CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 303324

Date	April 15, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	203324
Applicant	Avedro, Inc.
Date of Resubmission	October 16, 2015
PDUFA Goal Date	April 16, 2016
505(b)(2)	Yes
Proprietary Name / Established (USAN) names	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
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	NDA 303324-1: treatment of progressive keratoconus NDA 303324-2: treatment of corneal ectasia following refractive surgery
Recommended:	Recommended for Approval by the Division of Transplant and Ophthalmology Products

1. Introduction

Keratoconus is an 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, including laser in-situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). 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 are currently limited FDA-approved treatments in the United States (US) for 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 may no longer adequately correct vision, and the use of rigid, scleral, or hybrid contact lenses may be 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 otherwise 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 (b) (4) nm; 3 (b) (4) mW/cm^2 irradiation; (b) (4) 30 minutes' duration) induces crosslinking.

Normally an iso-osmotic riboflavin ophthalmic solution is used. However, if corneal thickness is <400 µm, a (b) (4) riboflavin ophthalmic solution such as one without dextran is used until the corneal thickness is at least 400 µm.

For additional introductory detail, see the CDER Medical Officer's reviews dated 3/7/14 and 3/24/15 and the CDER CDTL reviews dated 3/10/14 and 3/27/15.

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 photoenhancer.

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.

General Regulatory Background

This is a combination product submitted under NDA 203324, which was studied under two INDs. The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for this combination product under RFD070013.

This is a 505(b)(2) application. While the applicant is not relying upon a listed product, the applicant is relying on non-clinical toxicology information about riboflavin for which they did not have a right to reference. The majority of the toxicological data for riboflavin was generated following oral administration when used as a 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 formulation(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 keratotonus (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 had requested approval of a riboflavin drug product which had not been studied in any clinical trial. The application was considered 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.

Avedro was issued a second Complete Response letter on March 29, 2015, and asked to provide additional clinical information to bridge the combination product device constituent, KXL System, to the IROC UV-X device used in the clinical studies UVX-001, UVX-002 and UVX-003 (e.g., by providing literature or Avedro data).

On June 11, 2015, Avedro met with FDA to discuss the Complete Response letter. The Agency stated that it could not make an assessment that the two UVA devices are interchangeable until the Avedro provided the additional comparative information identified in Items 2a – 2e of the Complete Response Letter of March 29, 2015. On August 10, 2015, a second Type A meeting was held to discuss the approach and methodology for Avedro to address items 2(a) through 2(e) in the March 29, 2015, Complete Response letter. Avedro submitted a Complete Response to the NDA on October 16, 2015.

3. Product Quality

DRUG PRODUCT COMPOSITION

Each mL contains:

Ingredient	Photrexa Viscous	Photrexa	Function
Riboflavin 5'-Phosphate Sodium, USP	1.53 mg	1.53 mg	Active
Dextran 500	(b) (4)		
Sodium chloride, USP			
Sodium phosphate, monobasic, USP			
Sodium phosphate, dibasic, USP			
Sterile water for injection, USP			

*1.53% riboflavin 5'-phosphate sodium is equal to 0.146% riboflavin 5'-phosphate and equal to 0.120% riboflavin.

CONTAINER CLOSURE SYSTEM

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		
(b) (4)		

QUALITY CONTROL DRUG PRODUCT SPECIFICATIONS

The quality control specifications for both riboflavin ophthalmic solutions, Photrexa (riboflavin ophthalmic solution) 20% dextran and Photrexa (b) (4) (riboflavin ophthalmic solution) 0% dextran, are provided in the table below.

Table 1: Drug Product Specifications

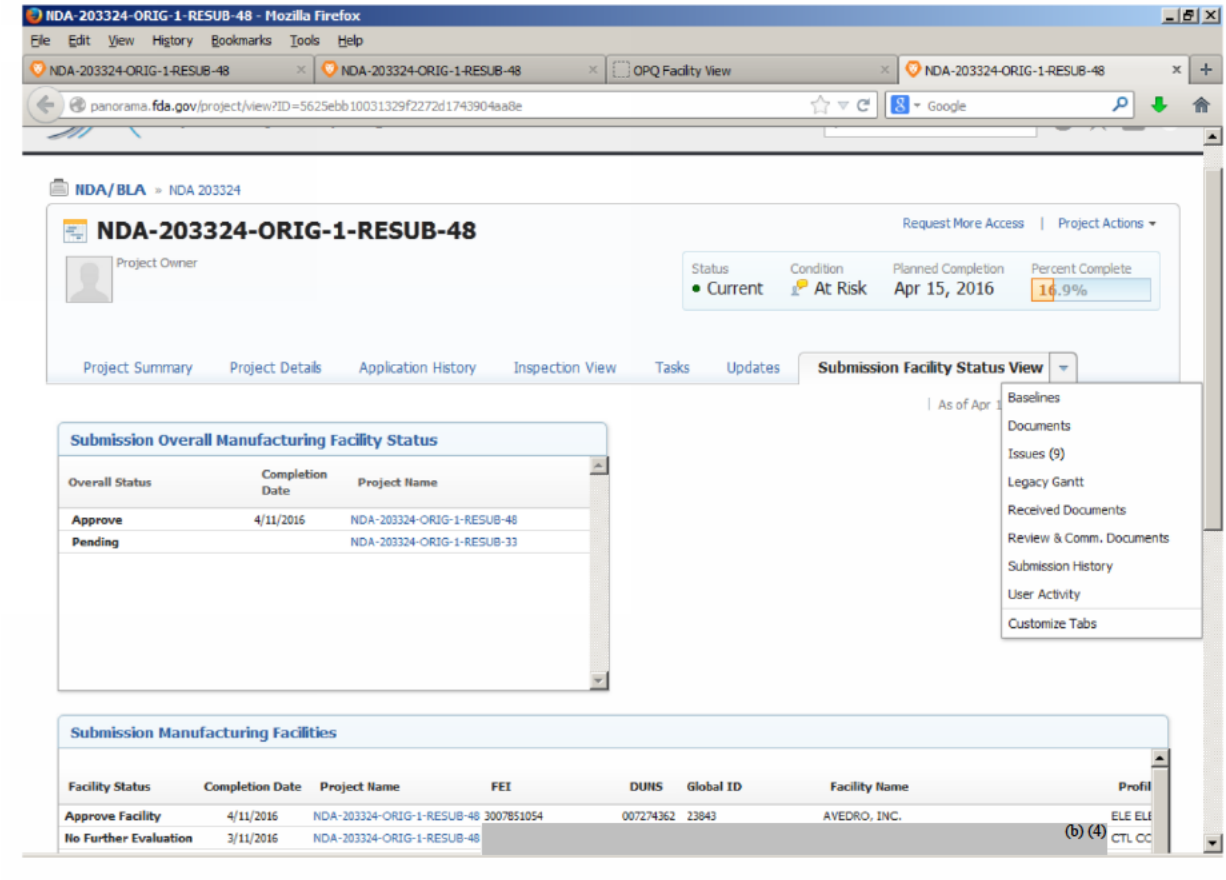
Test Description	Method	Acceptance Criteria
Appearance	Visual	A glass syringe containing a clear yellow solution, no visible particulates, and no leakage. May contain a minimal bubble
Identification	RP-HPLC	Retention time ((b) (4) %) and UV spectra conform
Assay	RP-HPLC	(b) (4) % LC ((b) (4) mg/ml)
Riboflavin 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 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) %

See Chemistry review dated 4/13/16.

This NDA is recommended for approval from the CMC perspective. All CMC issues concerning the drug substance and the drug product have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance.

FACILITIES

An overall recommendation of Acceptable has been made by the Office of Compliance.



4. Nonclinical Pharmacology/Toxicology

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

The subject of this NDA application is riboflavin 5'-phosphate ophthalmic solution 1.46 mg/mL 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 relies 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 photoenhancer.

The application is approvable from a Pharmacology/Toxicology perspective (i.e., Pharm/Tox recommends approval and has identified no deficiencies.

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. From the perspective of Clinical Pharmacology, it is recommended that this NDA be approved, provided that satisfactory agreement is reached between the applicant and FDA regarding the FDA revisions to the language in the package insert.

Riboflavin is used in corneal crosslinking as a photoenhancer, 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 eye drops, 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

The applicant's response to the March 29, 2015, Complete Response letter is located in SDN-048 (eCTD seq 0043) submitted 10/16/2015.

I. COMPLETE RESPONSE

The Complete Response letter cited the following items below as approvability issues.

Text in *blue italics* represents the applicant's response.

Text in *black italics* represents CDER Medical Officer/Reviewer Comments.

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.

   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.

Avedro: *At the June 11, 2015 Type A meeting, FDA agreed that Avedro may submit non-clinical data to address deficiencies 2(a) – 2(e) to bridge the KXL System to the IROC UV-X device and demonstrate that the two devices are interchangeable (June 11, 2015 Meeting Minutes). Subsequently, additional meetings were held on August 10, 19, 20, and 26 to discuss the non-clinical data necessary to address the device-to-device comparisons (August 2015 Meeting Minutes). As a result, Avedro submitted KXL UVA Equivalence Testing Protocol (DHF002-DV-22) containing a detailed description of the non-clinical tests to be conducted in order to comprehensively address the deficiencies 2(a) through 2(e). The Agency agreed that the protocol and acceptance criteria were appropriate to establish the bridge between the UVX and KXL devices (September 30, 2015 General Advice Letter). Avedro completed the non-clinical tests and all acceptance criteria for all studies were met (KXL UVA Equivalence Testing Report, DHF002-DV-23) therefore, establishing equivalence between the KXL and UVX devices.*

CDER: *This response is acceptable. See synopsis of KXL UVA Equivalence Testing Report, DHF002-DV-23, this section.*

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. 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.

Avedro: *Information to address Deficiency 2a is provided in the KXL UVX Equivalence Testing Protocol (DHF002-DV-22) and the KXL UVX Equivalence Testing Report (DHF002-DV-23).*

CDER: *This response is acceptable.*

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)

Avedro: *Information to address Deficiency 2b is provided in the KXL UVX Equivalence Testing Protocol (DHF002-DV-22) and the KXL UVX Equivalence Testing Report (DHF002-DV-23).*

Please note that the KXL irradiance maps provided in September 2013 and September 29, 2014 were not different from one another. However, the aperture design modification described in DHF002-DV-22 resulted in the submission of new irradiance maps contained in the aforementioned report which address deficiency 2b.

CDER: *This response is acceptable.*

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 crosslinking 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.

