CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig2s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 203324
Related INDs	IND 77,882 IND 78,933
Applicant Name	Avedro, Inc.
Date of Original Submission **Date of Receipt**	September 16, 2013 September 16, 2013
Review Type:	Priority
Complete Response Letter #1	March 14, 2014
Complete Resubmission #1	September 29, 2014
Complete Response Letter #2	March 29, 2015 (Sunday)
Complete Resubmission #2	October 16, 2015
Administrative Split of NDA **Original 1 Approved**	 April 15, 2016
Original 2 Major amendment	April 15, 2016
Original 2 PDUFA Goal Date	July 15, 2016
Proprietary Name / **Established (USAN) Name** **Proprietary Name /** **Established (USAN) Name**	PHOTREXA VISCOUS® riboflavin 5'-phosphate in 20% dextran ophthalmic solution, 0.146% PHOTREXA® riboflavin 5'-phosphate ophthalmic solution, 0.146%
Formulation **Use**	ophthalmic solution 1 drop topically on the eye every 2 minutes for 30 minutes following post epithelial debridement. Continue topical instillation 1 drop onto the eye every 2 minutes during the 30 minute UVA irradiation during which Photrexa Viscous is used if the corneal thickness is ≥400 microns and Photrexa is used if the corneal thickness is <400 microns
Device component of combination Product	The KXL® System is a portable electronic medical device and serves as a UVA light source
Proposed Indication(s)	Original 1: Treatment of progressive keratoconus Original 2: Treatment of corneal ectasia following refractive surgery
Action for Application(s)	*Original 1: Approved April 15, 2016* *Original 2: Approval during this review cycle*

Material Reviewed for this NDA	Names of discipline reviewers
Division Director Review	Renata Albrecht 3/14/2014, 3/29/2015, 4/15/2016
Medical Officer Review	William Boyd 3/7/2014, 3/24/2015
Deputy Division Director Review	Wiley Chambers, 3/7/2014, 7/15/2016
CDTL Review	Bill Boyd, Wiley Chambers 3/10/2014, 3/27/2015, 4/15/2016, 7/15/2016
CDRH ODE/DOED Memorandum CDRH Memorandum	William Maisel, Malvina Eydelman 4/13/2016 William Maisel 7/13/2016
CDRH Device Clinical Review	Bradley Cunningham, 2/10/2014 Maryam Mokhtarzadeh, 3/24/2015, 2/1/2016
CDRH EMC Review	Jeffrey Silberberg 3/24/2015, 3/27/2015
CDRH Electrical Safety Review	Sandy Weininger 1/9/2015
CDRH Software Review	Joseph Jorgens III 3/3/2014, 3/26/2015
CDRH Engineering Review	Dexiu Shi 3/26/2015, Bruce Drum 1/12/2016
Statistical Review Team Leader Review	Dongliang Zhuang, Yan Wang 2/28/2014, 8/13/2014, 3/12/2015 Yan Wang, Dionne Price 3/15/2015, 4/10/2016
Pharmacology/Toxicology Review	Aaron Ruhland, Lori Kotch 2/26/2014
Clinical Pharmacology Review	Gerlie Gieser, Philip Colangelo 1/17/2014
OPS/OTR/DPA	OPS/OTR/DPA Michael Trehy 12/20/2013
ProductQuality Microbiology	Denise Miller, Bryan Riley 2/18/2014
CDER/OC/Facilities Inspection	Linda Ng, Mahesh Ramanadham 3/5/2014
Product Quality Manufacturing Review/ OPQ	George Lunn, Balajee Shanmugam, Rapti Madurawe 2/20/2014 George Lunn, Dorota Matecka 3/5/2015, 4/13/2016
Biometrics	Tianhua Wang, 2/1/2016
Methods Validation	See CMC review
Product Quality Microbiology	See CMC review
CDER/OC/Facilities Inspection	See CMC review
OPQ RBPM	Erin Andrews, 12/4/2015
CHDR/OC/DMQ/ASDB Device Inspection	Felicia Brayboy, Ronald Swann 1/15/2014
OSI/DGCPC	Janice Pohlman, Kassa Ayalew 3/14/2014, 3/27/2015 Roy Blay 2/21/2014, 2/22/2014, 7/7/2014, 7/10/2014, 7/14/2014
OSE/DMEPA Proprietary Name Review Name granted	Rachna Kapoor, Yelena Maslov, Lubna Merchant 1/13/2015 Todd Bridges (Karen Townsend) 4/2/2014, 1/14/2015 Michelle Rutledge 1/29/2016 Karen Townsend 2/2/2016
OSE/DMEPA Labeling and Label Review	Aleksander Winiarski, Morgan Walker 12/19/2013 Rachna Kapoor, Yelena Maslov 3/9/2015 Yelena Maslov 3/17/2015 Michelle Rutledge 4/8/2016
SEALD Review	Jessica Voqui, Elektra Papadopoulos 2/23/2015
OPDP/DPDP (formerly DDMAC)	Christine Corser 3/21/2014 Zarna Patel, 3/30/2015 Meena Ramachandra 4/14/2016
Pediatric Review Committee	Orphan designation – PREA does not apply
Project Management	Jacquelyn Smith, Diana Willard

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP =Division of Medical Policy Programs
SEALD=Study Endpoint and Labeling Development
*OPQ review includes drug substance, drug product, manufacturing process, microbiology, facility and biopharmaceutics.
CDRH=Center for Devices and Radiological Health
ODE=Office of Device Evaluation
DOED= Division of Ophthalmic and Ear, Nose, and Throat Devices

NOTE TO THE READER:
This new drug application (NDA) was originally submitted as one NDA with two proposed indications which were studied in the same study as well as in separate studies. In April 2015, the NDA was Administratively Split due to the different regulatory action for the two indications. At that time NDA 203324 Original 1 was approved for the treatment of progressive keratoconus, while a major amendment was accepted for NDA 203324 Original 2 and an action was not taken for the treatment of corneal ectasia following refractive surgery, at that time.

