APPLICATION NUMBER:

203324Orig1s000

OTHER REVIEW(S)
## Application Information

<table>
<thead>
<tr>
<th>NDA # 203324/Original 1</th>
<th>NDA Supplement #: S-</th>
<th>Efficacy Supplement Type SE-</th>
</tr>
</thead>
</table>

### Proprietary Name: Photrexa Viscous, Photrexa
Established/Proper Name: riboflavin
Dosage Form: ophthalmic solution
Strengths: 0.146%
Device: KXL System
Applicant: Avedro, Inc.

Date of Receipt: October 16, 2015
PDUFA Goal Date: April 16, 2016
Action Goal Date (if different): April 15, 2016
RPM: Jacquelyn Smith
Proposed Indication(s): treatment of progressive keratoconus

## GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

   YES □  NO ☑

   *If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*
2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

<table>
<thead>
<tr>
<th>Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)</th>
<th>Information relied-upon (e.g., specific sections of the application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>published literature</td>
<td>Labeling Sections: Indications and Usage; Dosage and Administration; Contraindications; Drug Interactions; Overdosage; Description; Clinical Pharmacology; Non-clinical Toxicology</td>
</tr>
<tr>
<td>pharmacology and toxicology relied upon the published literature</td>
<td>Labeling Sections: Use in Specific Populations</td>
</tr>
</tbody>
</table>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature1. *See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*

**The applicant is not relying upon a reference product.**

*A majority of the toxicological data for riboflavin was generated following oral administration because of its use in food or as a dietary supplement. Topical riboflavin with concurrent exposure to UV-A light has been used for the treatment of keratoconus and corneal ectasia and both in vitro and in vivo nonclinical studies have been conducted using this methodology.*

**The applicant has conducted corneal crosslinking clinical trials utilizing the final formulations (s) of the to-be-marketed riboflavin.**

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4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the

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3For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.
approval of the proposed drug product (i.e., the application cannot be approved as labeled without the published literature)?

**YES** ☒  **NO** ☐

If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) listed drug product?

**YES** ☐  **NO** ☒

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

**YES** ☐  **NO** ☒
RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application rely on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES [ ] NO [x]  
If “NO,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

<table>
<thead>
<tr>
<th>Name of Listed Drug</th>
<th>NDA #</th>
<th>Did applicant specify reliance on the product? (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A [ ] YES [ ] NO [ ]
If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.
If “NO”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

   YES [ ] NO [ ]
   If “YES”, please list which drug(s).
   Name of drug(s) approved in a 505(b)(2) application:

   b) Approved by the DESI process?

   YES [ ] NO [ ]
   If “YES”, please list which drug(s).
   Name of drug(s) approved via the DESI process:

   c) Described in a final OTC drug monograph?

   YES [ ] NO [ ]
   If “YES”, please list which drug(s).
Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing? [ ] YES [ ] NO

If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness? [ ] YES [ ] NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

[ ] YES [ ] NO

If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
   YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
   N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(PHARMACEUTICAL ALTERNATIVES are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

   YES ☐ NO ☒
   If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
   YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
   N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in
Pharmaceutical alternative(s):

<table>
<thead>
<tr>
<th>PATENT CERTIFICATION/STATEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.</td>
</tr>
</tbody>
</table>

Listed drug/Patent number(s):

No patents listed  proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain?  (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). If Paragraph IV certification was submitted, proceed to question #15.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR
314.50(i)(1)(i)(A)(4) above). If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.


☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ONLY for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  

YES ☐ NO ☐

If “NO”, please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If “NO”, please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
04/27/2016
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 14, 2016

To: Jacquelyn Smith, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: PHOTREXA® VISCOUS (riboflavin 5’-phosphate in 20% dextran ophthalmic solution) 0.146% for topical ophthalmic use
PHOTREXA® (riboflavin 5’-phosphate ophthalmic solution) 0.146%
for topical ophthalmic use
NDA 203324

As requested in DTOP’s consult dated November 20, 2015, OPDP has reviewed
the draft PI and proposed carton and container labeling for Photrexa (riboflavin
5’-phosphate ophthalmic solution) and Photrexa Viscous (riboflavin 5’-phosphate
in 20% dextran ophthalmic solution).

OPDP reviewed the proposed substantially complete version of the PI titled,
“April 12 2016 CDER edits to proposed AVEDRO labeling edits
PNELSON_v2.docx” received via e-mail from Regulatory Health Project Manager
Jacquelyn Smith on April 13, 2016. OPDP’s comments are provided in the
attached clean version of the substantially complete labeling.

OPDP also received via e-mail from Regulatory Health Project Manager
Jacquelyn Smith on April 13, 2016 the following versions of the proposed carton
and container labeling titled “Avedro_Photrexa v4.pdf”, “AVEDRO_PHOTREXA
VISCOUS v11.pdf”, “Photrexa Foil Label Larger Size 70 mm X 50 mm_FDA
dits_April 12 2016.....pdf”, “Photrexa Tyvek Label Larger Size 63 mm X 40
mm_FDA edits_April 12 2016....pdf”, “Photrexa Viscous Foil Label Larger Size 70
mm X 50 mm_FDA Edits_April 12 2016..pdf”, “Photrexa Viscous Tyvek Label
Larger Size 63 mm X 40 mm_FDA edits_April 12 2016..pdf”, “RM-3136
Syringe_photrexa_Viscous_NDA_edits FDA....pdf” and “RM-3140
RevA_syringe_photrexa_NDA_FDA edits_April 12 2016......pdf”.

Reference ID: 3917433
OPDP notes that the graphic presented in conjunction with the tradename and on the top panel of the carton labeling makes representation of the product’s approved indication. Specifically, the graphic is representative of the eye, thereby rendering it promotional, which would require a PI to be included and possibly require the presentation of indication and risk information on the carton. Therefore, OPDP recommends deleting the graphic.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.
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/s/

MEENA RAMACHANDRA
04/14/2016
At CDER’s request, CDRH’s Office of Device Evaluation is providing a summary of recommendations concerning device issues pertaining to the above mentioned combination product/NDA. Avedro, Inc. (“Avedro”) has requested FDA approval of their drug/device combination product for the following indications: a) patients with progressive keratoconus and b) patients with post-refractive corneal ectasia. Because these are two distinct patient populations with different benefit-risk considerations, ODE’s recommendations are discussed separately for each of the indications. Please note this information and these recommendations were previously conveyed to CDER.

**Indication: Patients with 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. Specifically, 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 at the device settings proposed in the NDA submission in patients with progressive keratoconus.

CDRH/ODE recommends the submission be APPROVED for the keratoconus indication. In addition, we would like to clarify the following additional points:
MEMORANDUM RE: NDA 203324
April 13, 2016

1) 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.

2) CDRH/ODE recommends that the sponsor be required to collect postmarket clinical data on the indicated pediatric population with the approved device. This recommendation is based on the fact that: 1) the natural history of keratoconus in pediatric patients is different than adults; 2) there were very few pediatric patients included in the clinical study; and 3) the longer-term clinical outcomes of pediatric patients, even to 12 months post treatment, is poorly defined. CDRH will defer a final recommendation regarding the need for a postmarket clinical study for the keratoconus indication to CDER.

Indication: Patients with Post-Refractive Corneal Ectasia
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.