Avedro: *Information to address Deficiency 2c is provided in the KXL UVX Equivalence Testing Protocol (DHF002-DV-22) and the KXL UVX Equivalence Testing Report (DHF002-DV-23).*

CDER: *This response is acceptable.*

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.

Avedro: *Information to address Deficiency 2d is provided in the KXL UVX Equivalence Testing Protocol (DHF002-DV-22) and the KXL UVX Equivalence Testing Report (DHF002-DV-23).*

CDER: *This response is acceptable.*

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.

Avedro: *Information to address Deficiency 2e is provided in the KXL UVX Equivalence Testing Protocol (DHF002-DV-22) and the KXL UVX Equivalence Testing Report (DHF002-DV-23).*

CDER: *This response is acceptable.*

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.

Avedro: *EMC testing was completed on the KXL System, (b) (4) and the test report is provided in VAL-00095.*

CDER: *This response is acceptable.*

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) (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".

Avedro: *Avedro has updated the KXL Operator's Manual to include these minor administrative changes.*

CDER: *This response is acceptable.*

II. KXL UVA EQUIVALENCE TESTING REPORT, DHF002-DV-23 (SUMMARY)

This report contains results from bench testing and modeling experiments intended to demonstrate the equivalence of the KXL and UVX devices thereby addressing comments 2(a) - 2(e) of FDA's second Complete Response letter dated March 29, 2015. The experiments were conducted according to DHF002-DV-22 entitled KXL UVX Equivalence Testing Protocol. Both Avedro and FDA agreed to all methods, analytical procedures and acceptance criteria which were submitted to NDA 203324 on September 4, 2015. All acceptance criteria for all studies were met. Based upon the data submitted herein, Avedro considers the KXL and UVX devices are equivalent. As such, items 2a-2e of FDA's second Complete Response letter are considered fully addressed.

Table 1: Summary of Equivalence Testing Results

Report Section	Test	Acceptance Criteria	Result	Pass / Fail
8.4	Measurement of UV Irradiance Maps – Difference Between Profiles, No Eye Motion, Horizontal Axis	RMS Error (b) (4) %	(b) (4) %	PASS

Report Section	Test	Acceptance Criteria	Result	Pass / Fail
	Measurement of UV Irradiance Maps – Difference Between Profiles, No Eye Motion, Vertical Axis	RMS Error (b) (4) %	(b) (4) %	PASS
	Measurement of UV Irradiance Maps – Difference Between Profiles, With Eye Motion, Horizontal Axis	RMS Error %	%	PASS
	Measurement of UV Irradiance Maps – Difference Between Profiles, With Eye Motion, Vertical Axis	RMS Error %	%	PASS
9.4.1	Modeled UV Irradiance Maps – Difference in Total UV Irradiance, Front of Cornea	Difference %	%	PASS
	Modeled UV Irradiance Maps – Difference in Total UV Irradiance, Back of Cornea	Difference %	%	PASS
	Modeled UV Irradiance Maps – Difference Between Profiles, Front of Cornea	RMS Error %	%	PASS
	Modeled UV Irradiance Maps – Difference Between Profiles, Back of Cornea	RMS Error %	%	PASS
9.4.2	Modeled UV Irradiance Maps – Difference in Total UV Irradiance, Front of Lens	Difference %	%	PASS
	Modeled UV Irradiance Maps – Difference in Total UV Irradiance, Back of Lens	Difference %	%	PASS
	Modeled UV Irradiance Maps – Difference in Total UV Irradiance, Retinal Surface	Difference %	%	PASS
9.4.3	Retinal Safety Hazard – Visible Light Fluorescence	ISO 15004-2:2007 Eye Safe (No Potential Light Hazard)	Group 1	PASS
10.4	Measured Focal Plane Position – Range of Focal Plane Positions	Range of KXL ≤ Range of UVX	KXL Range = (b) (4) mm UVX Range = (b) (4) mm	PASS
	Measured Focal Plane Position – Standard Deviation of Focal Plane Positions	Std Dev of KXL ≤ Std Dev of UVX	KXL Std Dev = (b) (4) mm UVX Std Dev = (b) (4) mm	PASS

CDER: *The KXL and UVX devices are equivalent based on the Equivalence Testing Results provided. This response is acceptable.*

III. CDRH

CDRH Clinical Summary Statement Regarding Approvability Issues

Per the CDRH Clinical review finalized February 1, 2016:

Approval recommended for the progressive keratoconus indication in adults with the following conditions: 1) A Post-Approval Study Requirement, 2) Changes to the proposed Indication for Use to remove the word "treatment" (b) (4) (Given that the studies only captured a difference in the change in Kmax and did not demonstrate stability or slowed disease progression, we believe the indication should be modified from "treatment" to "slow the increase of maximum anterior corneal curvature as measured by corneal topography in adult patients with progressive keratoconus".) Not Approvable (Complete Response) recommended for the post-refractive corneal ectasia indication. A new clinical study is needed to support approval with 1) more clearly defined diagnostic and historical support for the iatrogenic disease studied as well as 2) improved methodology for collection of both safety and effectiveness data to reduce uncertainty with regard to adverse events and stability of benefit achieved, and 3) an appropriate study design to allow meaningful analysis of observed measurements rather than reliance on LOCF.

CDER: *CDER believes that both proposed indications should be approved because:*

a. whether created iatrogenically or naturally, each population has a thin cornea which is not structurally sound. The criteria for approval of a product do not differ as a result of prior harm.
b. the results are consistent with published literature demonstrating the safety and efficacy of corneal cross-linking.
c. the studies demonstrated efficacy because statistically significant differences between groups were demonstrated at both 3 and 12 months for the post-refractive ectasia patients and difference increased with time exceeding 1 D by 12 months in each study.
d. there are multiple published case series demonstrating the safety of corneal cross-linking for post-refractive ectasia patients. It is considered unethical to randomize post-refractive ectasia patients to a placebo treatment.
e. the Advisory Committee voted in favor of approving both indications.

CDER believes that the term "treatment "is acceptable as part of the indication statement because the definition of treatment does not require or imply a cure.

CDER believes that the proposed indication (b) (4) *should include pediatric patients aged 14 years old and older because:*

a. Keratoconus is the same disease in adults and teenagers and is often first detected in teenagers.
b. The cornea of children below the age of 2 years is not fully developed and behaves differently than the fully developed cornea. The cornea is fully developed by age 2 years.
d. Efficacy in pediatric patients above the age of 12 years can be extrapolated from studies in adults because the disease is the same in teenagers and adults.

e. Safety has been evaluated in pediatric patients aged 14 years and greater.

CDER believes that there is no identifiable safety concern upon which to require a postmarketing study. Current corneal crosslinking treatment patterns in both the United States and outside the United States include treatment with higher energy and shorter durations of UVA light exposure. Comparisons between the treatment regimens proposed in this application and those used in the community should be encouraged.

The applicant has provided a justification for the use of the LOCF method summarized below from page 16 of the applicant's Advisory Committee briefing document:

> The LOCF approach is valid for imputation of study data because keratoconus and post-refractive ectasia are progressive corneal ectatic conditions. Keratoconus and corneal ectasia patients do not experience spontaneous remission or become free of disease, rather a majority continue to progress and become worse as shown in the published literature. The LOCF approach does not account for any continued progression of disease in the control group, making it more difficult to demonstrate differences in mean change from baseline Kmax with CXL. As a result, the LOCF approach provides a conservative measure of success of the cross-linking procedure.

CDER believes that the LOCF analyses are relevant because the natural history of keratoconus and corneal ectasia does not suggest improvement without some type of intervention. In addition, the results were consistent with other methods of handling the missing data in this application.

CDRH Engineering/Physic Summary Statement Regarding Approvability Issues

Per the CDRH Engineering/Physics review finalized January 11, 2016:

> …If accurate, the newly submitted maps and profiles provide adequate evidence that the KXL device will produce UVA radiant exposure that is equivalent to that of the UVX device used in Avedro's cross-linking clinical trial. We note, however, that while Avedro represents the newly submitted color maps to be identical to the ones previously submitted, they are not actually identical…
>
> …Note in particular that the central peak energy density in the previous KXL map is less than that in the UVX map, whereas the central energy densities in the new maps are equivalent but thecentral color in the KXL map covers a larger area, in agreement with the corresponding profiles…
>
> …Rather than insisting upon the explanation from Avedro that is suggested in the above comment, I recommend officially accepting Avedro's assurance that the new color maps

are correct. However, my review and Avedro's last two submissions should be provided to the inspectors in the upcoming BIMO inspection of Avedro's manufacturing facility…

CDER: *The BIMO inspection of Avedro's manufacturing facility has received an overall recommendation of Acceptable by the Office of Compliance.*

8. Safety

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.

In keratoconus subjects, the most common adverse reactions in any CXL-treated eye were corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision. In corneal ectasia subjects, the most common ocular adverse reactions were corneal opacity (haze), corneal epithelium defect, corneal striae, dry eye, eye pain, punctate keratitis, photophobia, reduced visual acuity, and blurred vision. These events are expected sequelae following epithelial corneal debridement and occurred at a higher incidence than observed in control subjects, who did not undergo debridement or exposure to UVA light.

Adverse events reported in non-study, non-randomized CXL treated were similar in in terms of preferred terms and frequency to those seen in randomized study eyes.

For additional safety details, see the CDER Medical Officer's reviews dated 3/7/14 and 3/24/15 and the CDER CDTL reviews dated 3/10/14 and 3/27/15.

9. Regulatory Briefing/Advisory Committee Meeting

A Regulatory Briefing was held on Friday, March 20, 2015. For additional details, see the CDER CDTL review 3/27/15.

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. For additional details, see the CDER CDTL review 3/27/15.

10. Pediatrics

Submission of a pediatric assessment was not required because the application is for an orphan-designated indication.

For additional pediatric details, see the CDER Medical Officer's reviews dated 3/7/14 and 3/24/15 and the CDER CDTL reviews dated 3/10/14 and 3/27/15.