To be able to provide a summary of the approvals of Original 1 and Original 2 in one location, this Summary Review of July 15, 2016, repeats relevant information contained in the Summary Review dated April 15, 2016, and includes updates to the discussion and recommendations for Original 2.

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1. Benefit-Risk Assessment

All disciplines in CDER Division of Transplant and Ophthalmology Products within the Office of Antimicrobial Products recommended approval of NDA 203324 (clinical, statistical, pharmacology/toxicology, clinical pharmacology, chemistry) for both indications in April 2016. Clinical and statistical reviewers concluded that the clinical studies demonstrated the safety and efficacy for the two indications in NDA 203324, PHOTREXA VISCOUS and PHOTREXA, and KXL System, submitted by Avedro. The application was administratively split as follows, for the reasons provided below:

- NDA 203324 Original 1: treatment of progressive keratoconus
- NDA 203324 Original 2: treatment of corneal ectasia following refractive surgery

At the time an action was taken on Original 1, the CDRH, Division of Ophthalmic and Ear, Nose, and Throat Devices (DOED) within the Office of Device Evaluation (ODE) concluded that all device-related issues for the indication of progressive keratoconus had been resolved and recommended that NDA be approved for the treatment of progressive keratoconus. NDA 203324 Original 1 was approved April 15, 2016.

Also at the time an action was taken on Original 1, the CDRH staff concluded that the device-related issues for the indication of corneal ectasia following refractive surgery (Original 2) had not been resolved, as summarized in the April 13, 2016, Memorandum from Dr. William Maisel, Acting Director, ODE and Dr. Malvina Eydelman, Director, DOED. The applicant was asked to provide further information and complied on April 15, 2016.

During the review of Original 2, there were discussion in CDER and in CDRH as well as between CDER and CDRH Center Directors regarding the indication for corneal ectasia following refractive surgery. As summarized in Section 7 Efficacy, following these discussions, CDRH recommended that Original 2 be approved, based on the scientific evidence, the proposed labeling, and the post-approval study plan for longer-term outcomes.

A number of regulatory and scientific issues were identified during review of this application. I have addressed these issues in the review that follows.

See Benefit –Risk Table summary below

Benefit-Risk Summary and Assessment

Keratoconus and post-refractive corneal ectasia are diseases of the cornea for which there limited therapeutic options; the condition is associated with changes in visual function including visual acuity. Initially these ectatic conditions may be managed with glasses and contacts, in some patients corneal transplantation is used as a last measure. The current application includes 3 controlled clinical studies demonstrating that the corneal collagen crosslinking procedure (CCXL) using riboflavin and UVA light over the course of an approximately 60 minute procedure (See Section 2. for description of the procedure) is effective in reducing the corneal curvature, as measured by Kmax. In the corneal ectasia studies, the primary endpoint of reducing the Kmax by 1 diopter was achieved at Month 3 and maintained at Month 6 and Month 12, compared to sham controls. In the keratoconus studies, the same primary endpoint was achieved at Month 6 and Month 12. The adverse events associated with this procedure include corneal opacity (haze), corneal epithelial defects, and other ocular findings related to the procedure which consists of corneal epithelial removal, riboflavin instillation followed by UV light illumination. Most of the adverse events resolve in the first month, however, some continue for 6 to 12 months, and 1-6% of patients continue to report corneal haze and other symptoms at Month 12 (See Section 8. Safety). This process results in CCXL in the corneal stroma, thereby stabilizing the cornea, as is shown in the Figure in Section 7. Efficacy. If ophthalmologists are trained in performing the procedure and manage patients accordingly, including pre- and post-CCXL care, the benefits of the procedure outweigh the risks of the procedure in this population in whom this treatment addresses an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	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.	Progressive keratoconus and corneal ectasia following refractive surgeries represent orphan conditions for which effective treatments are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are currently limited FDA-approved therapies available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery. For both keratoconus and corneal ectasia, early treatment 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. The Intacs corneal implant is approved for the treatment of myopia and keratoconus. 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.	Corneal cross-linking procedures are currently unavailable for patients in the United States. Availability of an approved drug/device product would address an unmet medical need.
Benefit	The applicant has submitted adequate and well controlled trials for both the keratoconus (Studies UVX-001 and UVX-002) and corneal ectasia (Studies UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CCXL treatment for both indications. As shown in Section 7. Efficacy, the applicant met the predefined primary endpoint of a 1 Diopter reduction in the corneal curvature (Kmax) of Month 3 after CCXL in the corneal ectasia studies, and met the FDA requested primary endpoint of Month 12 in both the corneal and progressive keratoconus studies. In sensitivity analyses of pediatric patients, it was seen that they appeared to have a potentially greater response in terms of a larger decrease in the corneal curvature (Kmax) than older patients. It was also noted that while not statistically significant, the improvement in BCVA was numerically greater in the patients treated with corneal collagen-cross linking than patients who received sham treatment.	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.
Risk	The procedure, as described in Section 2. Background, involves removing the corneal epithelium to enhance the riboflavin solution's penetration through to the corneal stromal tissue during the first 30 minutes of administration, where the riboflavin acts as an enhancer when ultraviolet A (UVA) light is then shined on the stroma for the subsequent 30 minutes. As a result of the procedure, patients may develop a range of ocular adverse reactions including	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	corneal opacity (haze), corneal epithelial defects, punctate keratitis, corneal striae, eye pain, reduced visual acuity, blurred vision, dry eye, photophobia among others. These events are associated with the epithelial corneal debridement and the CCXL procedure; the events occurred at a higher incidence than observed in control subjects, who received riboflavin but did not undergo debridement or exposure to UVA light. As summarized in Section 8, many of these adverse reactions resolve in the first month, while others can take up to 12 months to resolve. In 1-6% of patients adverse reactions continued to be observed at 12 months.	
Risk Management	Ophthalmologists need to be trained to perform these procedures, and become familiar with the risks and benefits, and manage patients accordingly. The procedure is done under topical anesthesia and aseptic conditions. After surgery patients are often provided a bandage contact lens to protect the eye, and patient counseling includes: advising patients not to rub their eyes for the first five days after their procedure, that there may be discomfort in the treated eye and that sunglasses may help with light sensitivity. Patients may be sensitive to light and have a foreign body sensation. If patients experience severe pain in the eye or any sudden decrease in their vision, they are advised to contact their physician immediately. If a bandage contact lens falls out or becomes dislodged, patients are advised not to replace it and to contact their physician immediately.	This procedure has been performed using riboflavin and UVA light sources (including the device in this NDA) outside the US. Information has been presented at professional conferences and published in the professional literature.