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 (K<sub>max</sub>) 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.
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/s/

JACQUELYN E SMITH
04/18/2016
**LABEL AND LABELING REVIEW REVIEW**
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public ***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>April 7, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Transplant and Ophthalmology Products (DTOP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 203324</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td><strong>Photrex</strong>a (riboflavin 5’-phosphate ophthalmic solution) 0.146%</td>
</tr>
<tr>
<td></td>
<td><strong>Photrex</strong>a <strong>Viscous</strong> (riboflavin 5’-phosphate in 20% dextran ophthalmic solution) 0.146%</td>
</tr>
<tr>
<td>Product Type:</td>
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<tr>
<td>Rx or OTC:</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>Avedro</td>
</tr>
<tr>
<td>Submission Date:</td>
<td>October 16, 2015</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2015-2361</td>
</tr>
<tr>
<td>DMEPA Primary Reviewer:</td>
<td>Michelle Rutledge, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Yelena Maslov, PharmD</td>
</tr>
</tbody>
</table>
1  REASON FOR REVIEW
This review evaluates the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, carton labeling, and insert labeling for Photrex (riboflavin 5’-phosphate ophthalmic solution) and Photrea Viscous (riboflavin 5’-phosphate in 20% dextran ophthalmic solution), NDA 203324, for areas of vulnerability and could lead to medication errors.

2  MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C – N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D – N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System <em>(FAERS)</em></td>
<td>E – N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F – N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
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</table>

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3  OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
DMEPA evaluated the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, and carton labeling and as stated in DMEPA’s review #2014-2135, we continue to maintain it is important to ensure that Photrex is well differentiated from Photrea Viscous due to the use of 20% dextran to add viscosity to Photrea Viscous, so that these products are not confused. Although this may be an important issue for this product, it may be even more important for generic products that will not contain a proprietary name to ensure that they are well-differentiated from each other. Thus, we continue to recommend that a statement such as “in 20% dextran” should appear on the Photrea Viscous labels and labeling in addition to other differentiation features. Additionally, labels and labeling can be improved to increase the prominence and readability of important information on the label and labeling to promote the safe use of the product.

4  CONCLUSION & RECOMMENDATIONS
DMEPA concludes that the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, carton labeling, and insert labeling can be improved to increase the readability and prominence of important information.
of important information on the labels and to reduce the potential for formulation selection errors.

We also have recommendations for the prescriber information labeling regarding symbols to assist with the correct use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on previous and current reviews, DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Prescribing Information
   I. Highlights
      a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

         i. Spell out all ≤ symbols appearing in the Dosage and Administration area of the Highlights section to instead read such as less than or equal to.

      b. Additionally, the Dosage and Administration area in the Highlights sections should be congruent with product use information outlined in the Section 2 Dosage and Administration of the Prescribing Information. For example, terms (b)(4) are used. Additionally, it is not stated which actions can be repeated as necessary in the highlights sections however this information appears in the Section 2 Dosage and Administration of the Prescribing Information.

4.2 RECOMMENDATIONS FOR AVEDRO

   A. Photrexa and Photrexa Viscous Syringe Labels

      i. There is no sufficient differentiation between the syringe labels for the two products. The only difference is the product name (Photrexa vs. Photrexa Viscous) and the statement “in 20% dextran”. Thus, we recommend you provide additional differentiation between the labels to help prevent wrong product selection errors through coloring, boxing, or other means.
ii. Revise the strength to ensure the total drug content appears on the syringe to be as follows:

\[
\text{4.38 mg/3 mL} \\
\text{1.46 mg/mL}
\]

iii. Remove (b)(4) as this is not customary on U.S. labels and labeling and creates clutter.

iv. If space permits, add the statement (b)(4)

B. Photrexa Viscous Syringe Label Only

i. Bold the “in 20% dextran” statement in the name of Photrexa Viscous.

C. Photrexa and Photrexa Viscous Tyvek® pouch and Foil Pouch Labeling

i. See A.i, Aii, and Aiii and revise Tyvek® pouch and foil pouch labeling accordingly.

ii. Your product has not been provided an exception, therefore, we request you add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

D. Photrexa Viscous Tyvek® Pouch and Foil Pouch Labeling Only

i. Bold the “in 20% dextran” statement in the name of Photrexa Viscous to help reinforce the difference between Photrexa and Photrexa Viscous.

E. Photrexa and Photrexa Viscous Carton Labeling

i. Add the product barcode as required per 21 CFR 201.25(b)(1)(ii).

ii. Increase the font size of the established name to at least ½ the size of the proprietary name as required per 21 CFR 201.10(g)(2).

iii. Decrease the size of the company name and logo to help ensure that important product information such as proprietary name, established name, and strength statements are the most prominent information on the labeling.

iv. Reduce the prominence of the “eye” image to help ensure important product information is the most prominent information on the labeling.

v. The green or orange waves immediately under the eye image graphic can be misinterpreted as the place where the product should be administered.
Therefore, decrease prominence and move away for the eye image graphic or delete all together.

vi. The proprietary name, established name, and strength should appear as follows to ensure the total drug content appears on the carton labeling:

\[
\text{Photrea Viscous} \\
\text{riboflavin 5’-phosphate in 20\% dextran ophthalmic solution} \\
4.38 \text{ mg/3 mL} \\
(1.46 \text{ mg/mL}) \\
or \\
\text{Photrea} \\
\text{riboflavin 5’-phosphate ophthalmic solution} \\
4.38 \text{ mg/3 mL} \\
(1.46 \text{ mg/mL})
\]

vii. Bold the statements to increase the prominence of the route of administration and how the product should be used.

viii. Remove the following confusing statement in box from the right corner “for Administration”. Additionally, remove the duplicate proprietary name and revise the net quantity statement.

ix. Remove as this is not customary on U.S. labels and labeling and creates clutter.

F. Photrea Viscous Carton Labeling Only

i. Bold the “in 20\% dextran” statement in the name of Photrea Viscous to help reinforce the difference between Photrea and Photrea Viscous.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 2 presents relevant product information for Photrexa and Photrexa Viscous that Avedro submitted on October 16, 2015.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Photrexa and Photrexa Viscous</th>
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<tr>
<td><strong>Initial Approval Date</strong></td>
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<td><strong>Active Ingredient</strong></td>
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<td><strong>Indication</strong></td>
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<td><strong>Route of Administration</strong></td>
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<td><strong>Dosage Form</strong></td>
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<td><strong>Strength</strong></td>
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<td><strong>Container Closure</strong></td>
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APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods
On February 18, 2016, we searched the L:drive using the terms, Photrex and Riboflavin, to identify reviews previously performed by DMEPA.

B.2 Results
Our search identified 2 previous label and labeling reviews OSE RCM# 2013-2338 and 2014-2135, and we confirmed that some of our previous recommendations were not implemented.

Information to include in the citation for previous reviews:


APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Photrex and Photrex Viscous labels and labeling submitted by Avedro on October 16, 2015.

- Syringe Container label
- Tyvek® Pouch Labeling
- Foil Pouch Labeling
- Carton labeling
- Prescribing Information (not listed)
- Operator’s Manual (not listed)

G.2 Label and Labeling Images

Syringe Label for Photrex

7 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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

/s/

MICHELLE K RUTLEDGE
04/07/2016

YELENA L MASLOV
04/08/2016
CDRH
OFFICE OF DEVICE EVALUATION
CLINICAL REVIEW

From: Maryam Mokhtarzadeh, MD  DSDB/DOED/ODE
To: Bradley Cunningham, DSDB Branch Chief
Damia Jackson, Project Manager DOED
Dexiu Shi, Scientific Reviewer
Bruce Drum, Scientific Reviewer
Malvina Eydelman, DOED Division Director

Re: NDA 203324: Photrex A, Photrex Viscous, KXL Device
riboflavin ophthalmic solution (20% dextran), riboflavin ophthalmic solution (0% dextran), UV-A irradiation
Avedro, Inc.