CDER believes that the proposed indication (b) (4) should include pediatric patients aged 14 years old and older because:

a. Keratoconus is the same disease in adults and teenagers and is often first detected in teenagers.
b. The cornea of children below the age of 2 years is not fully developed and behaves differently than the fully developed cornea. The cornea is fully developed by age 2 years.
d. Efficacy in pediatric patients above the age of 12 years can be extrapolated from studies in adults because the disease is the same in teenagers and adults.
e. Safety has been evaluated in pediatric patients aged 14 years and greater.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the Biostatistics review dated 4/10/16:

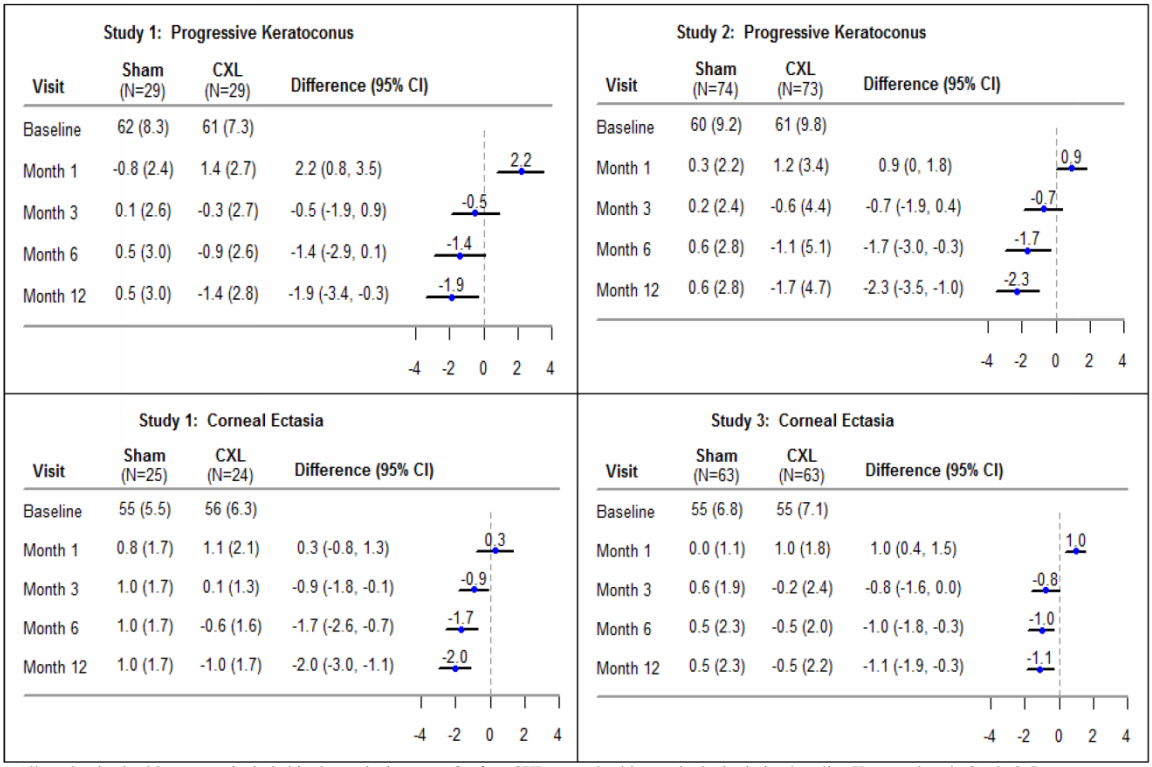
The applicant has received two Complete Response letters: one for the original NDA and one for the first resubmission. The two resubmissions did not include new clinical data. The first resubmission included additional literature and sensitivity analyses to further support the efficacy analysis methods and results from the three pivotal studies (UVX-001, UVX-002, and UVX-003) in the original NDA. The second resubmission provided responses to the device related issues. After reviewing the original NDA and the first resubmission, the statistical review team concluded that the three pivotal studies demonstrated evidence of efficacy of corneal collagen cross-linking (CXL) (using riboflavin ophthalmic solution and the UV-X system for the UVA light source) for the improvement of maximum corneal curvature (Kmax) in subjects with progressive keratoconus and subjects with corneal ectasia following refractive surgery. The two primary statistical reviews conducted by Dr. Dongliang Zhuang were finalized on February 28, 2014 and March 12, 2015, and a secondary review was finalized on March 15, 2015.

The following are recommendations for the CLINICAL STUDIES section of the drug labeling:

> … In each study, the maximum corneal curvature (Kmax) was assessed at baseline, Months 1, 3, and 12. The CXL-treated eyes showed increasing improvement in Kmax from Month 3 through Month 12 (Figure 1). For keratoconus subjects, at Month 12, the CXL-treated eyes had an average Kmax reduction of 1.4 diopters in Study 1 and 1.7 diopters in Study 2 while the sham eyes had an average increase of 0.5 diopter in Study 1

and 0.6 diopter in Study 2; the difference (95% CI) between the CXL and sham groups in the mean change from baseline Kmax was -1.9 (-3.4, -0.3) diopters in Study 1 and - 2.3 (-3.5, -1.0) diopters in Study 2. For corneal ectasia subjects, at Month 12, the CXL-treated eyes had an average Kmax reduction of 1.0 diopter in Study 1 and 0.5 diopter in Study 3 while the sham eyes had an average increase of 1.0 diopter in Study 1 and 0.5 diopter in Study 3; the treatment difference between the CXL and sham groups was: -2.0 (-3.0, -1.1) diopters in Study 1 and -1.1 (-1.9, -0.3) diopters in Study 3…

Figure 1: Mean (SD) (Diopter) Change from Baseline Kmax



All randomized subjects were included in the analysis except for four CXL-treated subjects who had missing baseline Kmax values in Study 3. Post-baseline missing data were imputed using last available K_{max} value. For the sham study eyes that received CXL treatment after baseline, the last K_{max} measurement recorded prior to receiving CXL treatment was used in the analysis for later time points.

SEALD

A Study Endpoints and Labeling Development (SEALD) consult request was made by the Division of Transplant and Ophthalmology Products (DTOP) for NDA 203324 on 2/12/15.

For additional details, see the CDER CDTL review 3/27/15.

FINANCIAL DISCLOSURE

See the original Medical Officer's review dated 3/7/2014. No issues precluding approval were identified.

OSI
A routine Office of Scientific Investigations (OSI) audit was requested. See the original Medical Officer's review dated 3/7/2014. No issues of data integrity were identified.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) issued a PROPRIETARY NAME REQUEST CONDITIONALLY ACCEPTABLE letter dated 2/2/16. The proposed proprietary names, Photrexa and Photrexa Viscous, were found acceptable.

DMEPA completed a review of the draft labeling on 4/8/16. They evaluated the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, carton labeling, and insert labeling for Photrexa and Photrexa Viscous ophthalmic solutions.

12. Labeling

The labeling for 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, has been revised consistent with recommendations provided by the Agency. The labeling submitted 4/13/2016 is acceptable.

13. CDER/Division of Transplant and Ophthalmology Products (CDER/DTOP) Recommendations/Risk Benefit Assessment

CDER/DTOP RECOMMENDED 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**.**

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.

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.

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.

The device used in the clinical trial was not the same as the device proposed to be marketed. The KXL and UVX devices are equivalent based on the Equivalence Testing Results provided.

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.

In the opinion of the CDER CDTL, the applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 29, 2015, as approvability issues.

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

CDER Clinical, Pharmacology/Toxicology, Clinical Pharmacology, CMC, Product Quality Microbiology, and Biostatistics 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.

14. Administrative Action

The NDA has been administratively split into two applications based on the submitted indications. NDA 203324-1 has been designated as the NDA (b) (4) NDA 203324-2 has been designated as the NDA for the treatment of corneal ectasia following refractive surgery.

As described in the April 13, 2016, memorandum from William Maisel, MD, MPH, Acting Director of the Office of Device Evaluation and Malvina Eydelman, MD, Director of the Division of Ophthalmic and Ear, Nose and Throat Devices, The Center for Devices and Radiologic Health/Office of Device Evaluation (CDRH/ODE) believes that the information that has been provided in the submission is sufficient to resolve the outstanding device-related issues for the progressive keratoconus indication. However, unlike the keratoconus indication, CDRH/ODE does not believe the information provided in the submission and the available valid scientific evidence is sufficient to resolve the device-related issues or to conclude that the product is safe and effective for the post-refractive corneal ectasia population. Therefore, CDRH/ODE recommends the submission not be approved for the post-refractive corneal ectasia indication.

CDRH/ODE's explanation for this position is:

> "The company has provided, 1) additional description, explanation, and clarification of device similarities and differences between the device proposed for marketing, the KXL System, and the device that was used in the clinical studies – the IROC UV-X, 2) additional non-clinical testing assessments, 3) additional analyses of existing clinical data, and 4) published clinical literature using the KXL System. Unlike the keratoconus patient population, the sponsor has not provided clinical data from either a clinical investigation or published literature on the KXL System at the settings proposed in the NDA submission in the proposed post-refractive corneal ectasia patient population.
>
> The following noteworthy considerations contribute to, but are not the sole basis for, CDRH/ODE's recommendation against approval for the post-refractive corneal ectasia indication. The CDRH review team has previously provided detailed review and documentation of the specific concerns raised by the available information submitted by the sponsor.
>
> 1) The 3 month data comparing the investigational arm with the control arm is insufficient, in and of itself, to support a determination that the product is safe and effective for the post-refractive corneal ectasia indication. Both the sponsor and FDA agree that later time points are better suited for evaluating the long-term clinical significance of the intervention because the corneal stromal remodeling associated with the healing response following treatment requires 6 to 12 months to stabilize. Therefore, the analysis of the 12 month follow-up data is of critical importance.

2) The Statistical Analysis Plan was not finalized until after study enrollment and follow- up were completed, and after some of the study data were analyzed and published. After study completion, the applicant redefined the primary efficacy endpoint.

3) Only 2 patients remained in the control group on their randomized treatment with a 12 month primary endpoint (Kmax) measurement (97% either crossed-over to the treatment arm or were discontinued from the study). The statistical methods and analyses used to analyze the 12 month data were not sufficient to account for the voluminous missing data.

4) No clinical data were provided in the submission, either from the clinical investigations or from published literature, for the KXL device at the settings proposed in the NDA submission for the post-refractive corneal ectasia population. The available clinical data for the IROC UV-X device, the non-clinical information, and the available published clinical literature on use of the KXL device are not sufficient to establish safety and effectiveness of the KXL device or the combination product for the post refractive ectasia population.

In summary, CDRH/ODE has concluded that the available valid scientific evidence is insufficient to conclude that the KXL device and the combination product are safe and effective for the post refractive corneal ectasia patient population."

In accordance with the agreement between the Review Divisions in CDER and CDRH on the approval of the treatment of keratoconus indication, NDA 203324-1 will be approved (b) (4) (b) (4)

Based on the disagreement between the Review Divisions in CDER and CDRH on the approval of the treatment of corneal ectasia following refractive surgery, the Division of Transplant and Ophthalmology will forward the two conflicting recommendations through the Office/Center for resolution.