2. Background

For a detailed discussion of drug development under IND, the Medical Officer and CDTL reviews should be consulted.

Regulatory Background

The product was developed under two INDs: IND 78,933 was submitted in July 2007 by Doyle Stulting, MD, Emory University, and he conducted Study UVX-001 in progressive keratoconus and corneal ectasia, in association with the original commercial sponsor, Peschke Meditrade. IND 77,882 was submitted in November 2007 by Peschke Meditrade and they conducted Study UVX-002 in patients with progressive keratoconus and Study UVX-003 in patients with corneal ectasia following corneal refractive procedures.

These sponsors met with the Division of Anti-Infective and Ophthalmology Products during which there was discussion of the study design, including the sponsors; concern of the low likelihood that patients would be willing to continue the sham arm past Month 3, and the Division's request for longer duration of follow up to Month 12. Peschke Meditrade sold the data and rights to UVX-001, UVX-002 and UVX-003 to Avedro in May 2010.

Avedro met with FDA at the pre-NDA Meeting held on September 21, 2011, during which CMC and clinical issues were discussed. The application was submitted March 8, 2012, and received a refuse-to-file letter because the proposed product had a different formulation than studied in clinical studies.

Following discussions with CMC, Avedro submitted NDA 203324 for Photrexa Viscous /Photrexa/KXL-System on 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. Among the responses were additional analyses of clinical studies and responses on study data quality; no new clinical studies were included.

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).

Avedro met with FDA on June 11, and August 10, 2015, to discuss the March 29, 2015, 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 2(a) – 2(e) of the letter, which was further discussed in several August teleconferences. Avedro submitted a Complete Response on October 16, 2015.

On April 15, 2016, NDA 203324 Original 1 was approved for the indication of "PHOTREXA VISCOUS and PHOTREXA are photoenhancers indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus." A major amendment was submitted to NDA 203324 Original 2.

Corneal Collagen Cross-Linking (CCXL) Procedure:
NDA 203324 is submitted by Avedro for the use of PHOTREXA VISCOUS (and PHOTREXA) with the KXL System (ultraviolet A light source) to treat patients with keratoconus or post-refractive corneal ectasia. These two products are used together in the following manner:

The ophthalmologist removes the corneal epithelium to a diameter of approximately 9 mm, using topical anesthesia and standard aseptic technique. Post epithelial debridement, 1 drop of Photrexa Viscous is applied topically on the eye every 2 minutes for 30 minutes. At the end of the 30 minute soaking period, the eye is examined under the slit lamp to look for the presence of a yellow flare in the anterior chamber, which is evidence that adequate riboflavin saturation has been achieved. If the yellow flare is not detected, 1 drop of Photrexa Viscous is administered every 2 minutes for an additional 2 to 3 drops and the eye is rechecked for the presence of a yellow flare. This process can be repeated until the yellow flare is achieved.

Once the yellow flare is observed, ultrasound pachymetry is performed to measure the corneal thickness. If corneal thickness is less than 400 microns, 2 drops of PHOTREXA are instilled every 5 to 10 seconds until the corneal thickness increases to at least 400 microns. Irradiation should not be performed unless this 400 micron threshold is met and the yellow flare is seen.

The eye is irradiated for 30 minutes at 3mW/cm^2 at a wavelength of 365 nm, centered over the cornea, using the KXL System. Instructions for the use of the device are found in the KXL Operator's Manual. During irradiation, topical instillation of PHOTREXA VISCOUS is continued onto the eye every 2 minutes for the 30 minute irradiation period.

The PHOTREXA VISCOUS and PHOTREXA products are for ophthalmic use, and one syringe can use used for one patient only. The syringe(s) is discarded after use.

In the literature, there are reports of other riboflavin solutions and devices used for CCXL. These report on variations on the use of riboflavin saturation through the corneal stroma and exposure to ultraviolet A (UVA) light (365 (b) (4) nm; 3(b) (4) mW/cm^2 irradiation; (b) (4)30 minutes' duration) to achieve CCXL.

3. Drug Product Quality & Device Constituent Part

Drug Substance
The chemical formula for riboflavin 5'-phosphate sodium (Vitamin B2) is $C_{17}H_{20}N_4NaO_9P$ with a molecular mass of 478.33 g/mol.

Drug Products

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

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

Dosage Form and How Supplied:

- PHOTREXA VISCOUS in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical administration.
- PHOTREXA in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution for topical administration.
- PHOTREXA VISCOUS and PHOTREXA 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. The packaging is further distinguishable by the color used on the cartons, foil and wrap: orange for PHOTREXA VISCOUS and green for PHOTREXA.

Intended Use:

PHOTREXA VISCOUS and PHOTREXA are intended for topical ophthalmic administration as part of corneal collagen cross-linking with the KXL System (an ultraviolet A light source).