Prior Clinical Reviews:
Initial Clinical Review 2/7/14
Response to Complete Response Letter Review 3/24/15
CDRH Off-the -Clock review of Post-Hoc Analyses 9/30/2015

Proposed Indications for Use:
- For the treatment of progressive keratoconus
- For the treatment of corneal ectasia following refractive surgery

Date: January 19, 2016 (minor revisions completed 2/1/2016)

Recommendation: 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” (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.

Reference ID: 3888790
Introduction:
The October 2015 resubmission did not include new clinical data. However, the literature review provided by the sponsor in September 2015 (off-the-clock) has not yet received official review in any of the prior CDRH clinical reviews listed above and therefore will be covered in the current clinical consult.

This consult will also include a final recommendation with potential questions to be addressed in the postapproval study. However, recommendations for labeling (KXL Operator’s Manual, riboflavin solution package insert, and patient labeling) will be provided in a separate addendum to this review – this will be done to allow a complete CDRH labeling review including recommendations across review disciplines.

Summary of Review Course
I provided an initial review on February 7, 2014 for this file prior to a Complete Response action taken by CDER. A meeting was held on August 6, 2014 with the Applicant to discuss the upcoming complete response submission that the Applicant intended to submit (prior to official review). These responses were received by the agency September 29, 2014 and preparations for an advisory committee began shortly thereafter. The joint advisory committee met on February 24, 2015. A second complete response letter was subsequently sent to the sponsor followed by months of interaction with the sponsor and off-the-clock review. The sponsor responded to the second complete response letter on October 15, 2015 leading to the current review memo.

As the CDRH clinical reviewer on this NDA, I am providing a consulting review on device related clinical concerns. The CDER clinical reviewer is the lead clinical reviewer for this combination product. In areas of device/drug overlap, I have only made requests for information when it was clear that critical data and analyses (from a device perspective) would not be considered without my involvement (i.e., evaluation of prespecified analyses from the protocol, refractive stability, outstanding concerns raised by the advisory committee, and the impact which differences between the device studied and the one to be marketed may have had on clinical study results.)

Evaluation of this file has been complicated by many factors outlined in my prior reviews.

Preclinical Review:
Reviewer Comment: I note that the device to be marketed has been modified in the current submission compared to the device reviewed in prior submissions. The modifications impact among other things. The intent of the modifications appears to have been to match the device to be marketed with the device that was studied. Therefore, I defer to other members of the CDRH review team (Dr. Dexiu Shi and Dr. Bruce Drum) to address the preclinical assessments included in the current submission to determine the equivalence the device to be marketed and the one used in the clinical study. I am happy to provide clinical correlation or support upon request. I note that the modifications proposed to the device resolve some clinical concerns previously documented regarding the device (i.e., the will now match the one studied). Other differences have undergone additional interaction and preclinical review since the prior clinical review pertaining to the device description. I defer to the preclinical review regarding the equivalence of the devices in light of the new modifications proposed in the current submission.
Literature Review:
“As requested by CDRH during the 9 September 2015 teleconference, Avedro conducted a literature review to identify published data regarding the use of the Avedro KXL System for corneal cross-linking for the treatment of keratoconus and corneal ectasia following refractive surgery.”

Reviewer Comment: Note that at the teleconference referenced in the submission, Avedro informed the agency that the device cited in the literature was almost identical to the device proposed for marketing with regard to the patient and physician interface (although there may be some software differences).

“The search is current over the period of January 1, 2010 through September 10, 2015. Marc D. Friedman, Ph.D., conducted the search and evaluation of the resultant literature triaging the abstracts for inclusion and collating their findings for inclusion.”

“Only papers relating to epithelium off procedures using the KXL System were included. Fifteen refereed papers were found using the PubMed database. In these papers, corneal cross-linking using the KXL System was performed on 463 eyes of 415 patients.”

“Within this cohort, 36 eyes of 36 patients (Shetty 2015) received 3 mW/cm2 for 30 minutes; 5.4 J/cm2. All other patients received various protocols utilizing accelerated cross-linking with irradiances ranging from 9 mW/cm2 to 30 mW/cm2 and doses ranging from 5.4 J/cm2 to 7.2 J/cm2.”

Reviewer Comment: While no clinical data has been presented to the agency derived from use of the exact device to be marketed, the literature review above cites at least 36 eyes of 36 patients with progressive keratoconus treated with a device with a similar (if not identical) patient and physician interface compared to the one to be marketed in a treatment similar to the one proposed in the device to be marketed. With wider treatment parameters and indications, up to 463 eyes of 415 patients have been treated as documented above. Therefore, this literature review reduces some of the uncertainty surrounding the aspects of the device to be marketed that have not been previously supported with direct clinical evidence.

PostApproval Study Recommendations:
Many areas of uncertainty were identified in prior CDRH clinical reviews and the following would merit collection of additional data in a postapproval study focused on the population specified in the indications for use (adult progressive keratoconus):

- Real world safety and effectiveness outcomes collected with the actual device to be marketed which has never before been used in humans. The need is further underscored by the paucity of observed data in the clinical trial for the experimental arm at 12 months due to a >10% loss to followup rate.

- Longterm safety and effectiveness outcomes (5 years) in this orphan product including appropriate methodology for data collection to reduce uncertainty with regard to real world data collected in the following areas:
  - Endothelial cell counts – particularly with respect to the potential for large losses
  - Kmax – including stability of the outcome, clinically significant improvement and treatment failures; Kmax values for the all eyes (treated and untreated fellow eyes) should be measured at all study visits (at least at baseline and months 1, 3, 6, 12, 24, 36, 48, 60) to allow analysis of the significance and stability of changes in mean Kmax value

Reference ID: 3888790
Disease Progression – this would require collection of a panel of data regarding historical data (changes in Kmax, corneal topography, etc.) for comparison to the same evaluations during the study to allow intra-subject comparison of disease progression
  - Corneal topographic assessments of disease progression by a masked reader (to evaluate the complete topographic image/output rather than just the single Kmax output parameter)

Secondary surgical interventions (including, but not limited to partial or full-thickness keratoplasty)

Corneal and refractive stability

Rate and significance of adverse events
  - Including, but not limited to loss of 2 or more lines of Best Corrected Visual Acuity (BCVA), corneal infiltrate, corneal edema, corneal opacity, and epithelial defects (recurrent and/or poor wound healing)
  - Corneal haze is reported in a large number of eyes in the pivotal trial results. An analysis of corneal haze captured at all visits including the grading, severity and visual acuity resulting (UCVA and BSCVA) is warranted as well as an assessment of the impact of corneal haze on visual function. Contrast sensitivity testing¹ and patient reported outcome measures could be more sensitive assessments of visual impact of haze but were not evaluated in the pivotal trials.
  - Given potential risks of UV in light of lack of post UV exposure pachymetry collection during the study which may have exposed corneas below the safety threshold to UV light for an unknown duration – recommend collection of relevant data, examples include: findings in potentially vulnerable ocular structures: crystalline lens, retina, corneal keratocytes, endothelium, limbal stem cells and corneal wound healing

Subgroup analyses with respect to potential differences in outcome related to age (given differences in disease progression), gender (ex. given potential hormonal influences on the cornea and gender effects noted in the pivotal trials), and disease severity (given potential differences in response) and possibly even topographic features (given advisory committee discussion regarding potential impact of cone location on outcomes or need for off-label use vs. modified instructions for use)

Minimal pachymetry at the initiation of UV exposure and at the completion of the UV exposure to allow capture of subjects who may be at risk for treatment below a safety threshold and to determine any correlation with outcomes. Furthermore, it is unclear whether effectiveness can be affected by corneal thickness <400 Microns at the time of UV exposure (could be due to off-label use, protocol deviations, or simply a function of loss of “swelling” during the 30 min treatment time).

