. Ectasia may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of both uncorrected visual acuity (UCVA) and BCVA.

There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery. For both keratoconus and corneal ectasia, early intervention usually involves 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 address the optical irregularity of the cornea. Surgically-implanted intrastromal ring segments may be used to improve contact lens wear in patients who are contact lens intolerant. These treatments do not halt the progression of keratoconus. Corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal transplantation is not without risk – postoperative complications include transplant failure, rejection, secondary cataract, secondary glaucoma, and recurrence of keratoconus in the transplanted graft (Raiskup-Wolf *et al* 2008).

The goal of corneal collagen cross-linking (CXL) is to biomechanically stabilize the weak cornea in keratoconus and postoperative corneal ectasia and decrease the clinical progression of these diseases. In the crosslinking procedure, riboflavin is administered topically to the eye (typically one drop every 2 minutes for 30 minutes). After riboflavin saturation into the corneal stroma, exposure to ultraviolet A (UVA) light (365 nm; 3 mW/cm^2 irradiation; 30 minutes' duration) induces crosslinking.

Normally riboflavin ophthalmic solution containing 20% dextran is used. However, if corneal thickness is < 400 µm riboflavin ophthalmic solution containing no dextran is used until the corneal thickness is 400 µm.

The primary original efficacy endpoint for the applicant's clinical trials was as the difference between the CXL group and the control group in maximum keratometry (Kmax) from baseline to Month 3. At the time the studies were initially planned, the Agency recommended a 12 month endpoint but the applicant believed that the primary efficacy endpoint could be analyzed at 3 months post-procedure based on their review of the existing literature. The applicant reviewed subsequent additional literature which suggested to them that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize.

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for the corneal ectasia indication. The datasets for the keratoconus indication from UVX-001 and UVX-002 contain errors (i.e., non-physiologic values). The applicant will be expected to reanalyze their keratoconus Kmax efficacy data from UVX-001 and -002 after non physiologic values are removed

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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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. The loss of control subjects makes the analysis of observed data challenging to interpret due to the decreasing sample size at later time points.

The most common adverse events for both the keratoconus and corneal ectasia indications occurring at 10% to 92% in UVX-001, -002, and -003 were corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following the corneal epithelial debridement which accompanied the procedure.

The benefits of the CXL procedure are considered to outweigh the risks for the corneal ectasia indication. The clinical trials performed by the applicant followed these criteria for clinical application of crosslinking:

- corneal epithelium removed to facilitate diffusion of riboflavin throughout the corneal stroma
- 0.1% riboflavin ophthalmic solution be applied for at least 30 minutes before the UV exposure
- UV irradiance of 3 m W/cm^2 and a wavelength of 370 nm must be homogenous
- cornea to be X-linked must have a minimal thickness of 400 µm to protect the endothelium (Spoerl *et al* 2007).

Any potential damage to the corneal endothelium, the lens or the retina is expected to be minimized when these criteria are fulfilled (Spoerl *et al* 2007).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Avedro's riboflavin ophthalmic solution/UVA irradiation is a combination product consisting of a UVA 365 nm wavelength light source and riboflavin administered in conjunction with the UVA light as a photosensitizer.

In the clinical trials, the drug product was a sterile, phosphate-buffered saline solution for topical ophthalmic use containing 0.1% riboflavin (Vitamin B2) with and without 20% dextran (b) (4)

The UVA irradiation system is a portable electronic medical device. The device's light emitting diode (LED) is used to deliver a metered dose of UVA light to a targeted treatment area for illuminating the cornea during CXL. System specifications are shown in the following table.

Table 2: UVA System Specifications

Function	Description
Light Source	(b) (4) UV-grade LED; LED Laser class (b) (4) (b) (4)
Wavelength	365 nm (b) (4)
Optical Power	Maximum (b) (4) mW
Beam Diameter	7.5 mm to 11.5 mm
Light Emission	Continuous wave
Intensity Setting	3.0 mW/cm^2 (±0.3 mW/cm^2)
Safety Class	Class II Equipment (b) (4)
Medical Device Class	(b) (4)
EMI.EMC Class	Class B (b) (4)
Power Supply	(b) (4) 9V; max. 1.7A

Source: 2.7.3 Summary of Clinical Efficacy

2.2 Tables of Currently Available Treatments for Proposed Indications

There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery.

As corneal protrusion and irregular astigmatism progress, spectacles are unable to adequately correct vision, and the use of rigid, scleral, or hybrid contact lenses is needed to address the optical irregularity of the cornea.

Surgically-implanted intrastromal ring segments may be used to improve contact lens wear in patients who are contact lens intolerant. Otherwise, corneal transplantation is the only option available when functional vision can no longer be achieved.

2.3 Availability of Proposed Active Ingredient in the United States

There are no approved riboflavin ophthalmic solutions in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Riboflavin (Vitamin B2) is a water-soluble vitamin that is the parent of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze many oxidation/reduction reactions in the body. Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photosensitizer.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for these combination products under RFD070013.

Avedro, Inc. opened IND 77,882 with a protocol submission dated November 7, 2007.

A pre-NDA Meeting was held on September 21, 2011. CMC indicated that the briefing document was inadequate and requested additional information on the composition of the material used for the Phase 3 studies and the composition of the proposed commercial formulation. Clinical stated it was not possible to determine whether the clinical program will be sufficient to support approval based on the information previously submitted. Clinical would need to review the final study report for study UVX-001, -002 and -003 to determine whether it is appropriate to combine patients from -001 into - 002 and -003. The lack of statistical significance between groups in the patients treated for keratoconus at Month 3 was noted as potentially problematic.

Avedro, Inc. submitted a New Drug Application (NDA) on March 8, 2012, for their riboflavin ophthalmic solution /KXL System.

They received a refuse to file letter dated May 4, 2012. The application was not sufficiently complete to permit a substantive review. The Agency refused to file this application under 21 CFR 314.101(d) for the following reasons:

1. None of the submitted trials, UVX-001, UVX-002 or UVX-003, utilized the commercial formulation proposed in the NDA. There was no safety or efficacy data in this application for the commercial formulation proposed in this NDA. The proposed commercial formulation was recommended to be revised to be consistent with the formulations utilized in the clinical trials or adequate and well controlled clinical trials for the two indications were to be performed with the currently proposed commercial formulation.

2. Chemistry, manufacturing and controls (CMC) information provided in the NDA for the drug substance was insufficient for a substantial review. Please provide the drug substance CMC information either in the NDA or by reference to a DMF with a letter of authorization (LOA) from the DMF holder.

3. Data from the following one-time studies for the proposed commercial drug product were not included in the NDA. Please provide this information.
    a. Freeze-thaw cycling studies (3 cycles)
    b. Weight loss through expiry on primary stability batches
    c. Leachables/extractables on container/closure by using screening analytical methods (such as HPLC, GC etc) and studies on at least one stability batch through expiry.

4. The NDA does not provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. Stability data submitted for the historical batches are inadequate. They were only tested for limited quality attributes at only a few time points. Furthermore, per the Code of Federal Regulations (CFR), 21 CFR 211.166(a)(4), evaluation of stability shall be based on the same container-closure system in which the drug product is proposed to be marketed. Please provide 12-months long-term and 6-months accelerated stability data for three batches of the commercial formulation in the commercial container-closure system (including, as appropriate, any secondary packaging and container label) as recommended in International Conference on Harmonisation (ICH) Q1A(R2) to evaluate the stability of the commercial drug product over the proposed shelf-life.

5. In addition to the change in formulation, the container closure system used in clinical trials (b) (4) is different from the proposed marketing packaging configuration (3 mL pre-filled syringes). Please provide a complete comparison of the clinical trial material (including container-closure system) and the proposed commercial drug product, including all similarities and differences.

6. The NDA should include product specific information for sterility assurance: container closure integrity tests, (b) (4) validation information, method suitability studies for endotoxin and sterility tests, and any hold time studies for the product. Please provide this information.

7. An accurate and complete English translation of any part of the application that is not in English is required. Publications by Kohlhaas M, Spoerl E, Speck A, et al., Schnitzler E, Spoerl E, Seiler T., Spoerl E, Schreiber J, Hellmund K, et al., were submitted in German without translation. Please provide English translations of these articles.

Additional potential review issues were identified in the letter:

1. In your resubmission, please list all manufacturing and testing facilities and assurance that all the listed facilities are ready for inspection.

2. The Clinical Study Reports (CSRs) for UVX-002 and UVX-003 do not contain unpooled demographic or adverse event data. The CSRs should be revised to contain both pooled and unpooled demographic and adverse event data. These CSRs should be separate, independent documents which adequately describe each individual trial without pooling. It is acceptable to include pooled efficacy data as secondary, supportive analyses in the CSRs.

3. The submitted twelve month data are not true observed values; they are "carried forward" observations. Twelve month data and analyses should be submitted which utilize the true observed values at 12 months, not “carried forward” observations.

4. The proposed labeling discusses (b) (4) the pre-filled syringe. Please provide a description (b) (4) and its use. If (b) (4) a previously cleared device, please provide verification of the 510(k). If it is not a cleared device, please provide the (b) (4) method and validation studies or a letter of authorization to a Drug Master File in which this information can be found.

5. The manufacturing process uses (b) (4) Please provide the (b) (4) method and validation for it or a letter of authorization to a Drug Master in which this information can be found.

6. As requested in the pre-NDA meeting on September 12, 2011, please provide a rationale for (b) (4) the finished drug product.

7. To support the proposed dosing regimen of (b) (4) /KXL, please provide a summary report that tabulates the descriptive statistics (e.g., mean, median, min, max) of the actual number of riboflavin drops per instillation, the total number of riboflavin drops administered during each of the treatment phases (i.e., after corneal debridement, anterior chamber penetration, corneal thickening, UVA irradiation) and the cumulative number of drops received during the entire corneal crosslinking treatment process for each Phase 3 clinical trial. Please provide these tables for analysis of both individual and pooled studies. Please include an analysis dataset in .xpt format providing the requested information for each patient enrolled in the Phase 3 trials. Please include in the dataset a data column to indicate the type of riboflavin formulation (e.g., 0% dextran; 20% dextran; etc.) administered.

8. When submitting riboflavin dosing datasets (e.g., RIB1D.xpt, RIBACD.xpt, HYPRIBD.xpt, RIB2D.xpt), please associate each dosing-time profile provided with the particular treatment received by including a data column similar to the TXRANDTX column of the TX.xpt dataset where 1=CXL study eye, 2=sham study eye, 3=CXL fellow eye, 4=crossover of control eye.

9. The study design allowed subjects in the control group to cross over to receive CXL treatment after Month 3. Please provide information on the timing of the crossover (You could use tabulation or graph as you see appropriate.), and for each visit, tabulate the number of subjects remaining in the study, staying with the randomized treatment, and the number of subjects who had Kmax measurements. This should be provided for each individual study and the pooled studies. You could use a table as follows.

Visit	CXL		Control		
	Stayed with randomized treatment	# of subjects with Kmax	Stayed with randomized treatment	Crossed over	# of subjects with Kmax
Month 1					
Month 3					
Month 6					
Month 12					

10. Please provide a pooled dataset including the following variables for all ITT subjects from Studies UVX-001, UVX-002, and UVX-003. You may want to change some of the variable names to be consistent with the names used in your raw datasets.

Variable	**Label**	**Type**	**Codes**	**Comment**
PROJ_ID	Study Identifier	Char	001, 002, 003	
SITE_ID	Site Identifier	Char		
Age	Age (years)	Num		
Race	Race	Char	Include all possible codes	
Ethnicity	Ethnicity	Char	Include all possible codes	
Sex	Sex	Char	Female, Male	
TRT	Randomized Treatment	Char	Sham, CXL	
Severity	Baseline disease severity	Char	mild, moderate, severe	
Completed	Did the subject complete the study?	Char	Yes, No	
Discont	Reason for discontinuing from the study	Char	Include all possible codes	

EYE_TYPE	Type of EYE	Char	Keratoconus, Corneal Ectasia	
VISIT_C	Visit identifier	Char	Baseline, Month 1, Month 3, Month 6, Month 12	
Visit	Visit identifier	Num	0, 1, 3, 6, 12	
Visit_dtn	Visit date	Num		
Eye	Eye	Char	Left, right	
Study_eye	Study eye	Char	Left, right	
TRT_SE	Treatment received at each visit for study eye	Char	Sham, CXL	
TRT_DT_SE	Treatment date for study eye	Num		
TRT_FE	Treatment received at each visit for follow eye	Char	Sham, CXL	
TRT_DT_FE	Treatment date for fellow eye	Num		
Kmax_SB	Baseline Kmax for study eye	Num		
Kmax_SO	Observed Kmax for study eye at each visit (measurement should be provided regardless of subject's treatment status)	Num		
Kmax_SL	LOCF Kmax for study eye at each visit	Num		
CKmax_SO	Change in observed Kmax from baseline for study eye	Num		
CKmax_SL	Change in LOCF Kmax from baseline for study eye	Num		
LOCF	LOCF flag for Kmax_SL	Char	Yes, No	
Kmax_FB	Baseline Kmax for follow eye	Num		
Kmax_FO	Observed Kmax for follow eye at each visit	Num		
CKmax_FO	Change in observed Kmax from baseline for follow eye	Num		

11. Please provide all available data that were collected for untreated fellow eyes. We noted that, for example, among 179 ectasia subjects, a total of 65 fellow eyes in the CXL group and 66 fellow eyes in the sham group didn't receive any treatment. We could not find data collected during the follow-up procedure and examination for these untreated fellow eyes. If data were collected for these untreated fellow eyes, please provide all data including their key efficacy data.