KXL System

The KXL System Operator's Manual provides specific device description and instructions. In brief, the KXL System is an electronic medical device which delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after Photrexa Viscous and/or Photrexa has been applied. Irradiating the riboflavin phosphates ophthalmic solution creates singlet oxygen, which catalyzes the formation of intermolecular bonds in corneal collagen. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system.

The Optics Head houses the UVA irradiation mechanism. The LED emits continuous UVA radiation at a wavelength of 365 nm at an intensity of 3 $mW/cm^2 \pm 10\%$.

A fixed aperture mounted in the UVA irradiation beam path is used to produce a circular area of irradiation at the treatment plane with a diameter of 9.5 mm. Alignment lasers are used to aid the user in focusing the beam on the patient's cornea. Fine alignment of the UV beam through observation of the alignment lasers is controlled by the user through a wireless remote. The KXL is a portable system 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 (Riboflavin Induction Period, Total UV Energy and UV Power) are confirmed through the user interface touch screen computer.

The IROC UV-X device was used in the clinical studies UVX-001 UVX-002 and UVX-003, and the KXL System proposed for marketing was not used. During review of the application, CDRH noted the similarities and differences between the two devices (discussed in prior reviews and at the February 24, 2015, Advisory Committee meeting), and sent information requests to Avedro to bridge the KXL System to the IROC UV-X device and demonstrate that the two devices are can be set to deliver an equivalent UVA dose. Deficiencies 2(a)-2(e) were included in the March 29, 2015 Complete Response Letter and asked about (in brief):

(a) complete and detailed description and explanation of the optical systems of both devices
(b) beam propagation differences between the two devices and the potential of how that beam differs on the cornea
(c) detailed description of all features and procedures used in the clinical trial to limit patient eye movements during the crosslinking procedure
(d) best estimates of the location of the focal plane relative to the cornea for both devices
(e) analysis of the 3-D distribution of UV energy in the corneal stroma for the two devices

Subsequently, meetings (and teleconferences) took place June 11, August 10, 19, 20 and 26, 2015, to provide detailed guidance to Avedro, and Avedro submitted their KXL UVA Equivalence Testing Protocol (DHF002-DV-22) containing a detailed description of the non-clinical tests to be conducted and the acceptance criteria for these in order to comprehensively address the deficiencies 2(a)-2(e). After the August discussions, CDRH agreed to the protocol and acceptance criteria (September 30, 2015 General Advice Letter). Avedro submitted the KXL UVA Equivalence Testing Report (DHF002-DV-23) on October 16, 2015. Based on the Summary of the Equivalence Testing Results, all 14 tests results were within the acceptance criteria, demonstrating the comparability equivalence of the two devices. CDRH concluded that the results from this testing supported the indication of progressive keratoconus but not the indication of corneal ectasia following refractive surgery.

Facilities inspection

An overall recommendation of Acceptable was made by the Office of Compliance on April 11, 2016. The inspections during the review cycles covered both the drug constituent part and the device constituent part.

The CDER CMC review team recommended approval of the drug products, and they were approved under NDA 203324 Original 1 on April 15, 2016. There have been no subsequent

changes to the drug products. The CDRH team recommended approval of the device for the progressive keratoconus indication (Original 1) in April 2016 and CDRH now recommends approval of the corneal ectasia indication (Original 2).

4. Nonclinical Pharmacology/Toxicology

This 505(b)(2) application that relies on published literature for the nonclinical information on riboflavin. 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.

Animal studies have not been conducted to determine the carcinogenic potential of photoexcited riboflavin. Photoexcited riboflavin has been shown to be genotoxic in the Ames Salmonella reverse mutation assay and in the SOS/umu test system.

The genotoxicity of riboflavin, in the absence of photoexcitation has been examined *in vitro* in bacterial reverse mutation assays, sister chromatid exchange assay, chromosomal aberration assays and *in vivo* in a mouse micronucleus study. The overall weight of evidence indicates that riboflavin, in the absence of photoexcitation, is not genotoxic.

Animal studies to determine the effects of the PHOTREXA/KXL corneal collagen cross-linking procedure on fertility were not conducted; however, labeling will advise that the CCXL procedure should not be conducted while the patient is pregnant.

The Pharmacology/Toxicology (P/T) review team recommended approval and their labeling recommendations were incorporated in the labeling approved April 15, 2016. No new P/T information has been submitted.

5. Clinical Pharmacology

Riboflavin 5'-phosphate sodium (Vitamin B2) is the precursor of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze oxidation/reduction reactions involved in a number of metabolic pathways.

Under the conditions used for corneal collagen cross-linking, riboflavin 5'-phosphate functions as a photoenhancer and generates singlet oxygen which is responsible for the cross-linking. The Clinical Pharmacology review team recommends approval.

There were no clinical pharmacology studies conducted with the PHOTREXA VISCOUS or PHOTREXA. The reviewer notes that assuming 100% bioavailability of riboflavin following topical ocular instillation of these 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).

The Clinical Pharmacology (CP) review team recommended approval; their labeling recommendations were incorporated in the labeling approved April 15, 2016. There is no additional CP information.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

In support of the present NDA, the Applicant submitted the following randomized, controlled, clinical studies: UVX-001, UVX-002, and UVX-003, the protocols have been summarized in the primary clinical and statistical reviews, and discussed at the open public advisory committee meeting on February 24, 2015. (See Section 9.)

The primary endpoint was at least a 1 diopter reduction in the corneal curvature (Kmax). The original protocols listed the timing as Month 3; however, the Division had advised the sponsors to choose a Month 12 endpoint.

Efficacy Results

The information on the outcome is summarized in the primary and secondary statistical reviews, and the clinical reviews.

UVX-001 enrolled 58 subjects with progressive keratoconus and 49 subjects with corneal ectasia following refractive surgery. UVX-002 enrolled 147 subjects with progressive keratoconus, and UVX-003 enrolled 130 subjects with corneal ectasia following refractive surgery. For keratoconus subjects in UVX-001 and UVX-002, approximately 56% and 89% of the subjects received corneal cross-linking (CXL) treatment in their sham study eyes by Month 3 and Month 6, respectively. For corneal ectasia subjects in UVX-001 and UVX-003, approximately 60% and 90% of the subjects received CXL treatment in their sham eyes by Month 3 and Month 6, respectively.