We recommend more rigorous IOP methodology for subjects with high astigmatism and to take concurrent pachymetry measurements for more interpretable results. One question we would like to answer in a postapproval study would be: “Does UV Xlinking cause under-estimation of IOP measurements?”

Data from untreated fellow eyes should include comprehensive data collection to allow a potential control – given the problems encountered in the current study with retaining an untreated control arm this is an important consideration. For the same reason, I recommend that study-eyes may serve as an additional control and recommend that historical data/measurements be collected to allow such a comparison.

- Stratification of data according to whether or not drug is received to swell the cornea in order to evaluate real world safety and effectiveness outcomes in swelled corneas. We note there were a number of protocol deviations in the pivotal trial related to the use of “artificial tears, BSS, or water” to swell the cornea which introduces additional uncertainty – such occurrences should be minimized in the postapproval study.

- Collection of data regarding eye movements during the procedure for correlation with outcomes in order to determine whether additional risk mitigation measures may be warranted. (e.g. A simple video eyetracker could be used to capture variations across patients as well as the average distribution)

- Patient reported outcomes, particularly with respect to ocular pain, dry eye, quality of vision, and visual disturbances (glare, haloes, etc.) While validated instruments may not be available to assess all relevant PRO concerns, every effort should be made to collect interpretable data where possible.

- Data collection on pulsed vs. continuous UV treatment is recommended in light of potential for pausing or restarting treatment and growing literature suggesting that pulsed treatment is more appropriate (despite the fact that the study was designed for continuous UV treatment).

- Additional longterm questions could include:
  - Effect on outcomes after future ocular surgery (cataract surgery or corneal transplant, for example)?
  - Effect on corneal permeability and ability to use topical medication to treat various ophthalmic diseases?

Given the definitive public health need, I also recommend that strong efforts be made to work towards approval in the pediatric progressive keratoconus population via a Phase IV study aimed at increasing the dataset for pediatrics for both short and long-term outcomes. Such data collection will also serve to better develop specific instructions for use and labeling, taking into consideration differences between the adult and pediatric populations (ex. ability to cooperate with the diagnostic testing, treatment procedure, postoperative examinations, self-care of corneal wound, as well as neuro-cognitive, behavioral, and other considerations which may create additional differences between adult and pediatric populations).

Reviewer comments:

1. I am happy to provide additional clinical knowledge in the planning of a postapproval study upon request. I recognize that as the device clinical reviewer I am not the lead clinical reviewer on this file. However, I note that CDRH input would be of great value in light of our regulatory experience with refractive and corneal re-shaping treatments and particularly with regard to device specific issues and methodology used for diagnostic devices in the postapproval study.

2. CDRH has repeatedly recommended either a panel homework assignment, Network of Experts call or some form of communication with experts in the field of cornea in order to determine critical study design issues for any future crosslinking trials.
CONCLUSIONS: Review Synopsis and Rationale for Recommendation

General Overview
In NDA 203324 Avedro proposed two indications for use for their combination product (riboflavin ophthalmic solution and KXL System): to treat progressive keratoconus and to treat postrefractive corneal ectasia. To support these indications, the sponsor provided data from three clinical studies (two studies are applicable to each indication). The protocol and SAP defined success criteria were not met for the primary effectiveness endpoint at 3 months for either indication in any of the three studies (i.e., either a statistically significant difference was not found or a clinically meaningful difference target was not met).

It would not be unreasonable to require a new study (or studies) for both indication based on the significant issues identified below and the failure to meet the prespecified success criteria for both indications. In fact, it would probably be the most scientifically sound decision.

However, due to the fact that the lack of approval of crosslinking in the US is a public health concern and a current unmet medical need for patients with keratoconus, despite a large body of global literature supporting the safety and effectiveness of the procedure in patients with progressive keratoconus (see numerous literature reviews provided over the course of this submission – the CDRH literature review in the clinical review from 3/24/2015, the sponsor’s literature, and the CDER presentation at the regulatory briefing meeting in March 2015), every effort was made to salvage data from these very flawed studied.

Previously identified significant issues on this file include the following:

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). Failure to meet prespecified (3 month) success criteria for either indication.
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 data which could be interpreted by PRO experts has not been collected.
7. Safety and effectiveness concerns in the postrefractive 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 longterm followup 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 (corneal stability, etc.) which means methodology and study design may not support such retrospective analyses.

While, *The protocol and SAP defined success criteria were not met for the primary effectiveness endpoint at 3 months for either indication in any of the three studies (i.e., either a statistically significant difference was not found or a clinically meaningful difference target was not met)*, note that any discussion of success for either indication at 3 months would not be sufficient to support approval anyway because both the agency and the sponsor agreed that a three month endpoint was inappropriate due to the fact that, according to the sponsor, “the corneal stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize (Wittig-Silva et al, 2008; Wollensak and Iomdina, 2009; Caporossi et al, 2010). This is consistent with the FDA’s comments, whereby the Agency strongly recommended that the Sponsor evaluate later time points.” These studies included a three month “controlled phase”, after which the control eyes were allowed to receive crosslinking treatment – and the vast majority chose to do so. FDA had previously informed the sponsor that a twelve month endpoint (rather than a three month endpoint) would be recommended. However, after purchasing the studies and data, a new sponsor revised the timing of the endpoint after the final subject had completed the final study visit, interim analysis had been performed, and after multiple publications had been submitted on a subset of study results. In order to modify the time of the endpoint assessment from 3 months post-crosslinking to 12 months post-crosslinking, it was proposed that last observation carried forward (LOCF) be used for effectiveness data to compensate for the disappearance of the control arm. In order to accept the LOCF method, particularly to compensate for the loss of almost every subject in the control arm, certain assumptions must be made. In order to accept the LOCF method, major assumptions must be made not only about the natural course of disease progression, but also related to performance of the diagnostic device measuring the primary endpoint, Kmax: (1) on average, Kmax (a poor, but often used diagnostic measure of corneal steepening) remains stable or does not improve and (2) the variability of Kmax will not increase over time.
**PROGRESSIVE KERATOCONUS – Rationale for Recommendation**

Progressive keratoconus is a naturally occurring disease in which the anterior transparent surface of the eye (the cornea) protrudes and thins, creating a cone-like shape. Diagnosis of the disease at an earlier age often correlates with a greater risk of disease progression. Current treatment options include glasses, contact lenses, corneal ring segments, and partial or full-thickness corneal transplantation (should it become necessary – as it does for approximately 10-20% of affected eyes)\(^2\,3\).

In the progressive keratoconus population studied, historical data documenting disease progression were collected at the time of enrollment which could be used to support the first assumption necessary to support LOCF. Despite the fact that precision and accuracy of Kmax (i.e., diagnostic device performance) is impacted by the presence of disease compared to a normal cornea, the second assumption may also be supported by the historical data obtained at the time of enrollment since the limits of disease severity were known in the population and therefore some degree of homogeneity in the population was established. With use of LOCF, success criteria were met at 12 months post-crosslinking to support effectiveness. Note the LOCF is still not an ideal approach, and accepting weak assumptions does not entirely replace the need for actual longterm data – it just may shift the collection requirement from the preapproval to the postapproval realm for the keratoconus population. With use of LOCF to impute ≥98.1% of the control data (101/103 eyes) and ≥12.7% of the CXL data (13/102 eyes) success criteria were met at 12 months post-crosslinking to support effectiveness.