12. Please examine the distribution of Kmax and conduct additional analyses (for example, nonparametric analysis) to examine the robustness of the primary efficacy analysis results.

13. Please conduct analyses of Kmax adjusting for baseline Kmax.

14. Please provide analyses for the proportion of subjects who experienced ≥1 D decrease in Kmax from baseline.

A post "Refuse-to-File" meeting was held with Avedro, Inc. on May 31, 2012, to discuss the Agency's comments in the RTF letter dated May 4, 2012.

A CMC Type A meeting was held on August 15, 2012, where Avedro committed to revise the commercial formulation information proposed in the NDA to be consistent with the clinical formulations used in the clinical trials.

A general advice letter was send on October 19, 2012, in response to the September 24, 2012, submission seeking Agency advice on Avedros' plan for cGMP manufacturing of the drug substance, riboflavin 5'-phosphate sodium and drug product process validation and registration stability.

2.6 Other Relevant Background Information

Avedro, Inc. submitted a request for orphan-drug designation dated May 26, 2011, for riboflavin ophthalmic solution and ultraviolet-A (LTVA) irradiation "for corneal cross-linking for the treatment of keratonus (sic)." The Office of Orphan Products Development granted orphan designation for treatment of keratonus (sic) on September 2, 2011.

Avedro, Inc. submitted a request for orphan-drug designation dated August 26, 2011, for riboflavin ophthalmic solution and ultraviolet-A irradiation for "treatment of corneal ectasia following refractive surgery." The Office of Orphan Products Development granted orphan designation for treatment of corneal ectasia following refractive surgery on December 2, 2011.

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 (Kmax), quantifies the pathognomonic feature of keratoconus and corneal ectasia. Based on the etiology and manifestation of keratoconus and corneal ectasia, Kmax was accepted by the Agency as a clinically meaningful and reproducible endpoint to be measured in these patient populations. For each study, the primary efficacy endpoint was corneal curvature, as measured by Kmax.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

See Section 6.1.4 regarding the reliability of the submitted datasets for the keratoconus indication. The datasets contain errors, i.e. non physiologic values for Kmax.

3.2 Compliance with Good Clinical Practices

The clinical trials reviewed in this application were conducted in accordance with good clinical trial practices.

3.3 Financial Disclosures

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2.

See Appendix 9.3 of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Photrexa (riboflavin ophthalmic solution) is a clear yellow solution containing 0.12% riboflavin 5'-phosphate sodium and 20% dextran in phosphate buffered saline.

Photrexa (b) (4) (riboflavin ophthalmic solution) is a clear yellow solution containing 0.12% riboflavin 5'-phosphate sodium in phosphate buffered saline. Photrexa (b) (4) does not contain dextran.

Table 1: Composition of Photrexa and Photrexa [(b) (4)] (3 mL)

Ingredient	Photrexa	Photrexa [(b) (4)]	Function	Quality Standard
	Amount per Syringe (w/w)	Amount per Syringe (w/w)		
Riboflavin 5'-Phosphate Sodium	0.12%	0.12%	Active ingredient	USP; EP
Dextran 500	[(b) (4)]			USP; EP
Sodium Chloride				USP; EP; JP
Sodium Phosphate, Monobasic				USP; EP
Sodium Phosphate, Dibasic				USP; EP
Sterile Water for Injection				USP

Source: 3.2.P.1

Photrexa and Photrexa [(b) (4)] are [(b) (4)] filled into 3 mL [(b) (4)] (USP/NF and EP), clear glass syringes with plastic rigid tip cap and stoppered with a rubber stopper. Information on the container-closure components is provided below.

Table 2: Container Closure System for Photrexa and Photrexa [(b) (4)]

Primary Packaging Components		
Component	Description	Manufacturer
Syringe Barrel	[(b) (4)]	
Plunger Stopper		
Plunger Rod		

Source: 3.2.P.1

Table 1: Drug Product Specifications

Test Description	Method	Acceptance Criteria
Appearance	Visual	Clear, yellow solution
Identification	RP-HPLC	Retention time and spectrum of sample corresponds to standard
Assay – Riboflavin	RP-HPLC	(b) (4) % nominal, min (b) (4), max (b) (4)
Chloride Content	USP <1065>	(b) (4) mg/100g
Phosphate Content	USP <1065>	mg/100g
pH	USP <791>	(b) (4)
Sterility	USP <71>	No growth
Viscosity	USP <911>	Report Result
Osmolality	USP <785>	Report Result
Particulate Matter	USP <789>	(b) (4) particles/mL (b) (4) particles/mL particles/mL
Endotoxin	USP <85>	(b) (4) EU/mL
Impurities	RP-HPLC	Total: Report Result Specified: Report Result Unspecified: (b) (4) % of solution

Source: 3.2.P.5

The KXL System is an electronic medical device that delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of Photrexa or Photrexa (b) (4) (riboflavin ophthalmic solution). UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The figure below provides an illustration of the KXL System.

Figure 1: Overview Illustration of the KXL System

Source: 3.2.R Regional Information

The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient's cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

Table 1: KXL System Specifications

SPECIFICATION	DESCRIPTION
Electrical	Battery Powered: 12V 35 Ah SLA Line voltages 100-240 volts AC, (b) (4) Current (b) (4) Single Phase RMS, 50/60 Hz, (b) (4) Remote 2x AAA batteries
User accessible Fuses	250 V~ (b) (4)
Energy Delivery	UV Radiation 3 mW/cm^2 365 nm
External Interfaces	USB 2.0
Physical Dimensions	Length: (b) (4) cm Width: (b) (4) cm Height: (b) (4) cm (all dimensions with arm retracted)
Weight (crated system)	NW 45 Kg GW 120 Kg
Battery Life (normal operating conditions)	16 hours
Environmental Operating Conditions	The system operates under the following atmospheric conditions (no condensation).

Table 1: KXL System Specifications (Continued)

SPECIFICATION	DESCRIPTION
Ambient temperature	+10 to +40°C
Relative humidity	30% to 75%
Transport and Storage Conditions	The instrument withstands the following transport and storage conditions without damage or performance deterioration.
Ambient temperature	-15 to +70°C
Relative humidity	10% to 100% including condensation

4.2 Clinical Microbiology

Not applicable to this review.

4.3 Preclinical Pharmacology/Toxicology

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Riboflavin or vitamin B2, a water soluble vitamin, is an essential nutrient and a natural component of many food products.

Two riboflavin 5'-phosphate ophthalmic solutions are proposed for marketing. Photrexa is a sterile (b) (4) solution containing 0.12% riboflavin (as the active moeity) and 20% dextran. Photrexa (b) (4) is a sterile (b) (4) solution containing 0.12% riboflavin and 0% dextran. In clinical trials, riboflavin ophthalmic solutions with riboflavin concentrations within (b) (4) % of the proposed labeled claim were used.

Corneal collagen crosslinking (CCXL) using the (b) (4) riboflavin ophthalmic solutions and UVA irradiation are proposed (b) (4)

Riboflavin is used in CCXL as a photosensitizer, allowing the cornea to absorb a greater amount of the UV irradiation. The oxygen free radicals produced induces the formation of intra- and inter- collagen fibril covalent bonds, leading to biomechanical stabilization of the cornea.

4.4.2 Pharmacodynamics

The systemic exposure to riboflavin (Vitamin B2) was not determined following topical ocular treatment with 0.1-0.12% riboflavin ophthalmic solutions.

4.4.3 Pharmacokinetics

Systemic riboflavin concentrations were not measured following topical administration of the riboflavin ophthalmic solutions at the proposed dosing regimen; it is not possible to explore the influence of intrinsic factors on riboflavin pharmacokinetics.

Assuming 100% bioavailability of riboflavin following topical ocular instillation of the proposed 0.12% riboflavin eyedrops, the average systemic exposure to riboflavin during one-time CCXL treatment of one eye in the 12-month UVX trials would not exceed (b) (4) mg, which is below the Joint FAO/WHO Expert Committee on Food Additives upper limit of acceptable oral daily intake of riboflavin (35 mg for a 70 kg person).

5 Sources of Clinical Data

The clinical development program of riboflavin ophthalmic solution/UVA irradiation in the treatment of keratoconus involved 2 studies, UVX-001 and UVX-002. The clinical

development program of riboflavin ophthalmic solution/UVA irradiation in the treatment of corneal ectasia following refractive surgery involved 2 studies, UVX-001 and UVX-003.

The studies were nearly identical in design and conduct. However, UVX-001 had a mixed population of subjects with corneal ectasia and keratoconus, whereas only corneal ectasia subjects were enrolled in UVX-003. Further, UVX-001 was a single-center study, and UVX-003 involved 9 sites. All sites were located in the US.

In response to potential review issue #2 from the RTF letter dated May 4, 2012[1], the CSRs for UVX-001, UVX-002 and UVX-003 were revised by Avedro, Inc. to describe each individual trial without pooling (Module 5.3.5.1). As secondary, supportive information, pooled keratoconus results (UVX-001 keratoconus data and UVX-002 data) and pooled ectasia results (UVX-001 ectasia data and UVX-003 data) were submitted for the primary efficacy parameter.

1 "The Clinical Study Reports (CSRs) for UVX-002 and UVX-003 do not contain unpooled demographic or adverse event data. The CSRs should be revised to contain both pooled and unpooled demographic and adverse event data. These CSRs should be separate, independent documents which adequately describe each individual trial without pooling. It is acceptable to include pooled efficacy data as secondary, supportive analyses in the CSRs."

5.1 Tables of Studies/Clinical Trials

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
Efficacy and Safety	UVX-001	5.3.5.1.1	Long Term; Efficacy and Safety	Randomized sham controlled	Riboflavin 0.1% solution; UVA light (365 nm; 3 mW/cm^2) Single Treatment Ophthalmic	107; (53 drug; 54 sham)	Patients with keratoconus and corneal ectasia following refractive surgery	Pre-treatment and during irradiation: Riboflavin 0.1% solution 1 drop every two min for 30 min UVA light: 30 min	Completed; Full
Efficacy and Safety	UVX-002	5.3.5.1.2	Long Term; Efficacy and Safety	Randomized sham-controlled	Riboflavin 0.1% solution; UVA light (365 nm; 3 mW/cm^2) Single Treatment Ophthalmic	147; (73 drug; 74 sham)	Patients with keratoconus	Pre-treatment and during irradiation: Riboflavin 0.1% solution 1 drop every two min for 30 min UVA light: 30 min	Completed; Full

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status;** **Type of Report**
Efficacy and Safety	UVX-003	5.3.5.1.3	Long Term; Efficacy and Safety	Randomized sham-controlled	Riboflavin 0.1% solution; UVA light (365 nm; 3 mW/cm^2) Single Treatment Ophthalmic	130; (67 drug; 63 sham)	Patients with corneal ectasia following refractive surgery	Pre-treatment and during irradiation: Riboflavin 0.1% solution 1 drop every two min for 30 min UVA light: 30 min	Completed; Full

Source: 5.2 Tabular Listing of All Clinical Studies

5.2 Review Strategy

The September 16, 2013, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All study reports were reviewed. The included clinical study reports, literature review, and package insert formed the basis for the review of efficacy and safety for the proposed indications.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Avedro, Inc. in this application for these indications.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 UVX-001: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking In Eyes with Corneal Ectasia or Progressive Keratoconus

Study UVX-001 was a single-center study conducted in the United States (US). The study was conducted under US Investigational New Drug (IND) application 78,933 submitted by R. Doyle Stulting, MD, PhD (Atlanta, GA).