Appendix

The labeling for 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, has been revised consistent with recommendations provided by the Agency. The labeling submitted 4/13/2016 is acceptable with the minor editorial revisions listed below:

In the HIGHLIGHTS, the space above "initial AP date" should be removed and the cross-reference number "(2)" should be added after all items under "Dosage and Administration."

In the CONTENTS (Table of Contents), (b) (4) should be removed under "INDICATIONS," PHOTREXA VISCOUS and PHOTREXA should be placed in all capital letters, and "6.1 Clinical Trial Experience" should be added under "ADVERSE REACTIONS."

Note: Photrexa Viscous (riboflavin phosphates ophthalmic solution) 1.46 mg/mL 20% dextran and Photrexa (riboflavin phosphates ophthalmic solution) 1.46 mg/mL 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.

13 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
04/15/2016

WILEY A CHAMBERS
04/15/2016

Cross-Discipline Team Leader Review

Date	March 26, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	203324
Applicant	Avedro, Inc.
Date of Submission	September 29, 2014
PDUFA Goal Date	March 29, 2015
505(b)(2)	Yes
Proprietary Name / Established (USAN) names	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
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	treatment of progressive keratoconus and corneal ectasia following refractive surgery
Recommended:	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). 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.

Progression

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study was a long-term evaluation of the natural history of keratoconus involving 1209 patients. Corneal curvature is the clinical variable most commonly used to monitor change in disease severity in keratoconus. The purpose of this analysis was to describe the longitudinal changes in corneal curvature during an 8-year period, encompassing the spectrum of disease severity found 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). This report uses 8 year follow-up data from 1032 patients who had penetrating keratoplasty in neither eye at baseline

and who provided enough data to compute the slope of the change with time in the FDACL or the flatter keratometric Reading (Flat K).[1]

Irregularity and steep curvature are used to monitor disease severity and progression in keratoconus. Mire distortion, present with most keratoconus corneas, makes keratometry more challenging and readings less repeatable because keratoconus leads to an irregular form of astigmatism in which the major axes are generally not orthogonal. Because irregularity is difficult to quantify using manual techniques, such as keratometry, most clinicians concentrate on the numeric curvature findings to document the progression of the disease.[2]

At CLEK Study entry, patients were aged 38.9 ± 10.8 years. Overall, 44 %of them were women, and 69% of them were white. These patients exhibited a slow but clear increase in corneal curvature. The slope of the change in FFDACL (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. Independent predictors of increased FDACL included younger age, poorer baseline high-contrast manifest refraction visual acuity, and nonwhite race. Younger age and poorer high-contrast manifest refraction visual acuity were independent predictors of a >3.00-D increase for both FDACL and Flat K.[3]

Corneal Scarring

CLEK also reported methods to define incident corneal scarring and baseline factors predictive of incident corneal scarring in nonsurgical eyes of CLEK Study keratoconus patients through their fifth year of follow-up. Of the 1209 patients, 878 patients with at least one unscarred cornea at baseline were included. The cumulative 5-year incidence of scarring was defined as the proportion of patients who developed central corneal opacification as detected by a clinician examining the patient with a slit-lamp biomicroscopy and by masked readings of corneal photographs at the CLEK Photography Reading Center.[4]

Multivariate analyses of 5-year prospective data from the CLEK Study cohort showed that baseline corneal curvature, contact lens wear, corneal staining, and younger age were predictive of the development of corneal scarring. Contact lens wear increased the risk of incident scarring more than 2-fold. These findings suggest a causal contribution of contact lens wear to corneal scarring in keratoconus and imply that corneal scarring might be reduced by modifying the contact lens fit.[5]

[1] McMahon TT, Edrington TB, Szczotka-Flynn L, Olafsson HE, Davis LJ, Schechtman KB; CLEK Study Group. Longitudinal changes in corneal curvature in keratoconus.. Cornea. 2006 Apr;25(3):296-305.
[2] McMahon TT, et al, 2006.
[3] McMahon TT, et al, 2006.
[4] Barr JT, Wilson BS, Gordon MO, Rah MJ, Riley C, Kollbaum PS, Zadnik K; CLEK Study Group. Estimation of the incidence and factors predictive of corneal scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Cornea. 2006 Jan;25(1):16-25.
[5] Barr JT, et al, 2006.

The 5-year incidence of corneal scarring was 14% (120 of 878) overall, 17% (102 of 609) for contact lens–wearing eyes, and 38% (46 of 121) for contact lens–wearing eyes with corneal curvature greater than 52 D. Baseline factors predictive of incident scarring included corneal curvature greater than 52 D (odds ratio [OR] = 4.79; 95% confidence interval [CI], 3.08, 7.45; P , 0.001), contact lens wear (OR = 2.50; 95% CI, 1.40, 4.76; P = 0.003), marked corneal staining (OR = 2.38; 95% CI, 1.49, 3.76; P = 0.0002), and age less than 20 years (OR = 6.34; 95% CI, 2.57, 15.00; P , 0.0001).[6]

BCVA

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). Outcome measures included these slopes and whether the number of letters correctly read decreased by 10 letters or more in at least one eye in 7 years.[7]

CLEK Study subjects with keratoconus exhibited a slow but clear decrease in BCVA during follow-up, with low-contrast acuity deteriorating more rapidly than high-contrast. Better baseline BCVA, steeper FDACL, and fundus abnormalities were predictive of greater acuity loss with time. Mean age of the subjects at the first follow-up visit was 40.2 ± 11.0 years (mean ±SD). Overall, 44% were female, and 72% were white. The slope of the change in high- and low-contrast BCVA (-0.29 ±1.5 and -0.58 ±1.7 letters correct/year, respectively) translated into expected 7-year decreases of 2.03 high- and 4.06 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. 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.[8]

Economic Burden

There have been no studies concerning the economic burden this chronic disease represents for patients and payors. The lifetime economic burden of keratoconus in terms of medical services has been estimated using a decision analytic method. The Markov model is an analytic tool that allows an investigator to estimate the costs and consequences of a disease process. A cohort of

[6] Barr JT, et al, 2006.
[7] Davis LJ, Schechtman KB, Wilson BS, Rosenstiel CE, Riley CH, Libassi DP, Gundel RE, Rosenberg L, Gordon MO, Zadnik K; Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. Longitudinal changes in visual acuity in keratoconus. Invest Ophthalmol Vis Sci. 2006 Feb;47(2):489-500.
[8] Davis LJ, et al, 2006.

people with a particular condition is subjected to recurring risks and costs over a period of time, representing a "Markov cycle."[9]

A hypothetical cohort of people was modelled with clinically significant incident keratoconus as defined by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. The costs of clinic visits, fitting fees, contact lenses, surgical procedures, and complications were included. Survival curves of corneal transplants and associated complications were modeled using data from the 2007 Australian Graft Registry. Medical treatment regimens after surgery were defined by expert opinion.[10]

The expected value of the lifetime cost of the treatment of keratoconus over myopia was $25,168 with a standard deviation of $16,247 and a median of $17, 596. The factors that most influenced the lifetime cost were the probability of initial corneal transplant and a subsequent regraft.[11]

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.

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9 Rebenitsch RL, Kymes SM, Walline JJ, Gordon MO. The lifetime economic burden of keratoconus: a decision analysis using a markov model. Am J Ophthalmol. 2011 May;151(5):768-773.e2. doi: 10.1016/j.ajo.2010.10.034. Epub 2011 Feb 18.

[10] Rebenitsch RL, et al, 2011.

[11] Rebenitsch RL, et al, 2011.

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.

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.

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.

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

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.

3. Product Quality

Per the CMC review dated 3/5/2015, this NDA is recommended for approval. All CMC issues concerning the drug substance and the drug product have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance.

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 the drug constituent components in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery in this application.

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) %

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.

Figure 2.1: Overview Illustration of the KXL System

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: 1 – 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) (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
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.

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

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

4. Nonclinical Pharmacology/Toxicology

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

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 relies 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 application is approvable from a Pharmacology/Toxicology perspective (i.e. Pharm/Tox recommends approval and has identified no deficiencies.

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. From the perspective of Clinical Pharmacology, it is recommended that this NDA be approved, provided that satisfactory agreement is reached between the applicant 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

I. CDER

Text in *blue italics* represents the applicant's response.

Text in *black italics* represents CDER Medical Officer/Reviewer Comments.

From the CDER Medical Officer Review dated 3/24/15:

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.

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).

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).

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.

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.

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.

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[12] 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.

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.

[12] (Wollensak and Iomdina 2009; Caporossi 2010; Wittig-Silva 2014)

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)[13], 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)[14], 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 D as documented on the Pentacam print out (See Figure 7 below), an apparent data entry error.*