A safety analysis of crosslinking in progressive keratoconus included 293 eyes in the pivotal studies. Based on the totality of the evidence provided and the fact that the evidence in the clinical studies is not inconsistent with the wide and growing body of global literature reporting the safety and efficacy of corneal collagen crosslinking to treat progressive keratoconus in adults (largely using the same device studied in the pivotal trial), we believe that there is adequate evidence across all sources to favorably

\(^2\) [https://nei.nih.gov/health/cornealdisease](https://nei.nih.gov/health/cornealdisease) [accessed 1/18/2016]: “In most cases, the cornea will stabilize after a few years without ever causing severe vision problems. But in about 10 to 20 percent of people with keratoconus, the cornea will eventually become too scarred or will not tolerate a contact lens. If either of these problems occur, a corneal transplant may be needed. This operation is successful in more than 90 percent of those with advanced keratoconus. Several studies have also reported that 80 percent or more of these patients have 20/40 vision or better after the operation.”

define the risk benefit profile in this population. I concur with the advisory committee (67% voted in favor of approval for progressive keratoconus; 10 yes, 4 no, 1 abstention) to recommend guarded approval for this indication with a strong Phase IV study to support the numerous outstanding concerns and areas of uncertainty within the current clinical studies documented in the prior clinical reviews and panel transcript. This recommendation is pending resolution of labeling and development of an adequate Phase IV study as well as (a) modification to the indication for use (b) and separate consideration of pediatric progressive keratoconus.

(a) With regard to the indications, we recommend modification of the benefit attributed to crosslinking based on the pivotal trials. While the indications are currently proposed for “treatment” of disease, this term is not an accurate reflection of what was actually studied in these 12 month studies with a 3 month controlled phase. The studies captured a difference in the change in Kmax between two treatment groups as the primary efficacy endpoint. Stability was not proved and neither was disease progression proved to be halted or slowed compared to the patients’ pretreatment pattern of Kmax progression. Note that results for other topographic outputs aside from Kmax (but including other keratometry results) were evaluated but “Differences between treatments for the change from baseline were not clinically relevant.”

While the Kmax endpoint alone may support an indication to crosslink the cornea (since such a change is scientifically and clinically supported), it seems an overstatement to use the difference in a change in Kmax between two arms as evidence of “treatment.” The disease processes studied have visual as well as topographic disease features that are not encompassed by Kmax alone. As stated by a member of the advisory committee member: “A lowering of Kmax by a diopter does not mean you stabilize the disease. It means you’ve lowered Kmax.” (see panel transcript) Given that the studies only captured a difference in the change in Kmax and did not demonstrate stability or slowed disease progression, we believe 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.” Ideally, the specific language in the indication would specify Kmax, but I am unclear whether that term can be used.

4 See CDRH literature review provided with CDRH clinical review on this file from 3/24/2015. Also noted is the keratoconus literature review presented by CDER in the March 2015 CDER regulatory briefing presentation.

5 “Several keratometry measures in addition to Kmax were made using the Pentacam.... For each measurement, the treatment groups were comparable at baseline. Differences between treatments for the change from baseline were not clinically relevant.” These included: Corneal front K1 (CFK1), Corneal front K2 (CFK2), Corneal front Km (CFKM), Corneal front axis flat (CF axis flat), Corneal front axis steep (CF axis steep), Index of Surface Variance (ISV), Index of Vertical Asymmetry (IVA), Keratoconus Index (KI), Center Keratoconus Index (CKI), Index of Height Asymmetry (IHA), Index of Height Decentration (IHD), and Smallest radius (steeper, RMin).

6 As an example in regulatory precedent, therapies targeted for glaucoma are often designated to lower intraocular pressure based on the actual endpoint studied in a pivotal trial, rather than indicated as treatment for glaucoma which is a complex disease requiring longterm followup to support such a claim.
in an IFU for regulatory reasons. I defer to my branch management regarding the final IFU language due to such cross-device regulatory considerations given the branch’s oversight of corneal diagnostic devices.

(b) Regarding progressive keratoconus in the pediatric population, we are limited by a paucity of data in the current studies upon which to base an approval. The studies were not designed to support a pediatric approval (lack of prespecified stratification of enrollment, analyses, etc.) despite known differences in disease progression that are age-related. The number of pediatric study eyes in UVX-001 (2 study eyes in the CXL arm and 4 study eyes in the control arm) is too small to support meaningful analyses. Therefore, there is only one study included in this NDA to support a pediatric indication (UVX-002), also with very small numbers (17 randomized to the CXL arm and 10 control eyes). Based on their regulatory experience with NDAs, I defer to CDER whether a pediatric indication can be supported with only one flawed trial given that this is an orphan product, despite the general NDA regulatory requirement of two adequate and well-controlled studies to demonstrate substantial evidence of safety and effectiveness.

In support of the pediatric indication, I note that the treatment effect captured for pediatric subjects in UVX-002 is large. Also of note, the safety population is larger than the effectiveness population given the potential inclusion of control eyes after crossover and treatment of fellow eyes in the study (but still too small for a meaningful safety analysis). Additional support for a pediatric indication in subjects with progressive keratoconus could be found in the corneal collagen crosslinking literature (while the reports are not specific to this combination product).

Given that there is a known difference in the disease process in relation to age, in the absence of specific data to guide a cutoff for analyses of data, it seems reasonable to use agency cutoffs which hold additional relevance based on behavioral, neurocognitive, and social differences that could be relevant. In fact, such differences are known to be relevant to other ophthalmic products regulated by the agency, such as contact lenses, in which compliance and self-care are known to be significant issues when relying on pediatric subjects to care appropriately for damaged corneas. In fact, concern regarding potential for corneal infections ultimately leading to corneal blindness in pediatric subjects due to noncompliance or poor self-care would be a potential concern post-crosslinking when subjects are discharged home with a large iatrogenic corneal abrasion with potential for infection or wound-healing problems.

Additionally, despite inclusion of pediatric subjects, the studies were not designed to support a pediatric approval (lack of prespecified stratification of enrollment, analyses, etc.) despite known differences in disease progression that are age-related. It is important to consider that we do not know the duration of the treatment effect for pediatric subjects (i.e., retreatments or even corneal transplant may be needed) and the benefit may not be the same as in adults due to the difference in disease progression. The uncertainty surrounding pediatric safety and effectiveness outcomes includes, but is not limited to the fact that the device proposed for marketing has never been used in humans and that neither pediatric-specific protocols nor
instructions for use have been studied. With regard to safety, I caution that a pediatric subject enrolled in this study (age 20) was reported to have committed two suicide attempts. In the absence of an evaluation of patient-reported outcome measures, it is very difficult to evaluate potentially significant information regarding the patient experience, quality of life, and severity of visual disturbances experienced. One 19 year old subject developed a corneal ulcer which was considered a serious ocular adverse event. Furthermore, endothelial cell data in pediatric subjects was inconclusive and the possibility of large losses could not be ruled out.

The advisory committee clearly recognized that pediatric corneas are different compared to adult corneas: “There is no question that pediatric corneas are different. They have different biomechanics, and they have different disease progression.”7

While I cannot support approval at this time due to the limited data in pediatric subjects, I recommend that strong efforts be made to work towards approval in the pediatric progressive keratoconus population in a Phase IV study aimed at increasing the dataset for pediatrics for both short and longterm outcomes. I believe that within the orphan populations designated, pediatric progressive keratoconus may benefit the most from this combination product once there is adequate evidence within a pediatric population to enable a discussion of risks and benefits relevant to this vulnerable sub-population and to support appropriate labeling and instructions for use specific to this population. There is a definite public health need to accomplish this goal.