The average age was 33 years for the progressive keratoconus subjects and 43 years for the corneal ectasia subjects. The average baseline Kmax values were 61 diopters for the progressive keratoconus subjects and 55 diopters for the corneal ectasia subjects. A majority (93%) of the corneal ectasia subjects had LASIK only, 5 (3%) subjects had photorefractive keratectomy (PRK) only, and 8 (4%) subjects had both LASIK and PRK.

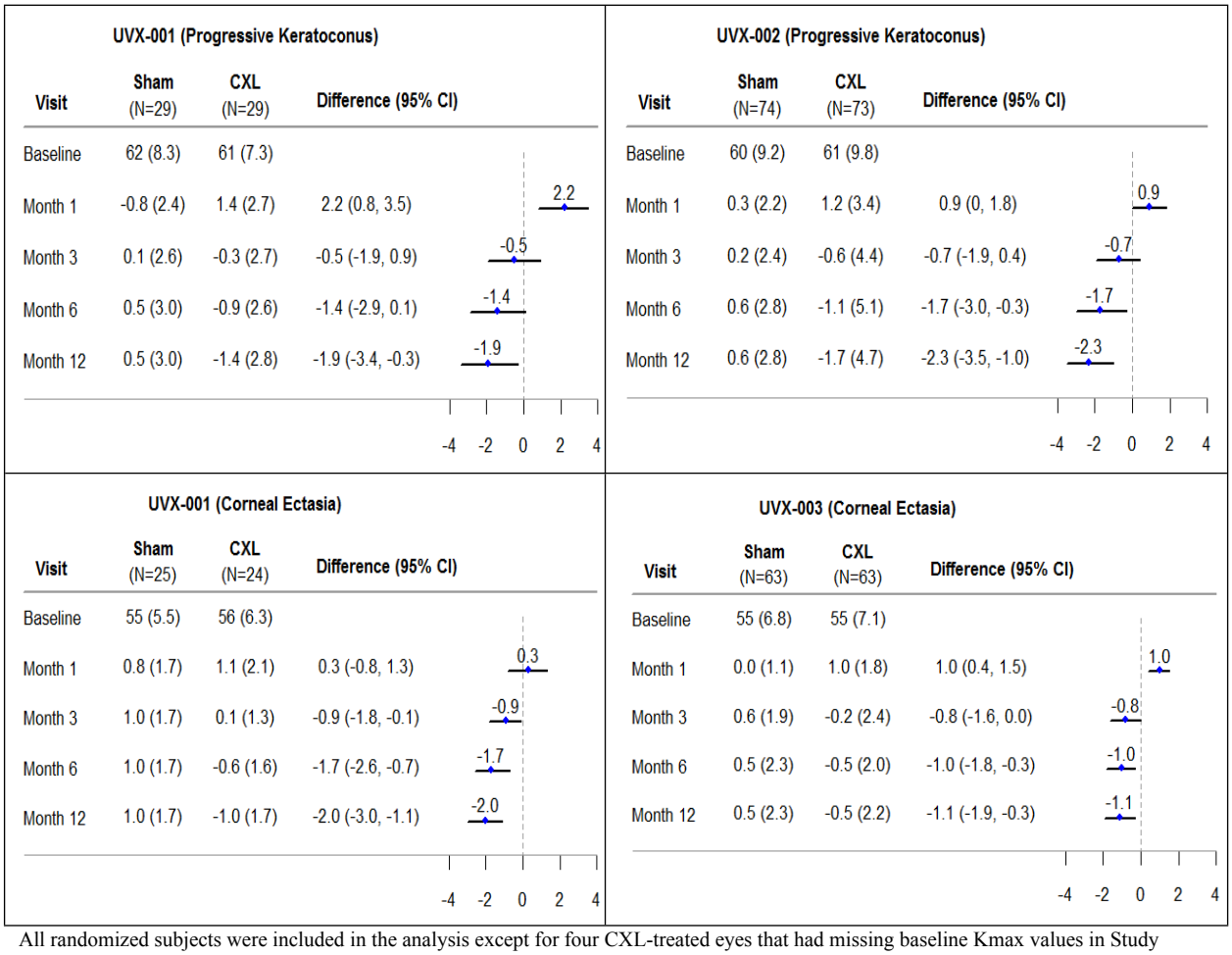
In each study, the maximum corneal curvature (Kmax) was assessed at baseline, Months 1, 3, and 12. The CXL-treated eyes showed increasing improvement in Kmax from Month 3 through Month 12 (Figure below).

For keratoconus subjects, at Month 12, the CXL-treated eyes had an average Kmax reduction of 1.4 diopters in UVX-001 and 1.7 diopters in UVX-002 while the sham eyes had an average increase of 0.5 diopter in UVX-001 and 0.6 diopter in UVX-002; 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 UVX-001 and - 2.3 (-3.5, -1.0) diopters in UVX-002.

For corneal ectasia subjects, at Month 12, the CXL-treated eyes had an average Kmax reduction of 1.0 diopter in UVX-001 and 0.5 diopter in UVX-003 while the sham eyes had an average increase of 1.0 diopter in UVX-001 and 0.5 diopter in UVX-003; the treatment difference between the CXL and sham groups was: -2.0 (-3.0, -1.1) diopters in UVX-001 and -1.1 (-1.9, -0.3) diopters in UVX-003.