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

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

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

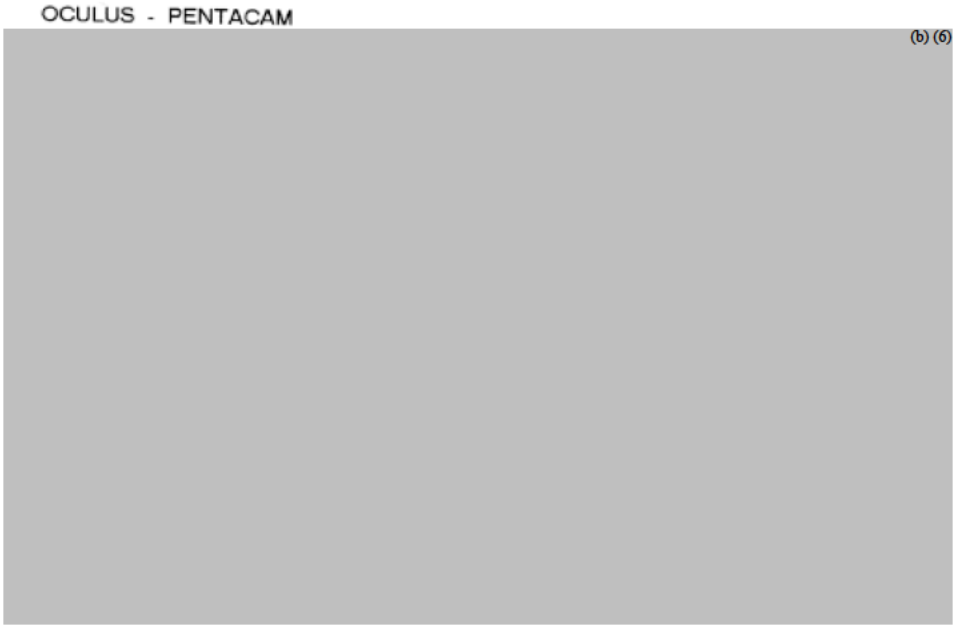
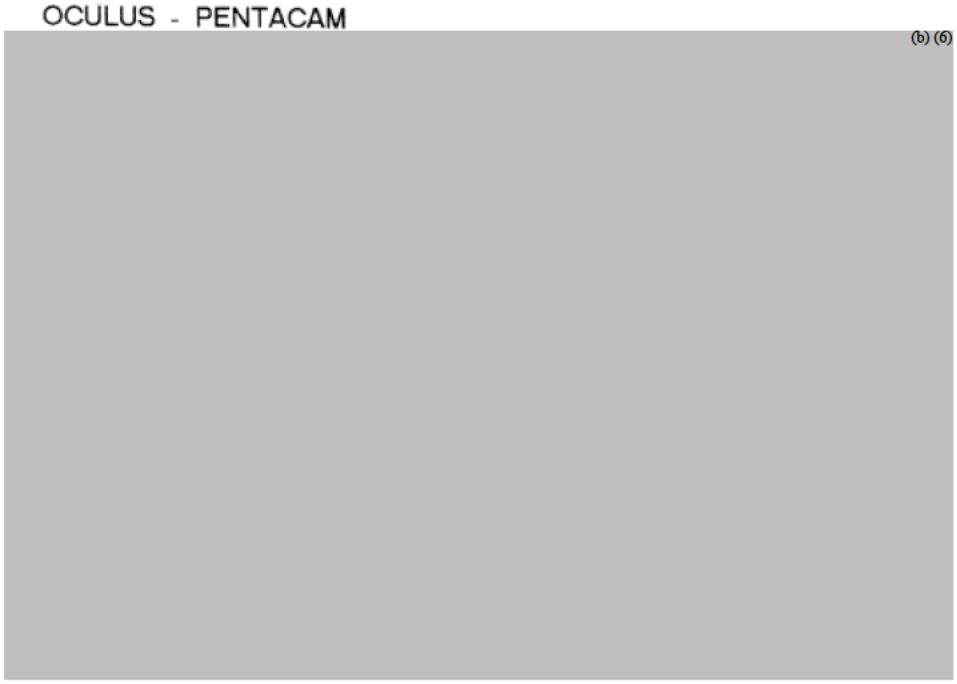


Figure 7: UVX-002 Subject (b) (6) Pentacam Measurement



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)

				Change from Baseline	
Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=29)	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)

				Change from Baseline	
Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	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 (b) (6) 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.

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) (4) *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.

CDER Medical Officer 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.

II. CDRH Clinical

Reference is made to the CDRH Clinical review finalized 3/24/15.

The CDRH Clinical review is organized as follows:

Pages 3-76 describe the complete response
Pages 77-112 describe the interactive review performed on this round

Page 111-113 describe the literature review conducted by CDRH's DEPI group
Pages 113-115 describes (1) the discussion at the advisory committee, (2) preliminary labeling comments in addition to the preliminary labeling review included as an attachment, and includes (3) preliminary risk/benefit section
Page 115-119 includes reviewer recommendations, concerns and major deficiencies to be communicated to the Applicant
Page 120 lists attachments to the review.

Regarding the items cited as approvability issues in the Complete Response letter dated March 14, 2014, CDRH Clinal has the following conclusions:

THE DRUG CONSTITUENT PART

(Items #1, #2, and #3) CDRH Clinical defers to CDER.

DRUG FACILITY INSPECTIONS

(Item #4) CDRH Clinical defers to CDER.

DEVICE CONSTITUENT PART
(Item #5 A) CDRH Clinical defers to other CDRH team members until preclinical review completed.

Optical Radiation Hazard
(Item #6) Response is adequate from CDRH Clinical perspective.

(Item #7) CDRH Clinical defers to other CDRH team members (i.e. engineering team).

Electro Magnetic Compatibility
(Item #8 a-g) CDRH Clinical defers to other CDRH team members (i.e. engineering team).

(Item #9) CDRH Clinical defers to other CDRH team members (i.e. engineering team).

(Item #10) CDRH Clinical defers to other CDRH team members (i.e. engineering team).

(Item#11) Labeling still under CDRH review. CDRH Clinical defers to other CDRH team members.

(Item#12) Labeling still under CDRH review. CDRH Clinical defers to other CDRH team members.

CDRH Clinical Summary Statement Regarding Approvability Issues

Per the CDRH Clinical review finalized 3/24/15**,** significant remaining issues include:

1. Device to be studied differs from device to be marketed (preclinical review of differences ongoing)
2. Extremely limited observed control data at 12 months based on randomized treatment due to control subjects electing to receive crosslinking at 3 months or later (lack of potential internal control data)
3. Controlled "phase" of 3 months (sham eyes) and lack of data obtained on fellow eyes prior to offering crosslinking to those eyes (at 3 months or later in the study)
4. Failure to meet primary prespecified effectiveness endpoint and success criteria for one of the indicated populations (progressive keratoconus)
5. Safety and effectiveness concerns in the pediatric population based on data above in addition to limited data collected and poor methodology to assess safety and effectiveness (for example, Kmax and endothelial data)
6. PRO's have not been formally evaluated by PRO experts and adverse event data in the labeling currently utilizes data from an un-reviewed PRO on visual disturbances (glare, haloes, etc.)
7. Safety and effectiveness concerns in the post-refractive corneal ectasia population – particularly when stratified by criteria such as type of prior refractive procedure (LASIK vs. PRK).
8. Use of Last Observation Carried Forward (LOCF) data.
9. Weak methodology used in data collection and resulting dataset contains "messy"/"noisy data.
10. Lack of long term follow up beyond 12 months (safety and effectiveness) – ex. Progression of crosslinking effect and/or progression of disease; does this actually delay timing of corneal transplant? Effect of CXL on accuracy IOP measurement? Effect on future surgery (cataract surgery or corneal transplant, for example)? Effect on corneal permeability and ability to use topical medication to treat various ophthalmic diseases?
11. Control arm received drug component. It is unclear why this was done. It could potentially confound results.
12. Failure to prespecify or perform significant supportive analyses and limitations of requesting now (refractive stability, impact of crosslinking on IOP measurement, etc.) which means methodology and study design may not support such retrospective analyses.

CDER CDTL Comment: *The majority of these items are discussed in length in the Risk/Benefit analysis found at the end of this CDTL memo.*

Issue #6 cited above is not a significant issue for CDER. The SEALD Study Endpoints Team did not believe this PRO warranted a review. Given that the RSVP was used for exploratory/descriptive purposes, the questionnaire did not distinguish between eyes and the applicant did not seek labeling claims, SEALD declined to perform a consultative review.

Regarding Issue #11, the applicant has stated that the original IND holder believed that allowing subjects to cross over at Month 3was necessary to ensure enrollment; otherwise, subjects would have procedures off-label elsewhere.

III. CDRH Electronics

Reference is made to CDRH Electronics review finalized 3/24/15. From that review:

Analysis (review of AI responses)

1. In Agency Request 9, we said that the EMC test reports that the sponsor provided identified modifications that were made to the KXL System in order to pass the tests. We advised the sponsor that the EMC testing should be done on the final version of the device (i.e., as proposed for marketing). Thus, any modifications made to the device for testing, in most cases, should be included features for the marketed device. Thus, we asked the sponsor to confirm that all of the modifications listed will be included in all units to be marketed. The sponsor confirmed that all the items listed will be included in the marketed version of the device, but that one modification, (b) (4), required that EMC testing be repeated.

   The sponsor said that the change involved (b) (4) According to the sponsor, this (b) (4) would be used during additional IEC 60601-1-2 (EMC) testing.

   I have not yet seen the test report for this additional EMC testing. Therefore, this response is not yet acceptable. The sponsor should be asked to submit this test report. This information is needed so that we can assess conformity of the (b) (4) KXL UV irradiation system with IEC 60601-1-2:2007.

2. In Agency Request 10, we said that IEC 60601-1-2:2007 specifies requirements for testing and for labeling. We said that in order to demonstrate conformity with the standard, in addition to evidence of meeting the testing requirements of the standard, the sponsor needed to submit evidence of meeting the labeling requirements. We asked the sponsor to modify the system technical description to include four tables of EMC guidance, based on compliance of the device with the individual EMC test standards.

   The sponsor submitted evidence that these tables had been added to the Operator's Manual. However, there were two minor errors in the tables. We asked the sponsor to correct them, as follows:

   - We said that in Table 5-2, the format of "U_T" in the NOTE should be the same as in the Voltage dips row: the capital "U" should be in Italics. The "T" appears correctly: not Italic, capital, and subscripted.

     The sponsor submitted Version F of the Operators Manual as evidence that this error has been corrected. This response is acceptable. However, I 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 do not make sense. The sponsor

should be asked to change, in the Voltage dips row, [redacted] to "0% U_T for 0.5 cycles", [redacted] to "40% U_T for 5 cycles", [redacted] to "70% U_T for 25/30 cycles", and [redacted] to "0% U_T for 250/300 cycles". This information is needed so that we can assess conformity of the [redacted] KXL UV irradiation system with IEC 60601-1-2:2007.

- We said that in Table 5-4, the "Rated maximum output power" heading cell, the "W" should be in parentheses: "(W)".

  The sponsor submitted Version F of the Operators Manual, which has evidence that this error has been corrected. This response is acceptable.

3. In Agency Request 12, we were not able to find any MRI warnings in the Operator's Manual. 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. Please 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".

   The sponsor replied that Avedro committed to updating the operators manual and device label to include "all the aforementioned items."

   The sponsor had submitted evidence that the "MR Unsafe" warning and symbol have been added to the Operator's Manual and has included in Version F of the Operators Manual evidence that the "MR Unsafe" symbol has been added to the device label. These responses are acceptable.

Additional observation

4. In the EMC guidance tables mentioned above, the sponsor has used the comma (,) as the decimal separator. (Note: IEC rules dictate such use in IEC standards.) While using the comma for the decimal separator is the convention in Europe, it is not the convention in the US. The sponsor should be asked to use the point (.) where needed in the EMC guidance tables for Operators Manuals for distribution in the US. This information is needed to help assure the usability of the Operators Manual.

IV. CDRH Software

Per the CDRH software review finalized 3/3/14,the firm has provided acceptable documentation demonstrating that they have developed the software for this device under appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way. It is recommended that from a software standpoint this submission be approved.