**Adult Postrefractive Corneal Ectasia: Rationale for Recommendation**

Postrefractive corneal ectasia is a loss of corneal integrity leading to corneal warpage and instability that sometimes resembles keratoconus on clinical exam, while the etiology and distribution of areas of corneal weakness are distinct depending on the refractive history. Current treatment options include glasses, contact lenses, corneal ring segments, and partial or full-thickness corneal transplantation (should it become necessary – as it does for approximately 8% of affected eyes according to one source)8.


8 Woodward MA, Randleman JB, Russell B, Lynn MJ, Ward MA, Stulting RD. Visual rehabilitation and outcomes for ectasia after corneal refractive surgery. J Cataract Refract Surg. 2008 Mar;34(3):383-8. “Initial publications report that 30% of eyes developing ectasia required corneal transplantation for visual rehabilitation, and some authors predict that corneal transplantation may be inevitable in most, if not all, cases of postoperative ectasia. In 2003, however, we reported a small case series in which only 10% of eyes required corneal transplantation and our clinical impression has been that most of these patients have been successfully visually rehabilitated without corneal transplantation. Here, we report our experience with visual rehabilitation in a large population of patients with ectasia after corneal refractive surgery.” In 74 eyes of 45 patients with mean follow-up was 42 months ±40 (SD) (range 1 to 180 months): “The final visual correction was achieved with RGP lenses in 57 eyes (76%), with 6 eyes (8%) having PKP...”
Only 40% of the advisory committee voted for approval for this indication (6 voted yes, 4 voted no, 4 abstained, 1 no vote) indicating that this population (and the supportive data provided) introduce a potentially different risk benefit consideration than was reflected in the vote for progressive keratoconus.

The study design, methodology and study conduct were severely flawed for this indication:

- Lack of criteria to define “postrefractive corneal ectasia” or disease progression- challenging the proposed IFU of “treatment of postrefractive corneal ectasia”;
- Absence of appropriate enrollment criteria resulting in study cohort with greatly diverse ocular history – leading to unfeasible post-hoc stratification to identify a subgroup with a favorable benefit/risk profile;
- Crossover of the control arm – making it impossible to evaluate safety beyond 3 months, despite the agreement between the sponsor and the Agency that at 3 month post-treatment corneal healing and remodeling is incomplete
- Did not meet prespecified success criterion at 3 months
- LOCF cannot be supported because there is insufficient evidence that Kmax remains stable or does not improve over one year during natural progression of disease for the heterogeneous postrefractive corneal ectasia population enrolled. LOCF would be required to impute ≥97.7% of the control data (86/88 eyes) and ≥16.5% of the CXL data (15/91 eyes) at 12 months post-crosslinking to support effectiveness for the postrefractive corneal ectasia population
- Insufficient support is available in the global literature determine efficacy for the treatment of post-refractive corneal ectasia. (see Systematic Literature Review on Corneal Collagen Crosslinking (CXL) Procedures For the Treatment of Keratoconus and Secondary Ectasia” written by Youlin Qi and included in the CDRH Clinical Review of NDA CR letter response submitted 3/24/2015).
First, the study design\textsuperscript{9}, methodology\textsuperscript{10} and study conduct\textsuperscript{11} were flawed to such an extreme\textsuperscript{12} that they could not support an indication for postrefractive corneal ectasia under any circumstances. This is a population defined to have experienced harm from a device and therefore they deserve an appropriate consideration of the safety and effectiveness data in light of the fact that their disease has been created

\textsuperscript{9} (1) Lack of criteria to define “postrefractive corneal ectasia” nor to define disease progression in that population, in stark contrast to the robust level of detail provided for keratoconus, (2) 3 month prespecified endpoint and 3 month controlled “phase” which severely crippled a safety determination due to crossover of the control arm which could not be compensated for by use of Last Observation Carried Forward (LOCF) as was done for effectiveness, (3) lack of data with the device to be proposed for marketing and instead, use of the study device with an illumination diameter setting on 17-20 eyes in either disease population which was determined by the advisory committee to be non-representative of the device to be marketed and therefore eyes treated with that larger diameter were recommended to be removed from the study datasets, (4) almost 100% imputation of data in order to enable evaluation of endpoints at the 12 month timepoint due to crossover of the control arm – and imputation specifically in the form of LOCF

\textsuperscript{10} Despite being the primary effectiveness endpoint, Kmax readings were taken without appropriate methodology to ensure good quality data – for example, nonphysiologic values and changes between visits are present in the dataset and multiple readings were not taken despite published data indicating that the error of this measurement in diseased corneas is significantly larger in diseased corneas compared to normal. Specifically, repeatability and reproducibility of a single Kmax reading were recently reported to be 0.71 and 0.83 respectively in keratoconic eyes compared to literature indicating that “a change of >1 D in the Kmax parameter [is routinely used in crosslinking trials because it]... is [thought to be] 3 times the standard deviation of measurement error” Hashemi K, Guber I, Bergin C, Majo F. Reduced precision of the Pentacam HR in eyes with mild to moderate keratoconus. Ophthalmology. 2015 Jan;122(1):211-2. Endothelial cell count data were particularly noisy as well for the same reasons as described above.

\textsuperscript{11} (1) Bias introduced by change in statistical analysis plan after interim analysis and publication of study data, (2) Large number of protocol deviations, (3) Study termination prior to completion of planned enrollment (4) enrollment of subjects in the postrefractive corneal ectasia population included some who had a recorded diagnosis of keratoconus or other abnormality prior to the refractive surgery history. Subjects with abnormal corneas prior to refractive surgery would not be poolable with those subjects who had an iatrogenic disease. Due to the absence of appropriate enrollment criteria specifying the disease to be studied with supportive historical data collected at the time of enrollment, the population enrolled is heterogeneous and data cannot be salvaged post-hoc as we cannot go back and collect the relevant history now to stratify data appropriately. This presumed (and in some cases proven) heterogeneity applies to numerous additional aspects of the ocular history including the number, type and dates of prior refractive interventions in addition to exclusion for prior crosslinking treatment to ensure that subjects enrolled were undergoing a primary exposure to crosslinking rather than a repeat treatment. In contrast, enrollment criteria for keratoconus precluded enrollment of such subjects.

\textsuperscript{12} Quotes from the advisory committee meeting transcript: “I think we need better data”, “this particular study is abysmal”, “I think these patients deserve evidence based interventions, and the study was so methodologically flawed that I could not come to the conclusion that it represented substantial evidence of efficacy.”
iatrogenically. Physicians are advised to “first do no harm” – this is a population we have already failed once and we must have great confidence to recommend approval of a second intervention.

Second, the safety population for postrefractive corneal ectasia is inadequate. The study was designed without a safety hypothesis. Safety assessment was performed using descriptive statistics on 219 total eyes with “postrefractive corneal ectasia”. Note that this does not provide the minimum 300 eyes which would be necessary to support a conclusion that adverse events expected to occur in 1% of patients would be captured.