General Study Design
This was a Phase 3, single-center, randomized, sham-controlled, open-label clinical study to investigate the safety and effectiveness of CXL (performed using riboflavin/UVA irradiation) for slowing the progressive changes in corneal curvature in eyes with corneal ectasia following refractive surgery or keratoconus. An unmasked sham control was used whereby subjects went through the same procedure but without UVA irradiation or epithelial debridement.

Eligible subjects were randomized into 1 of 2 treatment groups: the CXL group and the control (sham) group. The planned sample size was 160 subjects with corneal ectasia (80 eyes per treatment group) and 160 subjects with progressive keratoconus (80 eyes per treatment group).

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. 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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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.

The assessments in this study included manual keratometry, Pentacam measurements, corneal topography, manifest refraction, BSCVA, uncorrected visual acuity (UCVA), intraocular pressure, adverse events (AEs) and complications, dilated fundus examination, slit lamp examination, endothelial cell counts, and questionnaires for quality of vision (Refractive Status Vision Profile [RSVP] questionnaire) and subjective visual complaints.

On Day 0, eligible subjects were randomized into 1 of 2 treatment groups: the CXL group and the control (sham) group. Subjects with bilateral corneal ectasia or keratoconus had only 1 eye designated for study treatment (i.e., the study eye). 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 (1 drop instilled onto the cornea every 2 minutes, with additional drops as needed to achieve adequate riboflavin saturation). 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 (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 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 (both pretreatment and during the irradiation procedure). Subjects underwent the same UV irradiation procedure as described for subjects in the CXL group except the UVA light source was not illuminated during the procedure.

For both treatment groups, the total dose of riboflavin solution over the 30-minute pretreatment and 30-minute irradiation periods was calculated to be approximately 32 drops, or 1.6 mL (1 drop = 50 µL, 1.6 mL = 1.6 mg riboflavin).

Investigational Product

Riboflavin

The riboflavin ophthalmic solution with dextran was a phosphate buffered saline solution containing 0.1% riboflavin and 20% dextran (b) (4) and packaged (b) (4) for topical ophthalmic use. Lot numbers: 09MD0903, 81220, 80709, 80118, 80417.

The riboflavin ophthalmic solution without dextran was a phosphate buffered saline solution containing 0.1% riboflavin in sterile water, (b) (4) and packaged (b) (4) for topical ophthalmic use. Lot numbers: 12072007, 12112008.

UVA Irradiation
The UV-X Illumination System is a portable electronic medical device. The device's light emitting diode (LED) was used to deliver a metered dose of UVA light to a targeted treatment area for illuminating the cornea during CXL. System specifications are shown below.

Table 3: UVA System Specifications

Function	Description
Light Source	(b) (4) UV-grade LED; LED Laser class (b) (4) (b) (4)
Wavelength	365 nm (b) (4)
Optical Power	Maximum (b) (4) mW
Beam Diameter	7.5 mm to 11.5 mm
Light Emission	Continuous wave
Intensity Setting	3.0 mW/cm^2 (±0.3 mW/cm^2)
Safety Class	Class II Equipment (b) (4)
Medical Device Class	(b) (4)
EMI EMC Class	Class B (b) (4)
Power Supply	(b) (4) 9V; max. 1.7A

Source: 5.3.5.1 Section 9.4.2.1

Reviewer's Comments:

The UV-X Illumination System was utilized during the Phase 3 clinical studies reported in the NDA. Avedro, Inc. believes that the KXL System for which commercial approval is being requested is equivalent to the UV-X Illumination System which was used during the Phase 3 clinical studies. The following table compares the specifications of the UV-X Illumination System with the KXL System.

Table 8: Comparison of UV-X Illumination System (Phase III) Specifications with the KXL System (Commercial) Specifications.

	Phase III	***Commercial***
UVA System	*UV-X Illumination System*	*KXL System*
Device Type (Classification)	*LED illumination device (Class II)*	*LED illumination device (Class II)*
Wavelength	*Wavelength: 365 (b) (4) nm*	*LED: Wavelength: 365 (b) (4) nm*
Device Configuration	*Illumination system at end of an arm, attached to a floor stand or a patient bed*	*Illumination system at end of an articulated arm on top of floor stand, wireless remote control and a system console*
Light Emission	*Continuous wave (CW)*	*Continuous wave (CW)*
Illumination Intensity	*3.0 mW/cm^2*	*3.0 mW/cm^2*
Illumination Diameter(s)	*Variable steps 7.0, 9.0 and 11.0 mm*	*Fixed at 9.0 mm*
Treatment Time	*30 minutes*	*30 minutes*
Patient Positioning	*On bed*	*On bed*
Targeting System	*N/A*	*Laser crosshairs*
Focal Plane Setting	*Subjective (homogeneity of UV pattern)*	*Objective (crossed laser beams)*
Electric Power	*100V to 240 V*	*100 V to 240 V*
Intensity Check	*UV light meter delivered with UV-X System*	*Integrated UV light meter*
Laser and LED Safety Compliance	*IEC 60825-1*	*IEC 60825-1* *IEC 62471*
Electrical Safety Compliance	*IE 60601-1*	*IEC 60601-1*

Source: 3.2R Device Information

The illumination diameter is 9.0 mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm steps. The 9mm aperture was utilized in approximately 90% of patients studied.

Inclusion/Exclusion Criteria

Inclusion
To be included in the study, subjects had to be 14 years of age or older; provide written informed consent; and be willing and able to comply with the schedule of follow-up

visits. Subjects who had 1 or both eyes meet all of the following criteria were considered eligible for this study:

1. Had a diagnosis of:

   a. corneal ectasia after refractive corneal surgery (e.g., laser-assisted in-situ keratomileusis [LASIK], photorefractive keratectomy [PRK], or epi-LASIK) or
   b. progressive keratoconus defined as 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.

   [NOTE: Subjects with a clear history of progression but without prior documentation could have been followed and re-examined at a later visit to confirm progression.]

2. Had central or inferior steepening on the Pentacam map.
3. Had axial topography consistent with corneal ectasia
4. For progressive keratoconus, presence of one or more findings associated with keratoconus, such as:

   a. Fleischer ring
   b. Vogt striae
   c. Corneal thinning
   d. Corneal scarring
   e. Scissoring of the retinoscopic reflex

5. Steepest keratometry (K_{max}) value ≥ 47.00 D (progressive keratoconus only)
6. I-S ratio > 1.5 on the Pentacam map or Orbscan map (progressive keratoconus only)
7. Had a BSCVA worse than 20/20 (<53 letters on Early Treatment of Diabetic Retinopathy Study [ETDRS] chart)
8. Contact Lens Wearers Only:

Removal of contact lenses for the required period of time prior to the Screening refraction:

Contact Lens Type	*Minimum Discontinuation Time*
Soft	3 Days
Soft Extended Wear	1 Week
Soft Toric	2 Weeks
Rigid gas permeable	2 Weeks

Exclusion

Subjects who met any of the following criteria were excluded from this study:

1. Eyes classified as either normal, atypical normal (except corneal ectasia), or keratoconus suspect on the severity grading scheme.
2. For progressive keratoconus, a history of previous corneal surgery or the insertion of Intacs in the eye(s) to be treated.
3. Corneal pachymetry at the screening exam that was < 400 microns at the thinnest point measured by Pentacam in the eye(s) to be treated when the riboflavin with dextran solution alone was to be used or < 300 microns when the riboflavin without dextran was to be used.
4. Previous ocular condition (other than refractive error) in the eye(s) to be treated that could have predisposed the eye for future complications, for example:
    a. History of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.)
    b. Clinically significant corneal scarring in the CXL treatment zone that was not related to corneal ectasia or prior refractive surgery or, in the investigator's opinion, would interfere with the cross-linking procedure.
5. A history of chemical injury or delayed epithelial healing in the eye(s) to be treated.
6. Pregnancy (including plan to become pregnant) or lactation during the course of the study
7. A known sensitivity to study medications
8. Subjects with nystagmus or any other condition that would have prevented a steady gaze during the CXL treatment or other diagnostic tests.
9. Subjects with a current condition that, in the investigator's opinion, would have interfered with or prolonged epithelial healing.

Primary Efficacy Variable

The primary efficacy parameter was corneal curvature, as measured by maximum keratometry (Kmax) in the study eyes (based on Pentacam assessments). Study success was defined as a difference of ≥1 D in the mean change in Kmax from baseline to 12 months between the CXL group and control group.

Reviewer's Comment:

Originally, the primary efficacy endpoint was planned as the difference between the CXL group and the control group in Kmax from baseline to Month 3. At the time the studies were initially planned, the applicant believed that the primary efficacy endpoint could be analyzed at 3 months post-procedure based on their review of the existing literature. The Agency recommended a 12 month endpoint.

However, the applicant reviewed subsequent additional literature which suggested to them that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize (Wittig-Silva et al, 2008; Wollensak and Iomdina, 2009; Caporossi et al, 2010).

The Applicant extended the time point of the primary efficacy endpoint analysis to 12 months. The definition of clinically meaningful benefit continued to be a ≥1 D difference in the mean change in Kmax between the CXL group and the control group. Per the applicant, this extension of the primary efficacy endpoint analysis to 12 months occurred after all subjects completed the study but prior to any formal efficacy analyses and, therefore, did not have any impact on conduct of the study.

In a submission dated 2/26/14, the applicant stated that the extension of the primary efficacy timepoint analysis to 12 months was documented in the statistical analysis plans which were provided in the following NDA sections: UVX-001 Appendix 16.1.9, UVX-002 Appendix 16.1.9, and UVX-003 Appendix 16.1.9. Per the applicant, the protocols were not amended as they already contained efficacy measurements of Kmax (maximal corneal curvature) at the 12 month timepoint.

Analysis Populations

The intent-to-treat (ITT) population consisted of all treated subjects, analyzed according to the randomized treatment. All safety and efficacy analyses were performed using the ITT population. All subjects received the appropriate randomized treatment; therefore, the ITT and safety populations are the same.

The per protocol (PP) set was to consist of all ITT subjects in whom there were no major protocol deviations, as defined at end of study. Per the SAP, all efficacy analyses of the Kmax endpoint were to be conducted on the PP population. However, no per protocol population was defined, and no analyses were performed

Schedule of Visits

Table 4: 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[e]	X			X	X	X	X	X
Slit Lamp Exam[f]	X		X	X	X	X	X	X
Endothelial cell count[g]	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

Table 4: Schedule of Visits and Procedures (Continued)

Procedure	Screen	Treatment Visit[a]	Post-Treatment Visits: 1 Day	1 Week	1 Month	3 Months	6 Months	12 Months
Adverse Events		X	X	X	X	X	X	X
CXL or Sham Treatment		X						
Ultrasound Pachymetry[b]		X						

[a] Repeat measurements from the screening exam prior to study treatment were allowed if needed to provide accurate baseline measurements before CXL or sham 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] Intraocular pressure measurements were taken using Goldmann applanation tonometry at the slit lamp. Tonopen could have been used only if applanation tonometry was medically contraindicated.
[f] 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.
[g] Endothelial cell counts were obtained via specular or confocal microscopy.
[b] 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 sham treatment.

Source: 5.3.5.1 UVX-001 Section 9.5.1.1

Investigators 001

Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
01	107	R. Doyle Stulting, MD, PhD Emory Vision 875 Johnson Ferry Road, Suite 100 Atlanta, Georgia 30342	Brad Randleman, MD Maria Anneke Woodward, MD

5.3.2 UVX-002: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Progressive Keratoconus

Study UVX-002 was a multicenter study conducted at 9 centers in the United States. The study was conducted under US Investigational New Drug (IND) application 77,882. Study UVX-002 was administered and monitored by Avedro, Inc.

General Study Design
This was a prospective, randomized, parallel-group, open-label, sham-controlled, multicenter study to determine the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing CXL in eyes with progressive keratoconus.

This trial is nearly identical in design to UVX-001 with the following exceptions:

- Only patients with keratoconus were eligible to be enrolled
- Individuals who took Vitamin C supplements within one week were excluded.

Schedule of Visits
Identical to UVX-001 with the exception that Confocal Microscopy was optional in UVX-002.