V. CDRH Electrical Safety

Per the CDRH electrical safety review finalized 1/9/15, the applicant has identified appropriate system requirements and performed adequate risk management on the design to assure that hazardous situations have been identified and their risks appropriately controlled. The applicant has performed adequate safety and functional testing, using both internal and recognized (i.e. standards) methods and acceptance criteria. The applicant has provided updated electromedical safety testing dated April 2014 for IEC 60601-1, 3rd edition. I recommend the device be found safe from an electrical safety perspective.

VI. CDRH Office of Compliance

Per the CDRH Office of Compliance facility inspection review finalized 2/4/14, CDRH/OC is requesting no additional information from the applicant in order to complete the review of the application to ascertain compliance with the applicable 21 CFR part 820 regulations.
CDRH will concur with CDER's decision regarding NDA-203324 approval. NDA-203324 is approvable from the perspective of the Medical Device Regulations.

VII. CDRH DOED Engineering

Per the CDRH DOED Engineering review finalized 3/26/15,

Regarding the items cited as approvability issues in the Complete Response letter dated March 14, 2014, CDRH DOED Engineering has the following conclusions:

Item#5a: **DOED Engineering Reviewer Comment:** Although, the difference in focusing seems not affect device safety, however, may affect the device efficacy. DOED clinical reviewer has concern that not only is there a difference in the method of alignment (i.e., subjective vs. objective), and the related usability issues, but there potentially could be a difference in the targeted focal plane due to the fact that the KXL system alignment method occurs independent of riboflavin diffusion. In addition, it is unclear how that treatment plane may differ from the one studied and the resulting impact on safety and effectiveness. Please see DOED clinical reviewer's review for details on this issue.

Item #6: **DOED Engineering Reviewer Comment:** The proposed software lock-out is acceptable. I defer to software reviewer to ensure the validation of the software lock-out has been completed.

Item #7: **DOED Engineering Reviewer Comment:** The test report demonstrates that UV beam homogeneity measurement results were between (b) (4)% which met the predetermined acceptance criteria (i.e., within (b) (4)%). Deficiency#7 has been adequately addressed.

Summary CDER CDTL 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 Month 12 favoring the CXL treatment for the corneal ectasia indication.

In the opinion of the CDER CDTL, the applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 14, 2014, as approvability issues. CDRH has continued concerns about Approvability Items #5 (CDRH Clinical and DOED Engineering), Item #9 (CDRH Electronics), and Item # 11(CDRH Clinical).

8. Safety

From the CDER Medical Officer Review dated 3/24/15:

Disposition of Subjects

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

	UVX-001*		UVX-002		Pooled Studies	
Category	CXL Group (N=29)	Control Group (N=29)	CXL Group (N=73)	Control Group (N=74)	CXL Group (N=102)	Control Group (N=103)
Received Randomized Treatment (n)	29	29	73	74	102	103
Completed: n (%)**	20 (69.0)	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

Deaths

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

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

	Progressive Keratoconus		**Cornea Ectasia**	
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	-	-	-
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
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

	Keratoconus UVX-001 (N=74)	Corneal Ectasia UVX-001 (N=57)	Keratoconus UVX-002 (N=219)	Corneal Ectasia UVX-003 (N=162)
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.

Serious Adverse Events

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

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) (4) (keratoconus) had serious adverse events of two suicide attempts from baseline to Month 3. Subject (b) (4) (corneal ectasia) had a serious adverse event of head injury from baseline to Month 3.

Subject (b) (4) (keratoconus subject, control group) was a 20-year-old Caucasian, non-Hispanic female who received control treatment OD (b) (6) 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) (4) (corneal ectasia subject, control group) was a 50-year-old Caucasian, non-Hispanic male who received control treatment OS On (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) (4)); appendicitis requiring appendectomy (Subject (b) (4)); and an infectious cat bite requiring hospitalization (Subject (b) (4)). Each of these events occurred after Month 3.

Subject (b) (4) (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) (4) 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) (4) (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) (4) (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) (4) (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.

9. Regulatory Briefing/Advisory Committee Meeting

A Regulatory Briefing was held on Friday, March 20, 2015. Presentations were made by Wiley Chambers, MD (Clinical), Dongliang Zhuang, PhD (Biostatistics), and Maryam Moktarzahdeh, MD (CDRH).
The flaws in the conduct and reporting of UVX-001,-002, and-003 were discussed. It was noted that despite these flaws, the efficacy results for both indications were positive (or trending positive) in the sensitivity analyses presented. The adverse event profile of the crosslinking procedure appear to represent sequelae following corneal epithelial debridement There was discussion of the precedent of approving drugs and devices not actually used in clinical trials as long as adequate bridging were possible.

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

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Member Present (Voting): Richard M. Awdeh, MD (Acting Chairperson); Stephen S. Feman, MD, MPH, FACS, Mildred M.G. Olivier, MD

Dermatologic and Ophthalmic Drugs Advisory Committee Members Not Present (Voting): Lynn A. Drake, MD (Chairperson); Mary E. Maloney, MD; Robert Melendez (Consumer Representative), MD, MBA

Dermatologic and Ophthalmic Drugs Advisory Committee Member Present (Non-Voting): Gavin R. Corcoran, MD, FACP (Industry Representative)
Ophthalmic Devices Panel of the Medical Devices Advisory Committee Members Present (Voting): Jeremiah Brown, Jr., MS, MD; Andrew Huang, MD, MPH; Bennie Jeng, MD, MS; Stephen McLeod, MD; Cynthia Owsley, PhD, MSPH; Jayne Weiss, MD (Chairperson)

Ophthalmic Devices Panel of the Medical Devices Advisory Committee Members Not Present (Voting): Kuldev Singh, MD, MPH

Ophthalmic Devices Panel of the Medical Devices Advisory Committee Members Present (Non-Voting): Lawrence E. Leguire, PhD (Consumer Representative); Michael E. Pfleger, JD (Industry Representative)

Temporary Members (Voting): Michael W. Belin, MD; Scott Evans, PhD, MS; Scott MacRae, MD; Tracy Matson (Patient Representative); Joel Sugar, MD; David Yoo, MD

FDA Participants (Non-Voting): Wiley A. Chambers, MD; Malvina B. Eydelman, MD; William Boyd, MD; Dongliang Zhuang, PhD

Open Public Hearing Speakers: David B. Glasser, MD (The Cornea Society); Margaret Dayhoff-Brannigan, PhD (Center for Health Research); Catherine Warren, RN (National Keratoconus Foundation); Stephen Slade, MD, FACS (American European Congress of Ophthalmic Surgery); Paula Cofer; Thomas John, MD (The American Society of Cataract and Refractive Surgery); Katherine Chenault; Morris Waxler, PhD (statement read by Paula Cofer); Matthew Kotsovolos; Michael Patterson, PhD (statement read by Matthew Kotsovolos) ; Roger

Davis, PhD (statement read by Richard Smith, PhD) ; Richard Smith, PhD; Edward Boshnick, OD (statement read by Paula Cofer); Dean Kantis (statement read by Matthew Kotsovolos) .

A verbatim transcript will be available in approximately six weeks, posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/ucm431514.htm and
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OphthalmicDevicesPanel/default.htm.

From the unofficial "Quick Minutes" of the Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Devices Panel of the Medical Devices Advisory Committee held on February 24, 2015:

1. DISCUSSION: Please discuss and comment on the following Study Design Elements: Planned Enrollment and Size of Studies

- - 160 patients (80 per arm) originally planned in the studies below versus actual enrollment
- - Size of safety and effectiveness database

	CXL	Sham
UVX-001 and -002 Progressive Keratoconus	102	103
UVX-001 and -003 Corneal Ectasia	91	88

Committee Discussion: In general, the committee members were comfortable with the number of patients enrolled and the data that was pooled. With regards to UVX-001, there is still uncertainty as to whether the randomization of the patients was adequate. One committee member noted that looking at 12 month data in the treatment group, there is sufficient data to analyze some of the questions raised. Another committee member stated that just looking at the pooled data, there was the standard 80% power to detect the 1 diameter difference and that the conclusions are based on just the pooled data. One committee member noted that there were lots of failures in the study and poor data was collected. It was also noted that more detail is needed on the common complication of corneal haze, such as the grading and staging of haze, any data that correlated with the amount haze. Please see the transcript for details of the committee discussion.

2. DISCUSSION: For both proposed indications, the studies were to evaluate efficacy three months after treatment as reflected by the protocol-defined primary endpoint. For the progressive keratoconus population, statistical significance was not achieved at Month 3. Statistical significance was achieved at Month 3 for the corneal ectasia population. The Statistical Analysis Plan submitted after the last patient visit extended the evaluation of efficacy to Month 12, and the subsequent analysis used a last observation carried forward (LOCF) strategy to impute missing data resulting from patient withdrawal as well as to impute data for sham subjects receiving CXL treatment at Month 3 or 6. Please discuss the strengths and

weaknesses of the trial design and analysis including the effect of the following on your evaluation of product efficacy:

i. Potential introduction of bias
ii. Number of subjects available
iii. Use of LOCF
iv. Stability of corneal response to treatment

Committee Discussion: One committee member noted that sample size is relevant in trial design, but once a trial is over, what comes into play is the safety issue and a sample size of at least 300 would be needed to reasonably rule out harmful effects, particularly those that are more rare with reasonable confidence less than 1%. It was also noted that using the LOCF analysis, there would be a bias against the efficacy. One committee member noted that stability of corneal response to treatment was not present since the trial was changing from a month 3 to a month 12 end point, but noted that stability was not important as long as it was progressing in the right direction. Please see the transcript for details of the committee discussion.

3. DISCUSSION: In these studies, at the time of treatment there were the following number of pediatric patients enrolled (stratified by ≤ 21 years CDRH and ≤16 years CDER) :

	CXL	Sham
Keratoconus ≤ 21years	19	14
Keratoconus ≤16 years	6	4
Corneal ectasia ≤21 years	0	0
Corneal ectasia ≤ 16 years	0	0

For the proposed indication for progressive keratoconus, please discuss:

a. What is the minimum age supported by the data
b. Applicability of extrapolation from adult data?

Committee Discussion: There was not a consensus on what is the minimum age supported by data. Some committee members noted that nothing could be determined by the data to determine a minimum age for the procedure. On the other hand, some committee members agreed that the minimum age supported by the data is 14 years of age. Some committee members believed that there may be different biomechanics and disease progression in pediatric corneas, however, the literature seemed to support consistent results between pediatric and adult patients treated. Please see the transcript for details of the committee discussion.

4. DISCUSSION: Please discuss your Interpretation of Endothelial Cell Count Findings (See endothelial cell count tables).