The limitations in the safety data present a strong concern for the postrefractive corneal ectasia indication given that these subjects have already been harmed and deserve a clear and accurate documentation of risks should they elect to undergo another procedure. Randomized safety data is critical as it is difficult otherwise to determine which adverse events may be due to the disease process and which to the treatment (i.e., when adverse event rates in the treated group are higher than that expected in the natural course of the disease). From baseline to month three, 90.1% of CXL subjects reported any adverse events compared to 43.2% of control subjects. Adverse events are extremely common in crosslinking, particularly given that the intervention involves creation of a very large wound on the surface of an already diseased cornea which may have difficulty healing. Therefore it is unsurprising that the most common adverse events for either indication at greater than or equal to 10% are corneal epithelial defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. The most common adverse events included: corneal haze (68.1% in CXL subjects, 8.0% for controls subjects) corneal epithelial defect (26.4% in CXL subjects, 3.4% for control subjects), eye pain (26.4% in CXL subjects and 0% in control subjects), dry eye (14.3% in the CXL eyes and 4.5% in control eyes) and reduced visual acuity (11% in CXL eyes and 1.1 % in control eyes – note that the percentage across all CXL eyes in the safety cohort including fellow eyes and crossover control eyes outside the controlled phase of the study was 16.4%) . One subject experienced a serious ocular adverse event involving epithelial ingrowth beneath the LASIK flap which required lifting the flap and removing the ingrowth. Three postrefractive corneal ectasia eyes that received cross-linking (3/72 = 4%) lost significant vision at month 12 for unknown reasons. Persistent adverse events at 12 months included 2 corneal scars in the postrefractive corneal ectasia group. Large losses of endothelial cells were captured, but lack of SOPs for data collection and protocol deviations resulted in great uncertainty of the true risk. Given the iatrogenic nature of the condition, it is imperative to assure adverse event rates in the treated group to be lower than that expected in the natural course of the disease. In light of the great diversity within the 219 eye safety cohort, it is difficult to determine which adverse events may be due to the disease process and which to the treatment.

Finally, corneal haze is a poorly defined adverse event which occurred in a large number of crosslinked eyes in the study. The nature of such corneal opacities as well as the visual consequences are poorly understood based on the current dataset. In addition, large losses of endothelial cells were captured in the study, but poor methodology and noise in the data lead to great uncertainty with regard to the true risk (not to mention the fact that approximately a third of patients missed endothelial cell count assessments due to protocol deviations.)
As discussed at the advisory committee meeting, the vulnerability of the postrefractive corneal ectasia population must be considered in light of the potential safety concerns and uncertainty. While multiple speakers pleaded with the agency to approve for keratoconus, and often specifically for pediatrics, the postrefractive corneal ectasia community provided less support. Note the following concerns raised during the open public hearing per the panel transcript13:

- “Ectasia patients are vulnerable since they are attempting to cope with a sight-threatening disease. It would be devastating for these patients to be given hope of a cure through false advertising and then abandoned by the physician when the reality sets in that CXL on post-LASIK eyes is less effective than on keratoconus eyes.”

- “The current application states that progression needs to be shown for keratoconus, but it makes no mention of progression for ectasia. This oversight must be corrected or ectasia patients will undergo unnecessary CXL procedures with many risks.”

- “the emotional impact of surgically-induced corneal ectasia is often quite severe. Many of my patients have expressed thoughts of suicide. .. the FDA must ensure that crosslinking will not be misrepresented to these patients as a treatment that will undo the damage.”

- “the evidence indicates this treatment would do more harm than good for LASIK patients”

- “I am personally aware of 7 cases of suicide due to LASIK surgery”

- “I ask the panel to recommend the following: 1) postrefractive surgery indication not to be approved for cases without documented evidence of progression of disease, 2) if CXL is approved its labeling include a blackbox warning of potentially disabling eye condition”

Therefore, it is clear that this treatment includes risk and that, while some adverse events clearly occurred more commonly in the postrefractive corneal ectasia population, there is great uncertainty with regard to the real risks to this population due to poor methodology, loss of the control arm at 3 months (which cripples attempts at a safety comparison beyond that time), and study design and conduct issues summarized above.

Only 40% of the advisory committee voted for approval for this indication (6 voted yes, 4 voted no, 4 abstained, 1 no vote). Advisory committee members stated: “I think these patients deserve evidence based interventions, and the study was so methodologically flawed that I could not come to the

conclusion that it represented substantial evidence of efficacy.”; “I think we need better data”; “this particular study is abysmal”\textsuperscript{14}.

Due to study termination prior to completion of planned enrollment, the effectiveness cohort consisted of 91 eyes across 2 studies. The protocol and SAP defined success was not met for the primary effectiveness endpoint at 3 months for this indication. Both studies failed to reach protocol and SAP pre-defined primary effectiveness success criterion of a clinically meaningful difference of at least 1 D in the mean change from baseline in Kmax between the treatment groups. Additionally, 3 months post-crosslinking timing has been agreed to be too early for adequate evaluation by both the sponsor and the Agency. While the validity of LOCF to support an indication for Progressive Keratoconus is debatable, the use of LOCF to extend the endpoint to month 12 for effectiveness evaluation of treatment for post-refractive corneal ectasia is more obviously inappropriate due to unacceptability of the required assumptions (as discussed below).

With regard to effectiveness, only 91 postrefractive corneal ectasia eyes were randomized to the crosslinking treatment (88 control arm, 91 experimental arm across 2 studies). As mentioned above, the The protocol and SAP defined success criteria were not met for the primary effectiveness endpoint at 3 months for this indication in either of the two studies. This was due to a failure to reach a clinically meaningful 1 D difference in mean change in Kmax from baseline between the control and experimental groups. The 1D target is critical as the error in measurement of Kmax can be extremely large in diseased corneas (repeatability of 0.71 D and reproducibility of 0.83 D have been published\textsuperscript{15}) and the clinical significance of small changes in Kmax is debatable. While the sponsor reached statistical significance of differences of 0.8 D and 0.9 D between treatment groups, the timing of this data are inadequate to support effectiveness (3 months post-crosslinking is too early for evaluation as significant corneal remodeling occurs post-crosslinking and would not yet be complete). The use of LOCF to extend the endpoint to month 12, particularly to compensate for the loss of almost every subject in the control arm, would require supporting certain assumptions. These assumptions include: (1) on average, Kmax (a poor, but often used diagnostic measure of corneal steepening) remains stable or does not improve and (2) the variability of Kmax will not increase over time.

These assumptions are insupportable for the postrefractive corneal ectasia population for the following reasons:

\textsuperscript{14} Advisory committee meeting transcript: 
\url{http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphtalmicDrugsAdvisoryCommittee/UCM450253.pdf}

\textsuperscript{15} Repeatability and reproducibility of a single Kmax reading were recently reported to be 0.71 D and 0.83 D respectively in keratoconic eyes compared to literature indicating that “a change of >1 D in the Kmax parameter [is routinely used in crosslinking trials because it]... is [thought to be] 3 times the standard deviation of measurement error” Hashemi K, Guber I, Bergin C, Majo F. Reduced precision of the Pentacam HR in eyes with mild to moderate keratoconus. Ophthalmology. 2015 Jan;122(1):211-2.
1) For Kmax to be stable or not improve, it is implied that a disease process must be progressive (i.e., the corneal steepening is progressing) - Note that in the postrefractive corneal ectasia population, neither were data regarding disease progression collected at the time of enrollment, nor were the enrollment criteria as specific regarding the signs, symptoms, and ocular history relevant to the condition. The lack of such historical data in the postrefractive corneal ectasia population makes it difficult to justify assumptions regarding a population that was heterogeneous by design (see CDRH post-Hoc analyses of the ocular history in postrefractive corneal ectasia). Furthermore, any attempt at establishing disease progression in the control arm in the study is limited by the fact that only a couple measurements are available prior to month 3 (after which the majority of control eyes received the experimental treatment). With so few data points over so short a time, it is difficult to definitively conclude that changes in Kmax are due to disease progression rather than measurement error/variability. Furthermore, there may be inherent bias in measurements taken during the study as there was no masking.