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



All randomized subjects were included in the analysis except for four CXL-treated eyes that had missing baseline Kmax values in Study UVX-003. 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.
Source: Statistical TL Review 4/10/2016

As seen in the figure of outcomes for both indications, there is a numerical decline in Kmax in favor of the CXL arm at Month 3 in progressive keratoconus patients and a significant decline in Kmax in the corneal ectasia patients. At the subsequent visits, the statistically significant difference in the Kmax at Month 6 and Month 12 favor the CXL arms in reduction of corneal curvature.

The finding of greater improvement in the corneal curvature correlated with numerical improvement in BCVA as well as number of patients whose vision increased by 15 letters; however, these changes did not reach statistical significance.

Changes from Baseline in BSCVA in UVX-001
(Source: 5.3.5.1. clinical study report UVX-001, p 111-112 of 170)

In keratoconus subjects, mean improvements from baseline in BSCVA (LOCF) numerically favored CXL at Months 6 (5.7 vs. 3.4 letters, p=0.4157) and 12 (7.2 vs. 3.4 letters, p=0.1685). Similar results were noted at Month 6 when observed case data were used (6.1 vs. 4.4 letters, p=0.6189). The proportion of subjects with a ≥15-letter improvement in BSCVA was generally comparable between treatment groups at Months 6 (LOCF and observed cases) and 12 (LOCF).

In corneal ectasia subjects, mean improvements from baseline in BSCVA (LOCF) were greater in the CXL group compared to the control group at Months 6 (5.9 vs. –0.9 letters, p=0.0086) and 12 (5.0 vs. –0.9 letters, p=0.0184), and the proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group (Month 6: 30.4% vs. 4.2%; Month 12: 21.7% vs. 4.2%). When observed case data were used, mean change from baseline in BSCVA was 6.7 letters in the CXL group and –1.8 letters in the control group at Month 6 (p=0.0124), and the proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group (33.3% vs. 8.3%).

Changes from Baseline in BSCVA in UVX-002. Progressive keratoconus patients
(Source: 5.3.5.1. clinical study report UVX-002, p 86-87 of 121)

In addition to improvement in corneal curvature, CXL was associated with improvements in BSCVA. In the ITT population, mean improvements from baseline in BSCVA (LOCF) were greater in the CXL group compared to the control group at Month 6 (4.5 vs. 1.5 letters, p=0.0750) and Month 12 (5.0 vs. 1.4 letters, p=0.0280), and the proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group (Month 6, 14.5% vs. 2.8%; Month 12, 17.4% vs. 2.8%). When observed case data were used, mean change from baseline in BSCVA was 5.7 letters in the CXL group and – 2.0 letters in the control group at Month 6 (p=0.0064), and the proportion of subjects with a ≥15-letter improvement in BSCVA was several-fold higher in the CXL group (15.6% vs. 5.6%).

Changes from Baseline in BSCVA in UVX-003, corneal ectasia patients
(Source: 5.3.5.1. clinical study report UVX-003, p 84 of 118)

In addition to improvement in corneal curvature, CXL was associated with improvements in BSCVA. Mean improvements from baseline in BSCVA (LOCF) were greater in the CXL group compared to the control group at Month 6 (3.4 vs. –0.2 letters, p=0.0300) and Month 12 (5.0 vs. –0.1 letters, p=0.0014), and the proportion of subjects with a ≥15-letter improvement in BSCVA was approximately 2-fold higher in the CXL group (Month 6, 10.8% vs. 4.8%; Month 12, 9.2% vs. 4.8%). When observed case data were used, mean change from baseline in BSCVA was 3.8 letters in the CXL group and 0.6 letters in the control group at Month 6

(p=0.1854), and the proportion of subjects ≥15-letter improvement in BSCVA was approximately 2-fold higher in the CXL group (11.9% vs. 5.6%).

CDRH Recommendations
During earlier review cycles, CDRH did not agree with these interpretations of the study results (as discussed in their reviews, at the Advisory Committee meeting February 24, 2015, and at the Regulatory Briefing March 20, 2015).

Earlier in this cycle (review of October 16, 2015 resubmission), CDRH recommended that only the progressive keratoconus indication be approved (Original 1 was approved on April 15, 2016), but CDRH did not recommend approval of the corneal ectasia indication (Original 2).

Dr. William Maisel, Acting Director of the Office of Device Evaluation, and Dr. Malvina Eydelman, Director of the Division of Ophthalmic and Ear, Nose and Throat Devices, CDRH, sent a Memorandum April 13, 2016, summarizing the position. In brief,

- Progressive keratoconus
  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. CDRH/ODE supports CDER's recommendation that the product be indicated for patients 14 years of age and older. This is based on the age range of the patients included in the clinical study and the feedback from the Advisory Committee. CDRH also asks that the applicant be required to conduct a post-marketing study in pediatric patients.

  Dr. Maisel confirmed via email that, "There are no outstanding issues from CDRH concerning the keratoconus indication."

  CDER comment: The post-marketing study requested by CDRH to be a required postmarketing study is not consistent with the Food, Drug and Cosmetic Act, as amended and associated regulations for NDAs. The application has been submitted for an orphan designated population and pediatric studies are not required. The Agency can require studies to evaluate a specific safety issue, but no safety issue has been identified. It has been noted that the cornea finishes its development by age 2.

  Keratoconus in pediatric patients is not a specific pediatric indication different from that in adults. The NDA regulations allow extrapolation of efficacy from adults to pediatric patients but safety data need to be from the pediatric population. Safety data for patients 14 years and older were provided in the application, supporting labeling for patients 14 years and older. In addition, as demonstrated both by the CDER and CDRH sensitivity analyses, pediatric patients demonstrated a numerically greater and sustainable decrease in Kmax.

- Corneal ectasia post refractive surgery
  CDRH/ODE did not believe the information provided in the submission and the available valid scientific evidence was sufficient to resolve the device-related issues and listed the following (in brief):
  - The 3 month data comparing the investigational arm with the control arm is insufficient to conclude that the product is safe and effective for the post-refractive corneal ectasia population… Therefore, the analysis of the 12 month follow-up data is of critical importance,
  - The Statistical Analysis Plan was not finalized until after study enrollment and follow- up were completed,
  - 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),
  - 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.