Committee Discussion: In general, the committee agreed that the data shows great variability in measurements, but does not show evidence of toxicity in the pooled data and therefore no evidence of endothelial toxicity as defined in the protocol. One committee member noted the importance of looking at case-by-case basis where there is a cell drop of more than 25 – 30 %

along with a threshold count below 2000 to determine evidence of toxicity in endothelial cells. Please see the transcript for details of the committee discussion.

5. DISCUSSION: The studies were conducted on a different device (the IROC UV-X) than the one proposed to be marketed (KXL System). Differences include (but are not limited to):

- Illumination diameter (aperture)
- UV focal alignment

In light of the differences and lack of any data collected using the KXL System, please discuss the adequacy of the current dataset to assess safety and efficacy of the KXL System.

Committee Discussion: Some committee members agreed that looking at the illumination diameter (aperture) are equivalent from the studies conducted with the IROC UV-X and KXL System in terms of the variables affecting the patient. Some committee members noted that the peripheral cornea may be more important and it may be efficacious to have a larger treatment zone. The majority of the committee agreed that the 11.0 mm data should be taken out of the analysis. In general, the committee agreed that there was no data presented to determine UV focal alignment. Please see the transcript for details of the committee discussion.

6. DISCUSSION: Please discuss your recommendations regarding the need for analyses (if any) on the additional data that had been collected during the clinical trials to adequately characterize the safety and efficacy profile of this combination product.

Committee Discussion: A thorough analysis of the patient reported outcomes data, as well as, additional data on the Subjective Complaint Questionnaire as it could potentially reveal patient views about this intervention were recommended. Additional parameters for the Pentacam to be analyzed in this data set were also recommended. Please see the transcript for details of the committee discussion.

7. DISCUSSION: Please discuss any potential safety issues.

Committee Discussion: One potential safety issue expressed was the treatment of unnecessary cases in the younger populations unless adequate safeguards are established in terms of progression. Another committee member noted that safety cannot be assessed in the same manner for the ectasia eyes as the keratoconus eyes because of the difference between the number of treated eyes between the two eye groups. Corneal haze was also stated as a potential safety issue. Please see the transcript for details of the committee discussion.

8. DISCUSSION: The applicant proposes indication of progressive keratoconus. Please discuss applicability of extrapolation to general keratoconus population

Committee Discussion: In general, the committee members agreed that the there is no data to apply the proposed indication of progressive keratoconus to general keratoconus population. It was further stated that although it was ill-defined, the intent of the study and the majority of the literature was based on progressive keratoconus. One committee member noted that progressive

keratoconus was not clearly defined, so they would be more inclined to use the general term of 'keratoconus'. Please see the transcript for details of the committee discussion.

9. VOTE: 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

YES: 10 **NO:** 4 **ABSTAIN:** 1

a. If yes (recommend approval), do you have any suggestions regarding the draft labeling of the product?

b. If the product is recommended for approval are additional studies needed post-approval? If so, please comment on type of study; e.g., objectives, population, endpoints, duration, design.

c. If the product is not recommended for approval because additional studies are needed, please comment on the types of study(ies) that are needed.

Committee Discussion: The majority of the committee voted "Yes", agreed that substantial evidence of efficacy and safety has 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. Some committee members voted "No" stated that the study was poorly conducted and that there were issues with the design and analysis of the trial. One committee member who abstained from voting stated that there is a medical need, however, had trouble approving a machine without seeing any data on its efficacy. One committee member that voted "Yes" noted that they would like labeling to include that long-term effects of the treatment beyond 12 months is unknown. Another committee member that voted "Yes" noted that they would like labeling to include efficacy data based on age, specifically data for the pediatric group and a section that includes using the treatment based on a range of cornea thickness. Some committee members that voted "No" noted that long-term data is needed. Another committee member that voted "No" noted that the study needs to be repeated using appropriate machinery. Please see the transcript for details of the committee discussion.

10. VOTE: 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

YES: 6 **NO:** 4 **ABSTAIN:** 4 **NO VOTE:** 1

a. If yes (recommend approval), do you have any suggestions regarding the draft labeling of the product?

b. If the product is recommended for approval are additional studies needed post-approval? If so, please comment on type of study; e.g., objectives, population, endpoints, duration, design.

c. If the product is not recommended for approval because additional studies are needed, please comment on the types of study(ies) that are needed.

Committee Discussion: Some committee members who voted "Yes", agreed that substantial evidence of efficacy and safety has 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. One committee member noted that despite the problems with the data, that there was a biological effect in that the drug-device combination was safe. The committee members who voted "No" stated that the data presented is not with the device that is planned to be used and data is not available for this particular device with the medication. In addition, there was concern of the small sample size and the technology encompassing a larger area of the treatment in corneal ectasia vs. keratoconus. Some committee members who abstained from voting stated that there were issues with the data along with consideration of the public comments that were made balanced against patient medical need. One committee member was not present to vote as noted for the record.

In regards to draft labeling of the product, labeling to include that long-term effects of the treatment beyond 12 months is unknown as well as an explanation as to why use is not recommended beyond cornea thickness beyond 400 microns was suggested. In addition, it was suggested that labeling should include progressive ectasia. It was also recommended that labeling should indicate the type of refractive surgery, which was all laser-based vs. the all-inclusive term of "refractive surgery".

For those who did not recommend approval because additional studies are needed suggested a post-approval study to look into the set of the data from the last data entry from January 2011. One committee member that voted "No" further stated that there is a need to get results to data on younger patients, long-term outcomes, appropriate control data as well as focusing on functional outcomes for the patient. Please see the transcript for details of the committee discussion.

10. Pediatrics

From the CDER Medical Officer Review dated 3/24/15:

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
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

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the Biostatistics review dated 3/12/15:

The applicant resubmitted NDA 203324 for review on 29 September 2014. There were no new clinical data in the resubmission. In the original NDA submission, the applicant provided a number of publications to provide information on the natural history of keratoconus as well as to support the efficacy analyses and results. In addition to several publications elucidating the background information for keratoconus further, the resubmission included an article by Wittig-Silva, et al published in 2014. In the article, the authors evaluated the long-term effects of CXL treatment as well as progression of the disease as measured by Kmax over a 3-year follow-up period in a controlled trial. The applicant also submitted additional sensitivity analyses to support the efficacy results presented in the original NDA.

An extensive statistical review was conducted for the original submission. This review of the resubmission focused on the information that was submitted to address the deficiencies in the original submission.

There were two statistical issues associated with the applicant's primary efficacy analysis, which was based on the treatment comparison at Month 12.

The first issue is the change of the time-point for the primary efficacy analysis from Month 3 to Month 12 after the studies had been completed. The practice of changing the time-point of the primary efficacy analysis after the study completion can compromise the credibility of the study conduct and the study results. From a statistical perspective, a multiplicity issue could arise as a result of the change of the primary efficacy endpoint from Month 3 and Month 12 after the study completion. This statistical review would not be able to address this issue.
In addressing the first issue, the applicant acknowledged that the choice to evaluate the effectiveness at the 3 month time-period was not appropriate. Existing literature suggests that corneal healing after epithelial debridement is continuing at 3 months. The change from Month 3 to Month 12 for the primary efficacy endpoint seems justified from a clinical point of view.

The second issue concerns the lack of data in the control group at Month 12 in applicant's analysis. 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 very few subjects in the respective control groups remained in the assigned treatment and had efficacy data at Month 12. Therefore, the studies did not have adequate data to allow a direct treatment comparison at Month 12. In the applicant's analyses, the comparison between the CXL group and the control group after Month 3 was based on the imputed data using LOCF approach.
The validity of the applicant's analysis at Month 12 depends on the assumptions that keratoconus and post-refractive corneal ectasia are progressive diseases and consequently, the patients' corneal curvature will worsen over time. The applicant submitted literature including an observational study to evaluate the natural history of keratoconus and clinical studies that

showed the progression of the disease as measured by Kmax over a long follow-up period in a controlled setting. The Biostatistics review of the literature, including those provided by the applicant, concludes that Kmax increases over time or remains stable for untreated eyes and therefore, the sham subjects' data at an earlier time-point prior to receiving CXL could be used for the treatment comparison at a later time-point.

Although the study design did not allow a direct treatment comparison at Month 12, the analysis that uses the Kmax prior to receiving CXL treatment for sham subjects seems reasonable to establish the treatment effect at Month 12. Therefore, when it is viewed aside from potential multiplicity issue, the applicant's analysis demonstrated statistically significant and clinically meaningful efficacy of CXL in the treatment of keratoconus and post-refractive corneal ectasia.

The activity of CXL treatment in keratoconus and post-refractive corneal ectasia subjects was further supported by an alternative analysis that Biostatistics conducted according to the intent-to-treat principle in the review of the first submission. Sham subjects' efficacy data after receiving CXL treatment were included in the analysis. In contrast, the applicant's analysis had excluded these data. Therefore, Biostatistics analysis compared the efficacy in subjects who were treated with CXL at the randomization day to the efficacy in subjects whose CXL treatment was delayed by three months or six months depending on the visit at which the subject received CXL treatment. A statistically significant and clinically meaningful improvement in Kmaxwas demonstrated in UVX-002 for keratoconus subjects and in UVX-001 for corneal ectasin subjects. When compared to the applicant's analysis results, Biostatistics analysis showed that subjects in the sham group experienced an improvement in the corneal curvature at Month 12, reflecting the delayed effect of CXL treatment.

In the opinion of the Biostatistics reviewer, the two statistical issues in the CR letter have been adequately addressed in this resubmission. Based on the applicant's analysis at Month 12, sufficient evidence of a CXL treatment effect for the improvement of Kmax has been demonstrated for both indications.

SEALD
A Study Endpoints and Labeling Development (SEALD) consult request was made by the Division of Transplant and Ophthalmology Products (DTOP) for NDA 203324 on 2/12/15.

NDA 203324 submitted by Avedro, proposes the use of a riboflavin ophthalmic solution and UVA light with the goal to achieve corneal collagen cross-linking; this method is intended for the proposed treatment of progressive keratoconus and corneal ectasia. Results of three Phase 3 randomized sham-controlled studies have been submitted.

During the Phase 3 studies (UVX-001, UVX-002, UVX-003), patients were asked to complete the RSVP questionnaire. SEALD was asked to review and provide comment on the quality and validity of the questionnaire, its fitness for purpose, and interpretation of results.

In an email dated 2/20/15, SEALD responded:

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.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) issued a PROPRIETARY NAME REQUEST CONDITIONALLY ACCEPTABLE letter dated 1/14/15. The proposed proprietary names, Photrexa and Photrexa Viscous, were found acceptable.