Investigators 002

Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
01[a]	0	Perry S. Binder, M.D. Gordon, Binder & Weiss Vision Institute 8910 University Center Lane, Suite 800 San Diego, CA 92122	Michael Gordon, M.D. Jack Weiss, M.D.
02	11	Eric D. Donnenfeld, M.D. Ophthalmic Consultants of Long Island 2000 North Village Ave., Suite 402 Rockville Centre, NY 11570	Marguerite McDonald, M.D. David Sachs, M.D. Henry Perry, M.D. Samuel Berger, M.D. Raymond Mariani, OD Robert Rudman, OD Jay Fiore,M.D. Joan Fredrickson Teraza Conway
03	54	Peter Hersh, M.D. Cornea and Laser Eye Institute 300 Frank W. Burr Blvd., Suite 71 Teaneck, NJ 07666	Kristen Fry
04	26	Francis Price, Jr. M.D. Price Vision Group and Cornea Research Foundation of America 9002 N. Meridian St., Suite 100 Indianapolis, IN 46260	Kashif Baig, M.D. Vanessa Ngakeng, M.D. Kathe Kelley, OD Faye Peters, OD Andera Wills, OD Matt McCauley, M.D. Robert Kwon, M.D. Kathleen Kelley, OD Carlindo Pereira, M.D. Marianne Price, Ph.D. Brian Planchard, M.D. Clorissa Quillin Kelly Fairchild Amanda Lopez

Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
05	14	David Schanzlin, M.D. University of California, San Diego Shiley Eye Center 9415 Campus Point Drive, Suite 259 La Jolla, CA 92093	Tracy L. Purcell, Ph.D. Dorothy Wang, OD
07	4	Steven Trokel, M.D. Columbia University Edward S. Harkness Eye Institute 635 West 165th Street New York City, NY 10032	Richard Braunstein, M.D. Amilia Schrier, M.D.
08	16	Daniel Durrie, M.D. 5530 College Blvd., Suite 201 Overland Park, KS 66211	Jason Stahl, M.D. Marla Kennard, OD Kelly Grosdider, OD Timothy Cavanaugh, M.D. Joseph Tauber, M.D. Ryan Smith, M.D. Teresa K Nolan, OMA Diana L Collins, OMA Joel D. Hunter, M.D.
09	1	William Trattler, M.D. Center for Excellence in Eye Care 8940 North Kendell Drive, Suite 400E Miami, FL 33176	Carlos Buzengo, M.D. Charles Kaiser, M.D. Matty Infante Marcia Vallori

Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
10	16	David Hardten, M.D., FACS Minnesota Eye Consultants, P.A. 710 E. 24th Street, Suite 100 Minneapolis, MN 55404	Richard Lindstrom, M.D. Elizabeth Davis, M.D. Sherman Reeves, M.D. Parag Parekh, M.D. Marlane Brown, OD Scott Hauswirth, OD Deanna Harter, OD Ahmad Fahmy, OD Mona Fahmy, OD John Berdahl, M.D. Noumia Cloutier-Gill, OD Aarup A. Kubal, M.D. Jill M. Farenbaugh, CCRP Emily Tungseth Amanda E. Burbach, COA Sara M. Jenkins, CCRP Jessica Standefer,COMT Jill M. Adrian Jill M. Spude Kristal Jones Jacob A. Kozisek, OD Jaclyn G. Morin, OD Alyson Blakstad, OD Lindsay R. Fallenstein, CCRP Allison Parent Preeya K. Gupta, M.D.
11	5	Walter Stark, M.D. Wilmer Eye Institute Johns Hopkins Hospital 600 N. Wolfe Street Baltimore, MD 21287	Albert Jun, M.D., Ph.D. Roy Chuck, M.D., Ph.D. Alisa Kim , M.D. Huan Meng

[a] No patients enrolled

5.3.3 UVX-003: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Corneal Ectasia after Refractive Surgery

Study UVX-003 was a multicenter study conducted at 9 centers in the United States. The study was conducted under US Investigational New Drug (IND) application 77,882. Study UVX-003 was administered and monitored by Avedro, Inc.

General Study Design
This was a prospective, randomized, parallel-group, open-label, sham-controlled, multicenter study to determine the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing CXL in eyes with progressive keratoconus.

This trial is nearly identical in design to UVX-001 with the following exceptions:

- Only patients with corneal ectasia were eligible to be enrolled
- Individuals who took Vitamin C supplements within one week were excluded.

Schedule of Visits
Identical to UVX-001 with the exception that Confocal Microscopy was optional in UVX-003.

Investigators 003

Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
01	0	Perry S. Binder, M.D. Gordon, Binder & Weiss Vision Institute 8910 University Center Lane, Suite 800 San Diego, CA 92122	Michael Gordon, M.D. Jack Weiss, M.D.
02	19	Eric D. Donnenfeld, M.D. Ophthalmic Consultants of Long Island 2000 North Village Ave., Suite 402 Rockville Centre, NY 11570	Marguerite McDonald, M.D. David Sachs, M.D. Henry Perry, M.D. Samuel Berger, M.D. Raymond Mariani, OD Robert Rudman, OD Jay Fiore,M.D. Joan Fredrickson Teraza Conway
03	30	Peter Hersh, M.D. Cornea and Laser Eye Institute 300 Frank W. Burr Blvd., Suite 71 Teaneck, NJ 07666	Kristen Fry
04	21	Francis Price, Jr. M.D. Price Vision Group and Cornea Research Foundation of America 9002 N. Meridian St., Suite 100 Indianapolis, IN 46260	Kashif Baig, M.D. Vanessa Ngakeng, M.D. Kathe Kelley, OD Faye Peters, OD Andera Wills, OD Matt McCauley, M.D. Robert Kwon, M.D. Kathleen Kelley, OD Carlindo Pereira, M.D. Marianne Price,Ph.D. Brian Planchard, M.D. Clorissa Quillin Kelly Fairchild Amanda Lopez

Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
05	8	David Schanzlin, M.D. University of California, San Diego Shiley Eye Center 9415 Campus Point Drive, Suite 259 La Jolla, CA 92093	Tracy L. Purcell, Ph.D. Dorothy Wang, OD
07	5	Steven Trokel, M.D. Columbia University Edward S. Harkness Eye Institute 635 West 165th Street New York City, NY 10032	Richard Braunstein, M.D. Amilia Schrier, M.D.
08	6	Daniel Durrie, M.D. 5530 College Blvd., Suite 201 Overland Park, KS 66211	Jason Stahl, M.D. Marla Kennard, OD Kelly Grosdider, OD Timothy Cavanaugh, M.D. Joseph Tauber, M.D. Ryan Smith, M.D. Teresa K Nolan, OMA Diana L Collins, OMA Joel D. Hunter, M.D.
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Site No.	No. of Primary Eyes	Principal Investigator Name	Subinvestigators
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6 Review of Efficacy

Efficacy Summary

6.1 Indication

With the exception of Inclusion/Exclusion Criteria, the following Phase 3 studies utilized to evaluate safety and efficacy are essentially identical in design:

1. UVX-001: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking In Eyes with **Corneal Ectasia** or **Progressive Keratoconus**

2. UVX-002: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with **Progressive Keratoconus**

3. UVX-003: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with **Corneal Ectasia after Refractive Surgery.**

6.1.1 Methods

See Section 5.3 for specific trial study design.

6.1.2 Demographics

Table 4: Demographics: UVX-001 [Keratoconus Subjects], UVX-002 and Pooled Data (ITT Population)

		UVX-001		UVX-002		Pooled	
		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%)	56 (85.1%)	63 (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 based on the number of subjects reporting 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.
Source: Table 14.1.5 (Section 14.1.1), UVX-001; Table 14.1.5, UVX-002; Table 14.1.5, Section 8.1

In the pooled studies, the CXL and control groups were generally comparable with regard to demographic characteristics. The mean age (range) was 31years (range of 14 to 57 years) in the CXL group and 35 (15 to 63 years) in the control group. Most subjects in each treatment group were Caucasian (74%, CXL; 77%, control); the remaining subjects (overall frequencies) were black/African-American (11%), Asian (2%), or "other race" (12%). The majority of subjects in each treatment group were male (74%, CXL; 66%, control).

In the individual studies, the treatment groups were generally comparable with regards to demographic characteristics. The percentage of white subjects was higher in UVX-002 than in UVX-001. Otherwise, demographic characteristics for keratoconus subjects in UVX-001 and subjects in UVX-002 were similar.

Table 5: Demographics: UVX-001 [Corneal Ectasia Subjects], UVX-003 and Pooled Data (ITT Population)

		UVX-001		UVX-003		Pooled	
		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 based on the number of subjects reporting 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 Eastern, 1 Indian, 1 Latino, and 1 mixed.
Source: Table 14.1.5 (Section 14.1.2), UVX-001, Table 14.1.5, UVX-003, Table 14.1.5 (Section 8.2)

In the pooled population, the CXL and control groups were generally comparable with regard to demographic and baseline characteristics. The mean age (range) was 42years (22 to 63 years) in the CXL group and 42 years (24 to 62 years) in the control group. Most subjects in each treatment group were Caucasian (78%, CXL; 81%, control); the remaining subjects (overall frequencies) were black/African-American (10%), Asian (4%), or "other race" (7%). The majority of subjects in each treatment group were male (64%, CXL; 73%, control).

Demographic characteristics for corneal ectasia subjects in UVX-001 and subjects in UVX-003 were similar.

6.1.3 Subject Disposition

UVX-001
Keratoconus

Table 7: Subject Disposition (Keratoconus Subjects, UVX-001, ITT Population)

Category	CXL Group (N=29)	Control Group (N=29)	Total (N=58)
Received Randomized Treatment (CXL or Sham) (N)	29	29	58
Completed study (n, %)	20 (69.0%)	12 (41.4%)	32 (55.2%)
Discontinued study (n, %)	9 (31.0%)	17 (58.6%)	26 (44.8%)
Administrative[a]	9 (31.0%)	17 (58.6%)	26 (44.8%)

[a] The investigator left the site and the study was terminated by the Sponsor.
Source: Table 14.1.1 (Section 14.1.1)

Table 14.1.1
Subject Disposition
(ITT Population)

		CXL Group (N=29)	Control Group (N=29)	Total (N=58)
Reason for Study Exit	n	29	29	58
	Completed Study	20(69.0%)	12(41.4%)	32(55.2%)
	Voluntary Withdrawal	0	0	0
	Administrative	9(31.0%)	17(58.6%)	26(44.8%)
	Lost to Follow-Up	0	0	0

The ITT population consisted of 58 keratoconus subjects, with 29 subjects randomized to each of the 2 treatment groups.

As shown in the table above, more than half of the keratoconus subjects (55%) completed the study, with more subjects completing in the CXL group (69%) compared with the control group (41%). The proportion of subjects who discontinued the study was 31% and 59% in the CXL and control groups, respectively. All subjects who discontinued prematurely did so because the investigator left the site and the study was terminated by the Sponsor. None of the subjects discontinued due to an AE.

Corneal Ectasia

Table 8: Subject Disposition (Corneal Ectasia Subjects, UVX-001, ITT Population)

Category	CXL Group (N=24)	Control Group (N=25)	Total (N=49)
Received Randomized Treatment (CXL or Sham) (N)	24	25	49
Completed study (n, %)	20 (83.3%)	11 (44.0%)	31 (63.3%)
Discontinued study (n, %)	4 (16.7%)	14 (56.0%)	18 (36.7%)
Other[a]	3 (12.5%)	10 (40.0%)	13 (26.5%)
Lost to Follow-Up	1 (4.2%)	3 (12.0%)	4 (8.2%)
Administrative	0	1 (4.0%)	1 (2.0%)

[a] The investigator left the site and the study was terminated by the Sponsor.
Source: Table 14.1.1 (Section 14.1.2)

Table 14.1.1
Subject Disposition
(ITT Population)

		CXL Group (N=24)	Control Group (N=25)	Total (N=49)
Reason for Study Exit	n	24	25	49
	Completed Study	20(83.3%)	11(44.0%)	31(63.3%)
	Voluntary Withdrawal	0	0	0
	Administrative	0	1(4.0%)	1(2.0%)
	Lost to Follow-Up	1(4.2%)	3(12.0%)	4(8.2%)
	Other	3(12.5%)	10(40.0%)	13(26.5%)

The ITT population consisted of 49 corneal ectasia subjects, with 24 subjects randomized the CXL group and 25 randomized to the control group.

As shown in the table above, the majority of corneal ectasia subjects (63%) completed the study, with more subjects completing in the CXL group (83%) compared with the control group (44%). The proportion of subjects who discontinued the study was 17% and 56% in the CXL and control groups, respectively. The majority of subjects who discontinued prematurely did so because the investigator left the site and the study was terminated by the Sponsor.