  CDER comment: The four issues raised by CDRH discuss study design and analysis issues that impact the three studies in the application evaluating both indications. At Month 3, the Kmax endpoint of corneal curvature in the treatment group was statistically superior to control in Studies UVX-001 and UVX-003 for the corneal ectasia population, and by Month 12 it was both statistically significant and greater than 1 diopter for both indications. The statistical analysis plan, the use of the LOCF analysis of the study results, and the use of the IROC UV-X device (i.e., not the KXL System device) is applicable to all three clinical studies in the application. The clinical and statistical reviews provide support for why the Month 12 data analysis using the LOCF observation is a valid approach. It is also noted that the SAP identifying the Month 12 analysis is consistent with the CDER Division's recommendations on study design during the IND development stage. The bridge between the IROC UV-X device and KXL System device has been reviewed under Avedro's KXL UVA Equivalence Testing Protocol (DHF002-DV-22) and the KXL UVA Equivalence Testing Report (DHF002-DV-23) on October 16, 2015. Based on the Summary of the Equivalence Testing Results, all 14 tests results were within the acceptance criteria, demonstrating the comparability equivalence of the two devices.

During this review cycle of Original 2, there was discussion in CDER and in CDRH as well as between CDER and CDRH Center Directors regarding the indication for corneal ectasia following refractive surgery.

During the internal CDER discussions, including a briefing with Dr. John Jenkins, Director of the Office of New Drugs on May 20, 2016, and a briefing with Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research on June 8, 2016, CDER management agreed with the Division's recommendation for the approval of Original 2.

In the July 13, 2016, Memorandum, Dr. William Maisel, Deputy Director for Science in CDRH writes that there was an internal meeting with CDRH staff and the CDRH Center Director, followed by a meeting between the CDER and CDRH Center Directors. CDRH recommended to CDER that longer term clinical data should be collected, but given that the available non-clinical and clinical data are sufficient to support marketing approval, the longer term clinical data may be collected during a postmarket study. CDRH's recommendation was that the NDA (Original 2) be approved for the indication of corneal ectasia following refractive surgery, based on the scientific evidence, the proposed labeling, and the post-approval study plan for longer-term outcomes. An email from CDR Bradley Cunningham provided initial recommendations to be considered for the post-approval study design.

Therefore, Original 2 for the indication of corneal ectasia following refractive surgery will be approved during this review cycle.

8. Safety

The safety of the corneal collagen cross-linking procedure was evaluated in 3 randomized, parallel-group, open-label, sham-controlled trials (UVX-1, UVX-2 and UVX-3); patients were followed up for 12 months. Each CXL treated eye received a single course of CXL treatment only.

Safety data were obtained from 193 randomized CXL study eyes (102, keratoconus; 91, corneal ectasia), 191 control eyes (103 keratoconus, 88 corneal ectasia) and 319 non-study, nonrandomized CXL eyes (191, keratoconus; 128, corneal ectasia). Overall 512 eyes (293, keratoconus; 219, corneal ectasia) in 364 patients received any CXL treatment.

This was a single treatment; therefore, there were no dropouts during treatment. No deaths were reported. In keratoconus subjects, the most common ocular 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 (Table below). 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 vision blurred. These events are expected sequalae following epithelial corneal debridement and occurred at a higher incidence than observed in control subjects, who received riboflavin but did not undergo debridement or exposure to UVA light.

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

The majority of adverse events reported resolved during the first month, while events such as corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye and eye pain, and decreased visual acuity took up to 6 months to resolve and corneal opacity or haze took up to 12 months to resolve. In 1-2% of patients, corneal epithelium defect, corneal edema, corneal

opacity and corneal scar continued to be observed at 12 months. In 6% of corneal ectasia patients, corneal opacity continued to be observed at 12 months.
(Source: 1.11.3 Clinical Information Amendment, 4/13/2016)

Table: Most Common (≥1%) Ocular Adverse Reactions in CXL-Treated Study Eye in the Pooled Randomized Safety Population – N (%)

	Progressive Keratoconus Studies UVX-001 and UVX-002		Corneal Ectasia Studies UVX-001 and UVX-003	
Preferred Term	**CXL Group (N=102)[1]**	**Control Group (N=103)[1]**	**CXL Group (N=91)[1]**	**Control Group (N=88)[1]**
Anterior chamber cell	2 (2)	0	2 (2)	1 (1)
Anterior chamber flare	4 (4)	0	5 (6)	2 (2)
Asthenopia	1 (1)	1 (1)	2 (2)	0
Blepharitis	0	0	0	1 (1)
Corneal disorder	3 (3)	1 (1)	3 (3)	0
Corneal epithelium defect	24 (24)	1 (1)	26 (28)	3 (3)
Corneal oedema	3 (3)	0	3 (3)	0
Corneal opacity[2]	65 (64)	9 (9)	65 (71)	8 (9)
Corneal striae	24 (24)	12 (12)	8 (9)	6 (7)
Corneal thinning	1 (1)	2 (2)	0	0
Diplopia	2 (2)	1 (1)	1 (1)	0
Dry eye	6 (6)	2 (2)	13 (14)	4 (5)
Eye complication associated with device	2 (2)	0	1 (1)	0
Eye discharge	2 (2)	1 (1)	0	0
Eye oedema	7 (7)	0	0	0
Eye pain	17 (17)	3 (3)	24 (26)	0
Eye pruritus	2 (2)	0	0	0
Eyelid oedema	5 (5)	0	5 (6)	1 (1)
Foreign body sensation in eyes	15 (15)	1 (1)	13 (14)	2 (2)
Glare	4 (4)	1 (1)	2 (2)	0
Halo vision	1 (1)	0	2 (2)	0
Keratitis	1 (1)	0	3 (3)	0
Lacrimation increased	5 (5)	0	9 (10)	1 (1)
Meibomian gland dysfunction	1 (1)	1 (1)	3 (3)	2 (2)