DMEPA completed a review of the draft labeling on 3/9/15. They evaluated the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, carton labeling, and insert labeling for Photrexa and Photrexa Viscous ophthalmic solutions.

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

OSI
A routine Office of Scientific Investigations (OSI) audit was requested. See the original Medical Officer's review dated 3/7/2014. See also Section 7 of this review, BIORESEARCH MONITORING PROGRAM INSPECTION.

12. Labeling

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 drug product labeling found in the CDER Medical Officer Review dated 3/24/15.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED 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 the CDER Medical Officer Review dated 3/24/15.

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.

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.

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 $3.0 \pm 0.3 mW/cm^2$. 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.

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.

In the opinion of the CDR CDTL, 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.

CDER Clinical, Pharmacology/Toxicology, Clinical Pharmacology, CMC, Product Quality Microbiology, and Biostatistics and have recommended approval for this application.

DEFICIENCIES/COMMENTS FOR THE APPLICANT:
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 Month 12 favoring the CXL treatment for the corneal ectasia indication.

In the opinion of the CDER CDTL, the applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 14, 2014, as approvability issues. CDRH has continued concerns about Approvability Items #5 (CDRH Clinical and DOED Engineering), Item #9 (CDRH Electronics), and Item # 11(CDRH Clinical).

CDRH has the following comments for the applicant:

From the CDRH DOED Engineering review finalized 3/26/15:

1. In March 15, 2014, we requested clarification regarding your list of device differences between the UV-X System and the KXL System. In your response, you indicate that the original list was not comprehensive, and therefore, you provided additional information and an updated device description. However, our ongoing review efforts have determined that

the additional information you provide in your response does not support your rationale for equivalence between the two systems. Moreover, in light of your presentation at the advisory committee meeting, and interactive review correspondence received March 16, 2015, there appear to be additional differences, which you did not include in the your submissions. Therefore, we cannot determine how these differences impact safety and effectiveness of the combination product proposed for marketing. For example, you have not provided adequate information regarding the amount and spatial distribution of effective ultraviolet (UV) exposure to the cornea by the UV-X versus the KXL devices to enable us to evaluate the safety and effectiveness of the KXL device for which you are requesting approval. Please provide the following additional information:

a. Please provide a complete and detailed description and explanation of the optical systems of both devices, including but not limited to: important components (e.g., light sources, lenses, mirrors, filters, shutters, limiting apertures, beam homogenizers, etc.), dimensions, distances, angles of divergence (or convergence) at the cornea, and accurate ray trace diagrams. Please include explanations for any features intended to modify the beam energy distribution, compensate for corneal curvature, or limit scattered radiation beyond the nominal beam diameter.

b. Please 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. Also, please explain any differences between the KXL map and the previous KXL map that you provided (b) (4)

c. For both devices, please provide a detailed description of all features and procedures intended to limit patient eye movements during the cross-linking procedure, including but not limited to: fixation targets, instructions to patient and physician, eye position monitoring procedures, and fail-safe provisions in case of excessive movement. In addition, for both devices, please provide all available evidence regarding actual sequences of eye movements during the procedure, including but not limited to: 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.

e. Please 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.

f. Please 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.

From the CDRH Electronics review finalized 3/24/15:

More information is needed from the sponsor, as detailed below.

If you agree, please forward the following requests and recommendations to the sponsor. They are formatted so that they can be cut and pasted into a deficiency letter or e-mail.

1. In Agency Request 9, we said that the EMC test reports that you provided identified modifications that were made to the KXL System in order to pass the tests. We advised you that the EMC testing should be done on the final version of the device (i.e., as proposed for marketing). Thus, any modifications made to the device for testing, in most cases, should include the features of the marketed device. Thus, we asked you to confirm that all of the modifications listed would be included in all units to be marketed. You confirmed that all the items listed would be included in the marketed version of the device, but that one modification, (b) (4) required that EMC testing be repeated.

   You said that the change involved (b) (4) You said that this (b) (4) would be used during additional IEC 60601-1-2 (EMC) testing.

   We have not yet seen the test report for this additional EMC testing. Therefore, this response is not yet acceptable. Please submit this test report. This information is needed so that we can assess conformity of the (b) (4) KXL UV irradiation system with IEC 60601-1-2:2007.

2. In Agency Request 10, we said that IEC 60601-1-2:2007 specifies requirements for testing and for labeling. We said that in order to demonstrate conformity with the standard, in addition to evidence of meeting the testing requirements of the standard, you needed to submit evidence of meeting the labeling requirements. We asked you to modify the system technical description to include four tables of EMC guidance, based on compliance of the device with the individual EMC test standards.

   You submitted evidence that these tables had been added to the Operator's Manual. However, there were two minor errors in the tables. We asked you to correct them, including the following:

   - We said that in Table 5-2, the format of "U_T" in the NOTE should be the same as in the Voltage dips row: the capital "U" should be in Italics. The "T" appears correctly: not Italic, capital, and subscripted.

You submitted Version F of the Operators Manual as evidence that this error has been corrected. This response is acceptable. 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 do not make sense. Please change, in the Voltage dips row, [redacted] to "0% U_T for 0.5 cycles", [redacted] to "40% U_T for 5 cycles", [redacted]" to "70% U_T for 25/30 cycles", and [redacted] to "0% U_T for 250/300 cycles". This information is needed so that we can assess conformity of the [redacted] KXL UV irradiation system with IEC 60601-1-2:2007.

Additional observation

3. In the EMC guidance tables mentioned above, the sponsor has used the comma (,) as the decimal separator. (Note: IEC rules dictate such use in IEC standards.) While using the comma for the decimal separator is the convention in Europe, it is not the convention in the US. The sponsor should be asked to use the point (.) where needed in the EMC guidance tables for Operators Manuals for distribution in the US. This information is needed to help assure the usability of the Operators Manual.

From the CDRH Clinical Review finalized 3/24/15:

MAJOR DEFICIENCIES:

1. In light of our review and the input received at the advisory committee meeting, we believe the cohorts for assessment of safety and effectiveness need to be further stratified based on the following:
   a. Due anatomic and developmental differences, please provide separate analyses for subjects <22 years of age and subjects ≥22 years of age.
   b. There is concern that illumination diameter may impact safety and effectiveness. Since the device you propose to market only includes a fixed illumination diameter of 9.0 mm [redacted]
   c. There is concern that all subject enrolled in the studies may not have had progressive disease, as intended. Therefore, please remove [redacted] Please also remove [redacted]

For each study and each proposed indication, please provide revised analyses of safety and effectiveness (with corresponding accountability tables) based on the resultant cohort (from criteria a-c) and use this cohort in your response to the remaining CDRH clinical deficiencies

in this letter. Please clarify the number of eyes with observed safety data at 12 months post treatment.

2. Safety and effectiveness of corneas swelled to meet the minimum pachymetry may differ from outcomes in corneas that have not been manipulated in such a manner. Therefore, please:
    a. Stratify safety and effectiveness results for eyes which had a pachymetry <400 microns and received Photextra Viscous.
    b. Stratify safety and effectiveness results for eyes which received UV irradiation despite failing to have a pachymetry ≥400 microns (i.e., protocol deviations)
    c. Please clarify if any pachymetry data was obtained on any eyes after UV irradiation was completed. If so, please stratify results based on whether or not corneal thickness after treatment was <400 microns
3. Data was collected from two questionnaires in your trial, as required by the protocol. We believe that consideration of all patient reported outcome data collected is important, particularly since questionnaire results were prespecified to be safety endpoints in your protocol and impact adverse event data proposed in the labeling. For each of the two questionnaires used in these trials, please provide results and analyses including the following: Item frequency across the response categories, cumulative distribution function which is basically within person change over time, evidence that this questionnaire is an appropriate tool in this intended use population, and please specify the concept that the tool is measuring.
4. You have provided some literature in your submissions, however, you have not provided provided a comprehensive literature search stratified by key parameters of interest. In order to identify literature that is relevant to your submission, please provide a comprehensive literature review stratified by each of the following:
    a. The specific drug/device combination product you are requesting to market
    b. The specific drug/device combination product that was studied
    c. The KXL system with different settings/treatment parameters than proposed for marketing and please discuss the relevance of this literature to the product you are proposing to market (e.g. illumination diameter, focusing mechanism, etc.) 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. Existing publications or manuscripts presenting any data collected in the pivotal trials from this NDA

    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 were 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 articles.

5. You have provided analyses for loss of BSCVA of 3 lines or more. As per your pre-specified safety analyses in your protocols, please provide an analysis of eyes which lost 2 lines or greater of BSCVA at any visit in the study and provide a discussion regarding the etiology of these events.
6. Corneal haze is reported in your pivotal trial results. Please provide an analysis of corneal haze captured in these studies at all visits including the grading, severity and visual acuity resulting (UCVA and BSCVA). Please also address the impact of corneal haze on visual function.
7. For the following endothelial cell count (ECC) analyses, please use observed data only (no LOCF):
   For study eyes and all eyes (separately), please provide mean within eye change in ECC at each visit the measurement was performed. Also, please provide the mean change in ECC within eyes from baseline to 12 months for eyes that received crosslinking treatment. In these analyses please provide summary statistics including (but not limited to) range. Please provide distributions of change in ECC in +/-5% interval bins. Please provide a discussion regarding eyes which had a concerning level of change in ECC (eyes which lost >25% ECC and/or in which ECC dropped below 2000). Please provide additional information about these clinical course in these eyes (such as adverse events, etc. which may be related to or resulting from the change in ECC).
   Please remember to provide these analyses separately for pediatric eyes separately and for each indication separately.
8. There appear to be many variables in ocular history of subjects in the postrefractive corneal ectasia population that could impact outcomes. Therefore, please provide a stratification of results in the postrefractive corneal ectasia population based on the following:
   a. Number and types of prior refractive procedures (including non-laser based refractive procedures).
   b. Time between prior refractive treatment and enrollment in the clinical trial (if known) for these eyes.
   c. Documentation of progression of disease prior to crosslinking treatment.
   d. Prior corneal collagen crosslinking (if so, please provide details).
9. You stated at the advisory committee that you believe an optical zone of 9mm was specified and that epithelial debridement was limited to this area. Please specify where in the protocol such information appears. If such information was provided as part of site start up and training, please provide this information. Please also provide information regarding what additional information was provided during site start up and training and whether such information was consistent across all three studies. Please also clarify if such information will be included in your proposed instructions for use.
10. Please update your labeling based on the analyses above and in addition, provide patient labeling for review.

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.

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
03/27/2015

WILEY A CHAMBERS
03/27/2015