UVX-002
Keratoconus

Table 6: Subject Disposition (UVX-002, ITT Population)

	CXL Group (N=73)	Control Group (N=74)	Total (N=147)
Received Randomized Treatment (CXL or Sham) (N)	73	74	147
Completed study (n, %)	65 (89.0%)	62 (83.8%)	127 (86.4%)
Discontinued study (n, %)	8 (11.0%)	12 (16.2%)	20 (13.6%)
Voluntary withdrawal (unrelated to safety)	3 (4.1%)	8 (10.8%)	11 (7.5%)
Lost to follow-up	5 (6.8%)	4 (5.4%)	9 (6.1%)

Source: Table 14.1.1 (Section 14.1)

14.1.1 Subject Disposition (ITT Population)

		CXL Group (N=73)	Control Group (N=74)	Total (N=147)
Reason for Study Exit	n	73	74	147
	Completed Study	65(89.0%)	62(83.8%)	127(86.4%)
	Voluntary Withdrawal	3(4.1%)	8(10.8%)	11(7.5%)
	Administrative	0	0	0
	Lost to Follow-Up	5(6.8%)	4(5.4%)	9(6.1%)

A total of 147 subjects were randomized into the study (73, CXL group; 74, control [sham] group) (Table 6). Most subjects (86%) completed the study. The proportion of subjects who discontinued the study was 11% and 16% in the CXL and control groups, respectively. Reasons for discontinuation were voluntary withdrawal (unrelated to safety) and lost to follow-up.

Table 6: Subject Disposition (UVX-003, ITT Population)

	CXL Group (N=67)	Control Group (N=63)	Total (N=130)
Received Randomized Treatment (CXL or Sham) (N)	67	63	130
Completed study (n, %)	56 (83.6%)	48 (76.2%)	104 (80.0%)
Discontinued study (n, %)	11 (16.4%)	15 (23.8%)	26 (20.0%)
Other	5 (7.5%)	7 (11.1%)	12 (9.2%)
Lost to Follow-Up	6 (9.0%)	3 (4.8%)	9 (6.9%)
Voluntary Withdrawal (unrelated to safety)	0	5 (7.9%)	5 (3.8%)

Source: Table 14.1.1 (Section 14.1)

14.1.1 Subject Disposition (ITT Population)

		CXL Group (N=67)	Control Group (N=63)	Total (N=130)
Reason for Study Exit	n	67	63	130
	Completed Study	56(83.6%)	48(76.2%)	104(80.0%)
	Voluntary Withdrawal	0	5(7.9%)	5(3.8%)
	Administrative	0	0	0
	Lost to Follow-Up	6(9.0%)	3(4.8%)	9(6.9%)
	Other	5(7.5%)	7(11.1%)	12(9.2%)

The ITT population consisted of 130 subjects, with 67 subjects randomized to the CXL group and 63 subjects randomized to the control group.

As shown in the table above, most subjects (80%) completed the study. The proportion of subjects who discontinued the study was 16% and 24% in the CXL and control groups, respectively. Reasons for discontinuation were “other” (9%), lost to follow-up (7%), and voluntarily withdrawal (unrelated to safety) (4%).

6.1.4 Analysis of Primary Endpoint(s)

Mean Changes from Baseline Kmax in the Randomized Study Eye (LOCF)

6.1.4.1 UVX-001

Table 25: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF) - (Keratoconus Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline: CXL Group (N=29)	Change from Baseline: Control Group (N=29)	P-value[a]
Baseline	n	29	29			
	Mean	60.6	61.9			
	SD	7.34	8.32			
	Median	59.2	62.0			
	Min, Max	50, 79	48, 81			
Month 1	n	29	29	29	29	
	Mean	62.0	58.9	1.4	–2.9	0.0563
	SD	8.41	14.07	2.68	11.66	
	Median	60.1	58.9	0.9	–0.3	
	Min, Max	52, 89	–0, 79	–1, 14	–62, 5	
Month 3	n	29	29	29	29	
	Mean	60.3	62.0	–0.3	0.1	0.5085
	SD	8.23	9.38	2.68	2.61	
	Median	58.3	60.8	–0.7	–0.1	
	Min, Max	48, 86	48, 87	–5, 11	–7, 7	
Month 6	n	29	29	29	29	
	Mean	59.7	62.3	–0.9	0.5	0.0674
	SD	8.10	9.52	2.61	2.99	
	Median	57.7	60.8	–1.1	0.0	
	Min, Max	48, 83	48, 84	–5, 7	–7, 8	
Month 12	n	29	29	29	29	
	Mean	59.2	62.3	–1.4	0.5	0.0175
	SD	7.82	9.52	2.84	2.99	
	Median	58.4	60.8	–1.0	0.0	
	Min, Max	49, 83	48, 84	–8, 7	–7, 8	

[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)
Source: Table 14.2.1.1.2 (Section 14.2.1)

Reviewer's Comment:

The dataset contains errors. For example, Kmax cannot be zero (Control Group, Month 1); change from baseline cannot be -62 (Control Group, Month 1). This analysis will need to be re-run after non-physiological values are removed.

Based on the dataset provided, the difference between the CXL and control groups in mean change from baseline in Kmax progressively increased, in favor of CXL, from Month 3 through Month 12 for keratoconus subjects. The difference between treatment groups was < 1.0 D at Month 3 (–0.3 D vs. 0.1 D) and exceeded 1.0 D at Month 6 (–0.9 D vs. 0.5 D) and Month 12 (–1.4 D vs. 0.5 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant at Month 12 (p=0.0175).

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

Table 38: Mean Changes from Baseline K_{max} in the Randomized Study Eye (LOCF) - (Corneal Ectasia Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline		P-value[a]
				CXL Group (N=24)	Control Group (N=25)	
Baseline	n	24	25			
	Mean	56.3	55.0			
	SD	6.26	5.45			
	Median	56.2	55.2			
	Min, Max	47, 72	47, 68			
Month 1	n	24	25	24	25	
	Mean	57.4	55.8	1.1	0.8	0.6408
	SD	7.59	5.96	2.06	1.73	
	Median	57.2	55.5	0.9	0.5	
	Min, Max	43, 77	48, 67	–5, 6	–3, 7	
Month 3	n	24	25	24	25	
	Mean	56.4	56.0	0.1	1.0	0.0382
	SD	7.02	6.40	1.26	1.68	
	Median	55.1	56.0	0.0	0.7	
	Min, Max	48, 74	48, 70	–3, 3	–1, 7	
Month 6	n	24	25	24	25	
	Mean	55.7	56.0	–0.6	1.0	0.0010
	SD	6.60	6.19	1.61	1.69	
	Median	53.2	56.6	–0.8	0.6	
	Min, Max	48, 70	48, 70	–5, 3	–1, 7	
Month 12	n	24	25	24	25	
	Mean	55.3	56.0	–1.0	1.0	0.0001
	SD	6.62	6.19	1.68	1.69	
	Median	53.3	56.6	–0.9	0.6	
	Min, Max	47, 71	48, 70	–5, 3	–1, 7	

[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)
Source: Table 14.2.1.1.2 (Section 14.2.2)

Reviewer's Comment:

The difference between the CXL and control groups in mean change from baseline Kmax progressively increased, 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 (0.1 D vs.

1.0 D) and exceeded 1.0 D at Month 6 (–0.6 D vs. 1.0 D) and Month 12 (–1.0 D vs. 1.0 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant at Month 12 (p=0.0001).

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

6.1.4.2 UVX-002

The ITT population of UVX-002 consisted of all treated subjects, analyzed according to randomized treatment (N=147). The Safety population of UVX-002 consisted of all treated subjects, analyzed according to the treatment actually received (N=147). Although the total number of subjects in each population was the same, the actual subjects comprising the 2 populations was different because 2 subjects, 1 per treatment group, inadvertently received the incorrect randomized study treatment on Day 0 (Subjects (b) (6)).

Table 15: Mean Changes from Baseline K_{max} in the Randomized Study Eye: LOCF (UVX-002, ITT Population)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline		P-value[a]
				CXL Group (N=73)	Control Group (N=74)	
Baseline	n	73	74			
	Mean	61.0	59.8			
	SD	9.81	9.16			
	Median	58.0	57.5			
	Min, Max	48, 96	48, 90			
Month 1	n	73	74	73	74	
	Mean	62.2	59.3	1.2	–0.5	0.0678
	SD	9.37	11.91	3.36	7.18	
	Median	59.4	57.3	1.0	–0.0	
	Min, Max	49, 94	0, 91	–17, 8	–58, 8	
Month 3	n	73	74	73	74	
	Mean	60.4	60.5	–0.6	0.7	0.1142
	SD	8.92	10.91	4.44	5.58	
	Median	58.4	57.8	0.0	–0.1	
	Min, Max	48, 90	49, 108	–33, 6	–9, 44	
Month 6	n	73	74	73	74	
	Mean	59.9	61.0	–1.1	1.2	0.0129
	SD	8.34	11.25	5.06	5.71	
	Median	57.9	58.0	–0.5	–0.1	
	Min, Max	47, 88	49, 108	–36, 12	–9, 44	
Month 12	n	73	74	73	74	
	Mean	59.3	61.0	–1.7	1.2	0.0010
	SD	8.50	11.25	4.69	5.70	
	Median	58.0	58.0	–1.0	–0.1	
	Min, Max	47, 91	49, 108	–32, 7	–9, 44	

[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).
Source: Table 14.2.1.1.3 (Section 14.2.1)

Reviewer's Comment:

The dataset contains errors. For example, Kmax cannot be zero (Control Group, Month 1); change from baseline cannot be -58 (Control Group, Month 1). This analysis will need to be re-run after non-physiological values are removed.

Based on the dataset provided, the difference between the CXL and control groups in mean change from baseline Kmax progressively increased, in favor of CXL, from Month 3 through Month 12. The difference between treatment groups exceeded 1.0 D at Month 3 (–0.6 D vs. 0.7 D), Month 6 (–1.1 D vs. 1.2 D), and Month 12 (–1.7 D vs. 1.2 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant at Month 12 (p=0.0010).

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

6.1.4.3 UVX-003

The ITT population of UVX-003 consisted of all treated subjects (N=130).

Table 15: Mean Changes from Baseline K_{max} in the Randomized Study Eye: LOCF (UVX-003, ITT Population)

Visit	Statistic	CXL Group (N=67)[a]	Control Group (N=63)	Change from Baseline: CXL Group (N=67)[a]	Change from Baseline: Control Group (N=63)	P-value[b]
Baseline	n	63	63			
	Mean	55.1	54.7			
	SD	7.09	6.77			
	Median	53.9	52.9			
	Min, Max	45, 75	43, 76			
Month 1	n	67	63	63	63	
	Mean	56.0	54.7	1.0	0.0	0.0005
	SD	7.04	6.67	1.84	1.10	
	Median	55.7	53.4	0.6	0.1	
	Min, Max	45, 76	43, 75	–3, 6	–2, 2	
Month 3	n	67	63	63	63	
	Mean	54.9	55.3	–0.2	0.6	0.0386
	SD	6.99	6.81	2.38	1.88	
	Median	53.4	53.8	0.1	0.5	
	Min, Max	45, 77	43, 78	–9, 7	–3, 12	
Month 6	n	67	63	63	63	
	Mean	54.6	55.2	–0.5	0.5	0.0084
	SD	6.64	6.96	1.95	2.28	
	Median	53.3	53.8	–0.2	0.5	
	Min, Max	45, 71	43, 78	–8, 3	–9, 12	
Month 12	n	67	63	63	63	
	Mean	54.5	55.2	–0.5	0.5	0.0080
	SD	6.85	6.97	2.21	2.26	
	Median	53.5	54.1	–0.3	0.5	
	Min, Max	45, 74	43, 78	–10, 4	–9, 12	

[a] Four subjects did not have a K_{max} measurement at baseline.
[b] 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).
Source: Table 14.2.1.1.3 (Section 14.2.1)

Reviewer's Comment:

The difference between the CXL and control groups in mean change from baseline Kmax favored CXL from Month 3 through Month 12. The difference between treatment

groups was less than 1.0 D at Month 3 (–0.2 D vs. 0.6 D) and reached 1.0 D at Month 6 (–0.5 D vs. 0.5 D) and Month 12 (–0.5 D vs. 0.5 D). The difference between treatment groups in mean change from baseline Kmax was statistically significant (p=0.0080) at Month 12.

Regarding Observed Values, however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment.

6.1.5 Analysis of Secondary Endpoints(s)

See Section 7.3.5. Submission Specific Primary Safety Concerns.

6.1.6 Other Endpoints

See Section 7.3.5. Submission Specific Primary Safety Concerns.

6.1.7 Subpopulations

The primary efficacy endpoint was analyzed by the following subgroups: age (< median or ≥ median); gender (male or female); and race (white or non-white).