Preferred Term	Progressive Keratoconus Studies UVX-001 and UVX-002		Corneal Ectasia Studies UVX-001 and UVX-003	
	CXL Group (N=102)[1]	Control Group (N=103)[1]	CXL Group (N=91)[1]	Control Group (N=88)[1]
Ocular discomfort	0	0	8 (9)	0
Ocular hyperaemia	14 (14)	2 (2)	7 (8)	4 (5)
Photophobia	11 (11)	0	17 (19)	0
Punctate keratitis	25 (25)	8 (8)	18 (20)	3 (3)
Vision blurred	16 (16)	2 (2)	15 (17)	4 (5)
Visual acuity reduced	10 (10)	9 (9)	10 (11)	1 (1)
Visual impairment	3 (3)	2 (2)	4 (4)	1 (1)
Vitreous detachment	2 (2)	0	0	0

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

Headache was reported in between 4 to 8% of treated patients.

The CDER clinical reviewers and statistical reviewers recommended approval of both indications. CDRH recommended approval of progressive keratoconus and the indication was approved April 15, 2016. Approval of the corneal ectasia indication is recommended by CDRH at this time.

9. Advisory Committee Meeting

This application was discussed during the February 24, 2015, meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee (OP-MDAC). The meeting included an open public hearing where speakers expressed support for approval as well as concerns about potential off-label use. The committee listened to presentations, and discussed the issues presented. The majority voted for approval for each indication. The Briefing material, PowerPoint Slide presentations and transcript of this meeting is available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/ucm431514.htm (accessed 7/15/2016).

10. Pediatrics

The applicant has been granted Orphan Designation for both indications; therefore the Pediatric Research Equity Act does not apply to this application. The applicant studied patients 14 years of age and above for the indication of progressive keratoconus. The safety and effectiveness of corneal collagen cross-linking has not been established in pediatric patients below the age of 14 years. No pediatric patients were enrolled in studies of corneal ectasia following refractive procedures since these procedures (LASIK, PRK) are rarely performed in the pediatric age group.

11. Other Relevant Regulatory Issues

505(b)(2) Application
This is a 505(b)(2) application that relied on published literature to support non-clinical information, and does not rely on another NDA.

OSI Inspection of Clinical Data
Inspection of the studies was conducted and no data integrity issues that would preclude reliance on the data were identified. Three sites were inspected based on relatively large enrollment at these sites, and all three were classified as NAI.

Combination Product
Avedro has submitted request for designation (RFD), which was reviewed by the Office of Combination Products (OCP). OCP determined that CDER would be the lead for this application under RFD070013. The riboflavin component acts as a photoenhancer, enhancing corneal collagen cross-linking in conjunction with the UVA light source.

- **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 does not contain any dextran.

- **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.

Orphan Designation
Avedro, Inc. received orphan-drug designation "for corneal cross-linking for the treatment of keratonus (sic)" on September 2, 2011, and "treatment of corneal ectasia following refractive surgery" on December 2, 2011.

Financial Disclosure
As provided under 21 CFR 54.2, there were no disclosed financial interests/arrangements nor evidence to suggest that the results of the study were impacted by any financial payments.

Regulatory Briefing
NDA 203324 was presented at a Regulatory Briefing Friday March 20, 2015. This meeting was advisory and not decisional.

SEALD
SEALD provided a consult on the Patient Questionnaire used in the study, and noted that the instrument had not been tested or validated before use in the study. The applicant subsequently clarified that all adverse event reporting was obtained by the investigators.

Administrative Split
Because the application includes two indications, and one indiciation was ready for approval in April 15, 2016, NDA 203324 was administratively split into two:
- NDA 203324 Original 1: treatment of progressive keratoconus
- NDA 203324 Original 2: treatment of corneal ectasia following refractive surgery

12. Labeling

Package Insert
The insert is written in PLR format and revised to include information on the indication of corneal ectasia following refractive surgery to the package insert approved April 15, 2016, (Original 1) for the progressive keratoconus indication. The revised Highlights of Prescribing Information states:

> PHOTREXA VISCOUS and PHOTREXA are photoenhancers indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus (1.1) and corneal ectasia following refractive surgery (1.2).

Carton and Container
The Division of Medication Errors Product Assessment reviewed the proposed carton labeling, bottle label and prescribing information. DMEPA provided recommendations that were incorporated as appropriate. Labels were approved April 15, 2016; no revisions are proposed for Original 2.

Trade Name
DMEPA concluded that the proposed proprietary names PHOTREXA VISCOUS and PHOTREXA are acceptable on 2/2/2016, as reflected in the approved labeling.

KXL Operator's Manual
The manual was reviewed by CDRH and the recommended revisions were incorporated in the approved Manual. The manual is now further revised with the new indication. At CDRH's recommendation, information on the pediatric population is added for consistency with Section 8 of the package insert.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

Not applicable, no issues were identified during the review that would rise to the level of a REMS.

- Other Postmarketing Requirements (PMR) and Commitments (PMC)

The applicant has agreed to a PMC (3106-1) for the following study:

> A registry to provide long term evaluation of the durability of the treatment effect of the procedure in at least 100 corneal crosslinking-treated subjects at 3 years with a pre-treatment diagnosis of post-refractive corneal ectasia. The timetable was submitted on July 13, 2016, and states that the study will be conducted according to the following schedule:
>
> | | |
> |---|---|
> | Final Protocol Submission: | 01/2017 |
> | Enroll First Subject | 10/2017 |
> | Study Completion: | 07/2023 |
> | Final Report Submission: | 12/2023 |

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/s/

RENATA ALBRECHT
07/15/2016