Subgroup results were provided for the pooled studies (UVX-001 keratoconus data pooled with the UVX-002 data/ UVX-001 corneal ectasia data pooled with the UVX-003 data).[2]

The oldest subject enrolled was 63 (there were no protocol upper age limits). The youngest patient enrolled was 14 (there was a protocol lower age limit of 14).

There are no clinically relevant differences in the subgroups evaluated (age, race, gender) in the treatment of keratoconus or corneal ectasia versus the treatment groups as a whole.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Per the applicant, the frequency, duration, and intensity of the UVA exposure was based on several *in vitro* and clinical studies and scientific analysis mimicking the derived accepted guidelines from which human clinical trials have been conducted to date (Caporossi et al, 2006; Kanellopolous et al, 2006, 2009; Kohlhaas et al, 2005;

2 Source: 2.7.3 Corneal Ectasia; 2.7.3 Keratoconus

Mazzotta et al, 2006, 2008, and 2010; Schnitzler et al, 2000; Spoerl et al, 1998, 2000, 2007; Wollensak et al, 2003a, 2003b, 2003c, 2004a, 2004b, 2004c).

Per the applicant, UVA irradiation at a wavelength of 365 nm at an intensity of 3 mW/cm^2 (±0.3 mW/cm^2) for 30 minutes resulting in a total dose of 5.4 J/cm_2 was utilized. An analysis and safety justification of the frequency, duration, and intensity of this protocol was detailed by Spoerl et al (2007). The concentration of riboflavin was also selected based on several *in vitro* and clinical studies and scientific analysis (Caporossi et al, 2006; Kanellopolous et al, 2006, 2009; Kohlhaas et al, 2005; Mazzotta et al, 2006, 2008, and 2010; Schnitzler et al, 2000; Spoerl et al, 1998, 2000, 2007; Wollensak et al, 2003a, 2003b, 2003c, 2004a, 2004b, 2004c). Given the rate of riboflavin diffusion into the de-epithelialized corneal stroma, an application regimen of 1 drop every 2 minutes for 30 minutes was recommended before commencing the UV application, with additional applications at 2-minute intervals during treatment.

Reviewer's Comment:

A review of the comprehensive literature provided by the applicant (see Appendix 9.1) supports the applicant's choice of riboflavin ophthalmic solution concentration and UVA irradiation at a wavelength of 365 nm at an intensity of 3 mW/cm^2 (±0.3 mW/cm^2) for 30 minutes resulting in a total dose of 5.4 J/cm^2.

A review of the current literature and presentations supports a dose of irradiation at 5.4 J/cm^2; higher intensities can be substituted if given for shorter durations, i.e.30 mW/cm^2 for 3 minutes.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Corneal crosslinking is proposed as a single, one-time, treatment.

6.1.10 Additional Efficacy Issues/Analyses

Observed case analyses were conducted to measure the sensitivity of the LOCF analyses. Kmax results were summarized using observed values at each visit through Month 12; however, the number of observations in the randomized study eye dropped markedly 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 only 2 subjects in the control group of UVX-002 had an observation for the randomized study eye at Month 12: none of the subjects in the control group of UVX-001 and only 2 subjects in the control group of UVX-003 had an observation for the randomized study eye at Month 12.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following Phase 3 studies utilized to evaluate safety and efficacy are essentially identical in design:

1. UVX-001: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking In Eyes with **Corneal Ectasia** or **Progressive Keratoconus**

2. UVX-002: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with **Progressive Keratoconus**

3. UVX-003: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with **Corneal Ectasia after Refractive Surgery.**

7.1.2 Categorization of Adverse Events

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1. nomenclature.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See Section 7.4.1.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All CXL-treated eyes received the same UVA irradiation treatment (365 nm at an irradiance of 3 mW/cm^2 for 30 minutes). Sham-treated eyes underwent the same UV irradiation procedure except the UVA light source was not illuminated during the procedure. For both indications, the mean number of drops of riboflavin with dextran administered prior to the UVA procedure (or mock procedure in sham eyes) and during the UVA procedure (or mock procedure in sham eyes) was approximately 16 and 15 drops, respectively. CXL-treated eyes that did not meet the requirement for corneal thickness ≥ 400 microns after UVA pre-treatment with riboflavin plus dextran received a second solution of riboflavin without dextran. No subjects received CXL treatment more than once in the same eye. Subjects who received CXL in untreated fellow eyes (from CXL group) and untreated sham eye and untreated fellow eye (from control group) received CXL at least 3 months after the initial randomized treatment. The Table below summarizes the number of eyes treated with any CXL in the pooled keratoconus and corneal ectasia studies (i.e., primary study eyes randomized to CXL, primary study eyes randomized to control which subsequently received CXL, and fellow eyes in either treatment group which received CXL).

Table 3: Treatments Administered in the Pooled Keratoconus and Corneal Ectasia Studies: Primary (Study) Eyes and Secondary Eyes (Safety Population)

Randomization:	**Primary (Study Eye)**		**Secondary Eyes**			**Total**
	CXL n (%)	**Sham n (%)**	**Fellow Eye CXL**	**None n (%)**	**Sham Eye CXL n (%)**	
SUBJECTS WITH KERATOCONUS						
Subjects Randomized to CXL (N=102)	102 (100.0)	---	56 (54.9)	46 (45.1)	---	---
Subjects Randomized to Sham (N=103)	---	103 (100.0)	41 (39.8)	9 (8.7)	94 (91.3)	---
Total CXL (N=293)	102 (34.8)	---	97 (33.1)	---	94 (32.1)	293 (100.0
SUBJECTS WITH CORNEAL ECTASIA						
Subjects Randomized to CXL (N=91)	91 (100.0)	---	26 (28.6)	65 (71.4)	---	---
Subjects Randomized to Sham (N=88)	---	88 (100.0)	22 (25.0)	8 (9.1)	80 (90.9)	---
Total CXL (N=219)	91 (41.6)	---	48 (21.9)	---	80 (36.5)	219 (100.0

Source: 2.5 Clinical Overview Section 4.2.3

7.2.2 Explorations for Dose Response

See Section 6.1.8.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing indicated or performed.

7.2.4 Routine Clinical Testing

There was adequate monitoring of the anterior and posterior segments of the eye, intraocular pressure, visual acuity, and adverse events.

Clinical laboratory evaluations were not performed for any of the studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of riboflavin ophthalmic solution given by the topical route of administration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Riboflavin (Vitamin B2) is a water-soluble vitamin that is the parent of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze many oxidation/reduction reactions in the body. Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photosensitizer.

There are no approved topical photosensitizers for the treatment of ocular conditions; there are no approved topical water-soluble vitamins for topical ocular administration.

There was adequate monitoring of the anterior and posterior segments of the eye, intraocular pressure, visual acuity, and adverse events.

7.3 Major Safety Results

7.3.1 Deaths

There were no subject deaths in any treatment group in any trial.

7.3.2 Nonfatal Serious Adverse Events

UVX-001
In the CXL group, no keratoconus or corneal ectasia subjects experienced a serious adverse event during the study. Two subjects in the control group (1, keratoconus; 1, corneal ectasia) experienced a serious adverse event. Subject (b) (6) (keratoconus) had serious adverse events of two suicide attempts from baseline to Month 3. Subject (b) (6) (corneal ectasia) had a serious adverse event of head injury from baseline to Month 3.

Subject (b) (6) (keratoconus subject, control group) was a 20-year-old Caucasian, non-Hispanic female who received control treatment OD on (b) (6) (Day 26) and again on (b) (6) (Day 72), the subject attempted suicide, resulting in hospitalization on each occasion. Treatment included 1 liter IV N-acetylcysteine, 50g PO charcoal, and PO Mucomyst (dose unknown) for the first suicide attempt and 1 liter IV N-acetylcysteine and 50g PO charcoal for the second attempt. Outcome was reported as resolved (same day as onset). The subject remained in the study and received CXL treatment OD (crossover from sham) (b) (6) She completed the study and attended all follow-up visits through Month 12 (except for Month 1, which was missed due to the attempted suicide).

Subject (b) (6) (corneal ectasia subject, control group) was a 50-year-old Caucasian, non-Hispanic male who received control treatment OS on (b) (6) (Day 34), the subject experienced severe head injury and was hospitalized. The event was considered by the investigator to be unrelated to riboflavin, UVA light, and epithelial defect. Outcome was reported as resolved (date not reported). The subject received CXL treatment OS (crossover from sham) (b) (6) The subject's last evaluation was at Month 3; thereafter, the subject was lost to follow-up and was discontinued from the study.

UVX-002
None of the subjects in the keratoconus CXL group and 3 subjects in the control group experienced a serious adverse event during the study. In the control group, serious adverse events were corneal ulcer following CXL in the sham eye (Subject (b) (6)); appendicitis requiring appendectomy (Subject (b) (6)); and an infectious cat bite requiring hospitalization (Subject (b) (6)). Each of these events occurred after Month 3.

Subject (b) (6) (control group) was a 19-year-old Caucasian, non-Hispanic male who received sham treatment OS (b) (6) and subsequently received CXL treatment OU at the Month 6 follow-up visit (b) (6) He developed a corneal ulcer

(OS) with onset 3 days after receiving CXL treatment. The corneal ulcer persisted. On (b) (6) 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 corneal ulcer resolved (b) (6)

Subject (b) (6) (control group) was a 35-year-old, Caucasian (ethnicity not reported) female who developed appendicitis approximately 5 months after baseline. She was hospitalized and had an appendectomy. Outcome was reported as resolved.

Subject (b) (6) (control group) was a 52-year-old, Caucasian, non-Hispanic female who was hospitalized for treatment of an infectious cat bite approximately 9 months after baseline. Outcome was reported as resolved.

UVX-003
One subject in the corneal ectasia CXL group and no subjects in the control group experienced a serious adverse vent during the study.

Subject (b) (6) (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. The Lasik flap was lifted to remove the epithelial growth. The corneal epithelium defect resolved on Day 43.

Reviewer's Comment:

Subject (b) (6) in UVX-002, who developed a corneal ulcer OS, was originally a control patient OD and received CXL treatment OS at the six month OD follow-up. This adverse event appears directly related to the planned corneal epithelial debridement for CXL treatment.

7.3.3 Dropouts and/or Discontinuations

See Section 6.1.3.

7.3.4 Significant Adverse Events

See Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

Corneal Endothelial Cell Counts

Table 64: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed Values (Keratoconus Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline: CXL Group (N=29)	Change from Baseline: Control Group (N=29)	p-value[a]
Baseline	n	27	28			
	Mean	2564	2454			
	SD	595.61	369.13			
	Median	2612	2493			
	Min, Max	0, 3311	1600, 3304			
Month 3	n	26	29	24	28	
	Mean	2576	2548	–5.0	109	0.3152
	SD	335.29	403.79	534.8	243.3	
	Median	2543	2530	–69	106	
	Min, Max	1910, 3304	1615, 3387	–759, 2120	–327, 643	
Month 12	n	20	0	18	0	
	Mean	2652	----	65.8	----	----
	SD	381.78	----	574.2	----	
	Median	2728	----	76.9	----	
	Min, Max	1967, 3178	----	–666, 2032	----	

[a] p-value is on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)
Source: Table 14.3.4 (Section 14.3.5.1)

Reviewer's Comment:

The indicated values in the table above are not physiologically possible (e.g., Baseline, CXL Group) or are very unlikely to be physiologically possible (e.g. Month 3 and Month 12, Max Change from Baseline).

Table 70: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed Values (Corneal Ectasia Subjects, UVX-001, ITT Population)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline: CXL Group (N=24)	Change from Baseline: Control Group (N=25)	p-value[a]
Baseline	n	22	23			
	Mean	2392	2550			
	SD	250.72	429.50			
	Median	2472	2500			
	Min, Max	1831, 2761	1808, 3406			
Month 3	n	20	22	19	20	
	Mean	2338	2516	–42	–75	0.6458
	SD	275.93	384.46	196.8	241.3	
	Median	2360	2584	–39	–87	
	Min, Max	1818, 2961	1681, 3333	–389, 290	–562, 631	
Month 12	n	20	0	18	0	
	Mean	2309	----	–65	----	----
	SD	247.41	----	162.4	----	
	Median	2296	----	–55	----	
	Min, Max	1755, 2746	----	–388, 174	----	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)

Source: Table 14.3.4 (Section 14.3.5.2)

Table 37: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed Values (UVX-002, Safety Population)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline		p-value[a]
				CXL Group (N=73)	Control Group (N=74)	
Baseline	n	68	66			
	Mean	2600	2627			
	SD	395.84	398.20			
	Median	2571	2692			
	Min, Max	1387, 3546	1186, 3407			
Month 1	n	7	4	7	4	
	Mean	2576	2712	135	302	0.5694
	SD	472.57	513.43	521.3	265.3	
	Median	2591	2887	–37	223	
	Min, Max	2061, 3311	1968, 3106	–418, 970	97, 666	
Month 3	n	60	62	58	58	
	Mean	2486	2621	–88	–18	0.3698
	SD	387.77	433.99	475.7	362.8	
	Median	2467	2654	–67	–34	
	Min, Max	1086, 3185	1052, 3472	–2E3, 983	–872, 797	
Month 6	n	12	2	11	2	
	Mean	2598	2730	–71	130	0.2446
	SD	288.66	335.17	219.1	122.3	
	Median	2504	2730	–119	130	
	Min, Max	2169, 3106	2493, 2967	–382, 267	43, 216	
Month 12	n	60	1	58	1	
	Mean	2615	2996	3.6	330	0.4534
	SD	363.86		428.6		
	Median	2636	2996	67.5	330	
	Min, Max	1529, 3322	2996, 2996	–1E3, 966	330, 330	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)
Source: Table 14.3.4 (Section 14.3.5)

Table 37: Endothelial Cell Count (/mm^2) in the Randomized Eye – Observed Values (UVX-003, ITT Population)

Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline: CXL Group (N=67)	Change from Baseline: Control Group (N=63)	p-value[a]
Baseline	n	65	58			
	Mean	2518	2598			
	SD	578.76	417.76			
	Median	2525	2701			
	Min, Max	528, 5154	1629, 3592			
Month 1	n	7	5	7	5	
	Mean	2407	2384	–43	31.8	0.6207
	SD	334.16	527.49	268.0	223.6	
	Median	2494	2571	9.0	25.0	
	Min, Max	1919, 2786	1453, 2725	–433, 317	–182, 344	
Month 3	n	57	55	57	51	
	Mean	2447	2559	–45	–45	0.9977
	SD	377.06	386.68	435.1	354.1	
	Median	2467	2577	–51	–49	
	Min, Max	1232, 3049	1706, 3412	–886, 1641	–857, 771	
Month 6	n	5	4	5	4	
	Mean	2624	2725	–20	186	0.5755
	SD	482.75	348.15	644.3	295.8	
	Median	2584	2564	–252	248	
	Min, Max	2079, 3390	2525, 3246	–640, 933	–181, 430	
Month 12	n	49	2	49	2	
	Mean	2380	2283	–124	–343	0.4763
	SD	382.51	352.85	420.1	557.2	
	Median	2392	2283	–129	–343	
	Min, Max	1305, 3125	2033, 2532	–1E3, 1085	–737, 51	

[a] p-values are on difference between CXL and control by t-test (p-value is 2-sided, significance level 0.05)
Source: Table 14.3.4 (Section 14.3.5)

Reviewer's Comment:

Results are presented for baseline and Months 3 and 12 in UVX-001; Months 1 and 6 were not planned visits for endothelial cell count determinations. Results are presented for baseline, Month 1, Month 3, Month 6, and Month 12 in UVX-002 and -003; Months 1 and 6 were not planned visits for endothelial cell count determinations.

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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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.

≥ 15-Letter Loss in Best Corrected Visual Acuity

Table 67: Best Spectacle-Corrected Visual Acuity Loss of ≥15 Letters (Keratoconus Subjects, UVX-001, ITT Population)

Visit	Category		CXL Group (N=29)	Control Group (N=29)
Week 1	N		27	27
	No	n (%)	21 (77.8%)	27 (100.0%)
	Yes	n (%)	6 (22.2%)	0
Month 1	N		29	27
	No	n (%)	27 (93.1%)	26 (96.3%)
	Yes	n (%)	2 (6.9%)	1 (3.7%)
Month 3	N		29	27
	No	n (%)	28 (96.6%)	27 (100.0%)
	Yes	n (%)	1 (3.4%)	0
Month 6	N		28	17
	No	n (%)	28 (100.0%)	17 (100.0%)
	Yes	n (%)	0	0
Month 12	N		20	0
	No	n (%)	20 (100.0%)	0
	Yes	n (%)	0	0
Month 12 (LOCF)	N		29	28
	No	n (%)	29 (100.0%)	28 (100.0%)
	Yes	n (%)	0	0

Source: Table 14.3.9 (Section 14.3.5.1)

Table 73: Best Spectacle-Corrected Visual Acuity Loss of ≥15 Letters (Corneal Ectasia Subjects, UVX-001, ITT Population)

Visit	Category		CXL Group (N=24)	Control Group (N=25)
Week 1	N		22	24
	No	n (%)	16 (72.7%)	24 (100.0%)
	Yes	n (%)	6 (27.3%)	0
Month 1	N		23	24
	No	n (%)	21 (91.3%)	24 (100.0%)
	Yes	n (%)	2 (8.7%)	0
Month 3	N		22	23
	No	n (%)	21 (95.5%)	22 (95.7%)
	Yes	n (%)	1 (4.5%)	1 (4.3%)
Month 6	N		21	12
	No	n (%)	21 (100.0%)	12 (100.0%)
	Yes	n (%)	0	0
Month 12	N		19	0
	No	n (%)	18 (94.7%)	0
	Yes	n (%)	1 (5.3%)	0
Month 12 (LOCF)	N		23	24
	No	n (%)	22 (95.7%)	24 (100.0%)
	Yes	n (%)	1 (4.3%)	0

Source: Table 14.3.9 (Section 14.3.5.2)

Table 40: Best Spectacle-Corrected Visual Acuity Loss of ≥15 Letters (UVX-002, Safety Population)

Visit	Category		CXL Group (N=73)	Control Group (N=74)
Week 1	N		58	70
	No	n (%)	42 (72.4%)	69 (98.6%)
	Yes	n (%)	16 (27.6%)	1 (1.4%)
Month 1	N		67	68
	No	n (%)	64 (95.5%)	67 (98.5%)
	Yes	n (%)	3 (4.5%)	1 (1.5%)
Month 3	N		66	66
	No	n (%)	64 (97.0%)	63 (95.5%)
	Yes	n (%)	2 (3.0%)	3 (4.5%)
Month 6	N		64	17
	No	n (%)	62 (96.9%)	16 (94.1%)
	Yes	n (%)	2 (3.1%)	1 (5.9%)
Month 12	N		63	1
	No	n (%)	62 (98.4%)	1 (100.0%)
	Yes	n (%)	1 (1.6%)	0
Month 12 (LOCF)	N		69	71
	No	n (%)	68 (98.6%)	68 (95.8%)
	Yes	n (%)	1 (1.4%)	3 (4.2%)

Source: Table 14.3.9 (Section 14.3.5)

Table 40: Best Spectacle-Corrected Visual Acuity Loss of ≥15 Letters (UVX-003, ITT Population)

Visit	Category		CXL Group (N=67)	Control Group (N=63)
Week 1	N		60	58
	No	n (%)	41 (68.3%)	53 (91.4%)
	Yes	n (%)	19 (31.7%)	5 (8.6%)
Month 1	N		63	59
	No	n (%)	55 (87.3%)	56 (94.9%)
	Yes	n (%)	8 (12.7%)	3 (5.1%)
Month 3	N		61	58
	No	n (%)	60 (98.4%)	54 (93.1%)
	Yes	n (%)	1 (1.6%)	4 (6.9%)
Month 6	N		59	18
	No	n (%)	58 (98.3%)	17 (94.4%)
	Yes	n (%)	1 (1.7%)	1 (5.6%)
Month 12	N		53	2
	No	n (%)	51 (96.2%)	2 (100.0%)
	Yes	n (%)	2 (3.8%)	0
Month 12 (LOCF)	N		65	62
	No	n (%)	63 (96.9%)	57 (91.9%)
	Yes	n (%)	2 (3.1%)	5 (8.1%)

Source: Table 14.3.9 (Section 14.3.5)

Reviewer's Comment:

The number of subjects with a clinically significant decrease in vision after 12 months is very small for both treatment groups for both indications and favors CXL treatment.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 7: Summary of Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Keratoconus)

MedDRA System Organ Class/ Preferred Term	CXL Group (N=102)	Control Group (N=103)
Number (%) of Subjects Reporting Any AEs[a]	336:87 (85.3%)	75:44 (42.7%)
Eye Disorders	304:86 (84.3%)	59:40 (38.8%)
Corneal opacity	73:58 (56.9%)	4:4 (3.9%)
Punctate keratitis	28:25 (24.5%)	8:8 (7.8%)
Corneal striae	25:24 (23.5%)	12:12 (11.7%)
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%)
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%)
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
Other Ocular TEAEs		
Corneal scar	9:7 (6.9%)	5:5 (4.9%)
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%)

[a] 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.
Source: Table 14.3.1.2.1, Section 8.1

Table 16: Summary of Adverse Events Reported by ≥2% of Subjects in the CXL Group from Baseline to Month 3 (Safety Population: Corneal Ectasia)

MedDRA System Organ Class/ Preferred Term	CXL Group (N=91)	Control Group (N=88)
Number (%) of Subjects Reporting Any AEs	328:82 (90.1%)	66:38 (43.2%)
Ocular TEAEs	296:82 (90.1%)	53:33 (37.5%)
Corneal opacity	74:62 (68.1%)	7:7 (8.0%)
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%)
Photophobia	18:17 (18.7%)	0
Vision blurred	15:15 (16.5%)	4:4 (4.5%)
Dry eye	14:13 (14.3%)	4:4 (4.5%)
Visual acuity reduced	10:10 (11.0%)	1:1 (1.1%)
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 dysfunction	4:3 (3.3%)	2:2 (2.3%)
Ocular hyperaemia	3:3 (3.3%)	1:1 (1.1%)
Corneal scar	3:3 (3.3%)	1:1 (1.1%)
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

Note: Ocular events in the fellow eye are excluded.
Source: Table 14.3.1.2.1, Section 8.2

Reviewer's Comment:

These are pooled common adverse event tables (i.e. UVX-001 and -002 for keratoconus and -001 and -003 for corneal ectasia). Note: subjects in the CXL group

had topical anesthetic administered to the study eye, and the corneal epithelium was removed; subjects in the sham treatment group had topical anesthetic administered to the study eye but did not have the corneal epithelium removed.

The most common adverse events for either indication at ≥ 10% are corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following corneal epithelial debridement.

These adverse event tables only represent reported events through Month 3. . 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 eyes (from CXL group) and untreated sham eye and untreated fellow eye (from 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.

By the last study visit, 165/248 (66.5%) eye disorders resolved. The percentage of events that resolved (resolved events/total number of events) by the last study visit was 9798% for vision blurred 93% for corneal epithelium defect, 90% for punctate keratitis, and 83% for corneal opacity (haze).[3]

By the last study visit for corneal ectasia subjects, 118/190 (63%) eye disorders resolved. The percentage of events that resolved (resolved events/total number of events) by the last study visit was 90% for punctate keratitis, 89% for vision blurred, 89% for corneal epithelium defect, and 80% for corneal opacity (haze).[4]

3 Table 14.3.5.14
4 Table 14.3.5.14

Table 56: Summary of Ocular Adverse Events with Incidence ≥5% in Any CXL Eye at Any Time (Keratoconus Subjects, UVX-001, Safety Population)

Preferred Term	CXL Group (N=29)	Any CXL Eye (N=74)
Number (%) of Subjects With Any AEs[a]/ Number (%) of CXL Eyes With Any AEs[b]	29 (100.0%)	72 (97.3%)
Corneal opacity[c]	23 (79.3%)	64 (86.5%)
Corneal epithelium defect	13 (44.8%)	40 (54.1%)
Corneal striae	13 (44.8%)	32 (43.2%)
Punctate keratitis	12 (41.4%)	27 (36.5%)
Visual acuity reduced	5 (17.2%)	17 (23.0%)
Vision blurred	7 (24.1%)	16 (21.6%)
Corneal scar	5 (17.2%)	12 (16.2%)
Eye pain	4 (13.8%)	10 (13.5%)
Eye irritation	6 (20.7%)	7 (9.5%)
Lacrimation increased	2 (6.9%)	7 (9.5%)
Foreign body sensation in eyes	3 (10.3%)	6 (8.1%)
Photophobia	5 (17.2%)	6 (8.1%)
Conjunctival hyperaemia	3 (10.3%)	5 (6.8%)
Eye discharge	2 (6.9%)	4 (5.4%)

[a] Applicable to column 2 of this table.
[b] Applicable to column 3 of this table.
[c] One case of corneal opacity (CXL group) was reported as "mild stromal opacities – OD". All other cases of corneal opacity were reported as haze (Listing 16.2.16.4).
Source: Table 14.3.1.2.1 (Section 14.3.1.1), Table 14.3.1.2.2 (Section 14.3.1.1)

Table 62: Summary of Ocular Adverse Events with Incidence ≥ 5% in Any CXL Eye at Any Time (Corneal Ectasia Subjects, UVX-001, Safety Population)

Preferred Term	CXL Group (N=24)	Any CXL Eye (N=57)
Number (%) of Subjects With Any AEs[a]/ Number (%) of CXL Eyes With Any AEs[b]	23 (95.8%)	56 (98.2%)
Corneal opacity[c]	22 (91.7%)	54 (94.7%)
Punctate keratitis	5 (20.8%)	24 (42.1%)
Corneal epithelium defect	10 (41.7%)	20 (35.1%)
Photophobia	6 (25.0%)	17 (29.8%)
Corneal striae	3 (12.5%)	15 (26.3%)
Vision blurred	4 (16.7%)	12 (21.1%)
Visual acuity reduced	3 (12.5%)	12 (21.1%)
Eye pain	6 (25.0%)	11 (19.3%)
Lacrimation increased	4 (16.7%)	6 (10.5%)
Corneal disorder	2 (8.3%)	5 (8.8%)
Foreign body sensation in eyes	2 (8.3%)	5 (8.8%)
Ocular discomfort	3 (12.5%)	5 (8.8%)
Dry eye	2 (8.3%)	4 (7.0%)
Anterior chamber flare	2 (8.3%)	3 (5.3%)
Conjunctival hyperaemia	0	3 (5.3%)
Corneal oedema	1 (4.2%)	3 (5.3%)
Meibomian gland dysfunction	0	3 (5.3%)
Ocular hyperaemia	0	3 (5.3%)
Ulcerative keratitis	0	3 (5.3%)

[a] Applicable to column 2 of this table.
[b] Applicable to column 3 of this table.
[c] Almost all cases of corneal opacity were reported as haze (Listing 16.2.16.4).
Source: Table 14.3.1.2.1 (Section 14.3.1.2), Table 14.3.1.2.2 (Section 14.3.1.2)

Reviewer's Comment:

The preceding tables present all treatment emergent adverse events with incidence ≥ 5% observed at any time during follow-up in any eye receiving CXL in keratoconus or corneal ectasia patients in UVX-001. The results for the CXL group from baseline to Month 3 are provided for comparison.

The proportion of CXL eyes with a treatment emergent adverse event (at any time) was generally comparable to the incidence of treatment emergent adverse events from baseline to Month 3 (controlled phase).

Table 35: Summary of Ocular Adverse Events with Incidence ≥2% in Any CXL Eye at Any Time (UVX-002, Safety Population)

Preferred Term	CXL Group (N=73)	Any CXL Eye (N=219)
Number (%) of Subjects With Any AEs[a]/ Number (%) of CXL Eyes With Any AEs[b]	58 (79.5%)	177 (80.8%)
Corneal opacity[c]	35 (47.9%)	114 (52.1%)
Eye pain	13 (17.8%)	48 (21.9%)
Corneal striae	11 (15.1%)	38 (17.4%)
Punctate keratitis	13 (17.8%)	35 (16.0%)
Visual acuity reduced	5 (6.8%)	31 (14.2%)
Corneal epithelium defect	10 (13.7%)	29 (13.2%)
Vision blurred	9 (12.3%)	26 (11.9%)
Photophobia	6 (8.2%)	22 (10.0%)
Dry eye	4 (5.5%)	15 (6.8%)
Conjunctival hyperaemia	7 (9.6%)	14 (6.4%)
Eye irritation	4 (5.5%)	11 (5.0%)
Lacrimation increased	3 (4.1%)	11 (5.0%)
Corneal scar	2 (2.7%)	10 (4.6%)
Eyelid oedema	5 (6.8%)	10 (4.6%)
Corneal thinning	1 (1.4%)	7 (3.2%)
Anterior chamber flare	3 (4.1%)	6 (2.7%)
Eye oedema	4 (5.5%)	6 (2.7%)
Glare	2 (2.7%)	6 (2.7%)
Ocular discomfort	0	6 (2.7%)
Eye pruritus	0	5 (2.3%)
Visual impairment	2 (2.7%)	5 (2.3%)

[a] Applicable to column 2 of this table.
[b] Applicable to column 3 of this table
[c] Once case of corneal opacity in any CXL eye was reported as "corneal epithelium opacity." All other cases of corneal opacity were reported as haze (Listing 16.2.16.4).
Source: Table 14.3.1.2.1 (Section 14.3.1), Table 14.3.1.2.2 (Section 14.3.1)

Reviewer's Comment:

The preceding table presents all treatment emergent adverse events with incidence ≥ 5% observed at any time during follow-up in any eye receiving CXL in keratoconus patients in UVX-002. The results for the CXL group from baseline to Month 3 are provided for comparison.

The proportion of CXL eyes with a treatment emergent adverse event (at any time) was generally comparable to the incidence of treatment emergent adverse events from baseline to Month 3 (controlled phase).

Table 35: Summary of Ocular Adverse Events with Incidence ≥2% in Any CXL Eye at Any Time (UVX-003, Safety Population)

Preferred Term	CXL Group (N=67)	Any CXL Eye (N=162)
Number (%) of Subjects With Any AEs[a]/ Number (%) of CXL Eyes With Any AEs[b]	59 (88.1%)	135 (83.3%)
Corneal opacity[c]	40 (59.7%)	94 (58.0%)
Corneal epithelium defect	14 (20.9%)	33 (20.4%)
Eye pain	18 (26.9%)	32 (19.8%)
Punctate keratitis	13 (19.4%)	27 (16.7%)
Photophobia	11 (16.4%)	25 (15.4%)
Visual acuity reduced	7 (10.4%)	25 (15.4%)
Vision blurred	11 (16.4%)	24 (14.8%)
Dry eye	11 (16.4%)	23 (14.2%)
Lacrimation increased	5 (7.5%)	14 (8.6%)
Ocular discomfort	5 (7.5%)	14 (8.6%)
Conjunctival hyperaemia	4 (6.0%)	13 (8.0%)
Eye irritation	7 (10.4%)	13 (8.0%)
Corneal striae	5 (7.5%)	12 (7.4%)
Eyelid oedema	4 (6.0%)	10 (6.2%)
Foreign body sensation in eyes	3 (4.5%)	10 (6.2%)
Meibomian gland dysfunction	3 (4.5%)	9 (5.6%)
Visual impairment	3 (4.5%)	9 (5.6%)
Anterior chamber flare	3 (4.5%)	6 (3.7%)
Blepharitis	0	6 (3.7%)
Halo vision	2 (3.0%)	5 (3.1%)
Ocular hyperaemia	3 (4.5%)	5 (3.1%)
Corneal abrasion	2 (3.0%)	4 (2.5%)
Corneal scar	1 (1.5%)	4 (2.5%)
Keratitis	3 (4.5%)	4 (2.5%)

[a] Applicable to column 2 of this table.
[b] Applicable to column 3 of this table.
[c] For 2 subjects, corneal opacity in any CXL eye was reported as "small anterior stromal opacity OS" or "superficial dot corneal opacities OS." All other cases of corneal opacity were reported as haze (Listing 16.2.16.4)
Source: Table 14.3.1.2.1 (Section 14.3.1), Table 14.3.1.2.2 (Section 14.3.1)

Reviewer's Comment:

The preceding table presents all treatment emergent adverse events with incidence ≥ 5% observed at any time during follow-up in any eye receiving CXL in corneal ectasia patients in UVX-003. The results for the CXL group from baseline to Month 3 are provided for comparison.

The proportion of CXL eyes with a treatment emergent adverse event (at any time) was generally comparable to the incidence of treatment emergent adverse events from baseline to Month 3 (controlled phase).

7.4.2 Laboratory Findings

Clinical laboratory evaluations were not performed for any of the studies.

7.4.3 Vital Signs

Vital signs (i.e., blood pressure, pulse, respiration) were not evaluated or recorded for any of the studies.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in any of the studies.

7.4.5 Special Safety Studies/Clinical Trials

A 120-Day Safety Update was submitted on February 19, 2014.

Per the update, the Phase 3 studies in support of the original NDA were completed with the final study reports submitted in the original NDA. Per the applicant, there are no additional safety data from these studies.

The applicant markets the similar product, VibeX, in Europe. The applicant will be expected to submit any postmarketing data on the VibeX product(s) which could be relevant for the safety profit for Photrexa.

7.4.6 Immunogenicity

Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No drug dose relationship to adverse effects was observed.

7.5.2 Time Dependency for Adverse Events

A review of time to onset of adverse events did not identify any safety concerns.

7.5.3 Drug-Demographic Interactions

Subgroup analyses were conducted for the primary efficacy endpoint based on age (< median or ≥ median); gender (male or female); race (white or non-white); and baseline disease severity (mild or moderate/severe). Disease severity was only reported for keratoconus subjects.

An analysis of adverse events by age category, gender, and race did not identify any safety concerns for any demographic subpopulation.

7.5.4 Drug-Disease Interactions

No drug-disease relationships were observed.

7.5.5 Drug-Drug Interactions

No adverse drug interactions have been identified. No specific drug interaction studies have been performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

The CXL treatment has not been evaluated in pregnant or lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of corneal collagen cross-linking has not been established in patients less than 14 years of age. In the Phase 3 studies, there were 16 patients between 14-18 years of age.

Submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Riboflavin or vitamin B2, a water soluble vitamin, is an essential nutrient and a natural component of many food products. It is considered to be non-toxic.

Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) are intended for topical ophthalmic use only. No pharmacological evidence of any potential for drug abuse with riboflavin ophthalmic solution exists. No studies related to overdosage in humans have been conducted.

7.7 Additional Submissions / Safety Issues

No additional submissions are expected in this review cycle:

- The applicant will be expected to reanalyze their keratoconus Kmax efficacy data from UVX-001 and -002 after non physiologic values are removed.

- The applicant will be expected to reanalyze their Endothelial Cell count data from UVX-001 after non physiologic values are removed.

8 Postmarket Experience

Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solution) are not presently marketed in any country. Therefore, there are no postmarketing reports for either Photexa formulation.

The applicant markets the similar product, VibeX, in Europe. The applicant will be expected to submit any postmarketing data on the VibeX product(s) which could be relevant for the safety profile for Photrexa.

9 Appendices

9.1 Literature Review/References

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Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol. 2006;17(4):356-60.

9.2 Advisory Committee Meeting

No Advisory Committee was necessary or convened for this drug product.

9.3 Financial Disclosure Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: 203324

Submission Date(s): 9/16/13

Applicant: Avedro, Inc.

Product: Photrexa and Photrexa (b) (4)/KXL System

Reviewer: William M. Boyd, M.D.

Covered Clinical Studies (Name and/or Number): UVX-001; UVX-002; UVX-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: UVX-001: 1; UVX-002: 11; UVX-003: 11		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 4 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 4 Significant equity interest held by investigator in sponsor of covered study: 4		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators.* Study designs *were* randomized with predominately objective endpoints; With the exception of Hersch MD, the clinical investigators identified in Form 3455 provided minimal contribution to study data.

After the clinical portion of the application was preliminarily reviewed; an inspection was requested for the following 5 sites:

	UVX-001	Stulting, M.D.	107 total patients
	UVX-002/003	Hersh, M.D.	84 total patients
	UVX-002/003	Price, M.D.	47 total patients
	UVX-002/003	Hardten, M.D.	31 total patients
	UVX-002/003	Donnenfeld, M.D.	30 total patients

Each of these 5 sites has a significant impact on the study results

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Attached (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study UVX-002 and UVX-003 (*Name of clinical study*) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☒ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Rhonda Bracey	Chief Accounting Officer
FIRM/ORGANIZATION: Avedro, Inc.	
SIGNATURE	Date (mm/dd/yyyy): 01/15/2012

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

FORM FDA 3455 (10/09) PSC Graphics (301) 443-1090 EF

(b) (6)

9.4 Labeling Recommendations

Incomplete, draft labeling is located in this review; additional requests for clinical information will necessitate revision to this labeling. CDRH recommend labeling for the device portion of this application has not been provided in this review cycle.

An edited version of the package insert submitted by the applicant on 9/16/13 is found in the Appendix of this review.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
03/07/2014

WILEY A CHAMBERS
03/07/2014