2) As a disease progresses, the variability of Kmax may increase since there is data that the precision of this diagnostic measurement is reduced in diseased corneas compared to normal corneas. Given that the postrefractive corneal ectasia population may be highly heterogeneous with regard to disease severity and progression (based on the CDRH post-hoc analyses reported in our 9/30/2015 review), this may be extremely problematic since the study did not include adequate methodology for obtaining the diagnostic measurement in a manner to minimize variability and erroneous readings. The methodology used in the study was not of adequate rigor to engender confidence in the accuracy of Kmax readings (i.e., the error in the measurement or methodology alone may lead to instability in Kmax values or perceived “improvement”). Therefore, the use of LOCF introduces uncertainty with regard to the benefit captured in the study at month 12. This uncertainty is magnified for the postrefractive corneal ectasia population since support for LOCF is weaker due to differences in the enrollment criteria and resultant population. Some of the variability noted above might be averaged across many values taken in a large study. We note that these were not large studies (see accountability tables), however, they may have been sufficiently large to blend such effects. Regardless, the lack of historic data at the time of enrollment to support disease progression is insurmountable as it cannot be deduced post hoc which subjects with missing data had progressive disease and which were relatively stable and the blind use of LOCF confounds data already weakened by numerous study design and conduct issues (premature termination of one study, failure to complete planned enrollment for any study, etc. See CDRH clinical reviews for additional detail). As a result, we believe that data from the postrefractive corneal ectasia population cannot be salvaged at month 12 using LOCF and the study failed the requisite success criteria for a clinically meaningful difference at the month 3 endpoint analysis.

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Furthermore, when requested to respond to the observation the “the ectatic group did not get as much benefit as the progressive keratconus group. Is there any thoughts on why?” The sponsor’s team (specifically, Dr. Hersh, the sponsor’s medical monitor and a cornea expert) responded “We don’t know exactly why, but there are a few possibilities. First, you’re dealing with an older age group. And we know that older patients with keratoconus and possibly ectasia tend not to be as progressive. Secondly, the baseline Kmax in ectasia was about 10 diopters less than in keratoconus, and there seems to be a more robust improvement effect in patients who have worse degrees of disease. Finally, it may be something to do with cone location. Ectasia patients tend to have a lower cone, and we find that more centralized cones may have a more robust topography improvement effect.” This introduces a significant area of uncertainty since the cone location may be critical to predicting outcomes and may also explain why the size of the illumination diameter used (i.e., area of treatment) appeared to have opposite effects between keratoconus and postrefractive corneal ectasia (see prior CDRH clinical reviews). Therefore, there is evidence within the dataset as well as the sponsor’s interpretation of the results to indicate that benefit in postrefractive corneal ectasia with the device to be marketed is reduced (or at least inconsistent) compared to the benefit experienced in the progressive keratoconus population. This issue may be further supported by limited effectiveness observed in certain subgroups within the postrefractive corneal ectasia population (ex. post PRK vs. Post LASIK – see prior CDRH clinical reviews).

However, the population was not adequately designed to stratify data to identify a clear, consistent and identifiable subgroup in which effectiveness is supported. The population enrolled in the clinical trials under postrefractive corneal ectasia included subjects with diverse and inconsistent collection of ophthalmic history. While this is an orphan population, the numbers are, again, extremely small. This is perhaps a greater problem in the postrefractive corneal ectasia population due to the variability in the population with regard to number of, type of, and duration since prior refractive treatments, not to mention the potential heterogeneity with regard to disease progression and pre-existing keratoconus prior to any refractive intervention. Note that some postrefractive corneal ectasia subjects were clearly documented to have had such a history of keratoconus. Adequate historical data (and documentation of “normal” topography prior to refractive surgery) was not collected across the study population to determine if any of the subjects enrolled truly had an iatrogenic condition or whether the “postrefractive corneal ectasia” population was actually just an extension of the keratoconus population, specifically those who had undergone prior surgical refractive treatment. Great variability in a small population may lead to poolability issues and in the absence of adequate numbers of subjects by criteria of interest, poolability cannot be adequately determined. At this time, adequate data do not exist to determine what subset of postrefractive corneal ectasia subjects would be more likely to achieve (any) benefit.

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Finally, the effectiveness endpoint evaluates the change in Kmax between the control and experimental arms, however, neither the history collected nor the enrollment criteria establish disease progression (i.e., changing Kmax preoperatively). In the absence of evidence that the disease was progressive preoperatively, this endpoint loses relevance as a marker of treatment. Rather, it may reflect a refractive effect, which, in the absence of evidence that corneal stability had been reached at the time of evaluation, is difficult to interpret.

One advisory committee member explained why he voted differently for the postrefractive corneal ectasia indication compared to the keratoconus indication as follows: “I voted differently from the first question. I voted no. My major concern is that the corneal ectasia after the LASIK surgery is intrinsically a little bit different from the keratoconus. Keratoconus tend to be paracentral, in the central location, so the current regimen probably is going to offer some effective treatment. However, most of the corneal ectasia that I have encountered, usually they are in the periphery, and then also that the cornea itself is really not well-centered and the topography itself may not totally represent the pathology. So based on the technology and the small sample size, and also that the technology doesn’t encompassing the larger area of the treatment, I voted no.”

I agree with the concerns expressed at the advisory committee meeting by both advisory committee members and the public at the open public hearing. In light of the uncertainty surrounding the safety and effectiveness of the combination product in the postrefractive corneal ectasia population, I do not recommend approval for the postrefractive corneal ectasia indication. Support of this indication in the future will require data from a new, appropriately-designed clinical study (e.g., with clear definitions for diagnosis and progression of the iatrogenic disease studied as well clear SOPs for collection of both safety and effectiveness data).

**Recommendation:** 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”

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.

18 Advisory committee meeting transcript:
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/s/

JACQUELYN E SMITH
02/18/2016
Memorandum

Date: November 10, 2015
Digitally signed by Bruce A. Drum -S
Date: 2015.12.21 13:23:14 -05'00'

From: Bruce Drum, Ph.D.
Physicist, CDRH/DOED/DSDB

Dexion Shi, Ph.D.
Physicist, CDRH/DOED/DSDB

To: Bradley Cunningham, CMR, Branch Chief, DSDB/DOED/ODE/CDRH
Damia Jackson, Project Manager, DOED/ODE/CDRH
Jacquelyn Smith, Project Manager, DTOP/OAP/CDER

Subject: NDA 203324 Avedro, Inc. system for corneal collagen cross-linking by application of riboflavin ophthalmic solution and exposure to UVA light via the KXL light delivery system.

Engineering/Physics/Vision Review

Introduction: Avedro has submitted the results of pre-clinical bench testing and modeling experiments intended to demonstrate the equivalence of the KXL and UVX devices thereby addressing comments 2a-2e of FDA’s second Complete Response Letter (second CRL) dated 29 March 2015. Avedro wishes to market the KXL device even though all clinical data submitted in support of approval for NDA 203324 were obtained using the UVX device. The purpose of this review is to determine whether the results of the non-clinical comparison studies support the requested substitution. The substantive information in the submission regarding these non-clinical comparison studies is contained principally in direct responses to deficiencies 2(a) – 2(e) in the complete response letter and in the KXL UCX Equivalence Testing Protocol and Testing Report. These deficiencies are listed below in bold text, with each followed by a copy or summary of Avedro’s response in plain text with reviewer comments in outlined text.

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 Response to Deficiency 2a:** 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).
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.
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 Response to Deficiency 2c: 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).

EYE MOTION ANALYSIS: Eye motion is present and expected during all corneal cross-linking procedures.

The equivalence of the eye motion for the UVX and KXL devices is supported by the fact that management of eye motion by device features and by instructions for use are equivalent for the two devices. Neither the KXL nor the UVX device provides any features to limit patient eye movement during the procedure. Neither device contains an eye tracking system or an automated
motion controller to measure or compensate for eye movement. The two devices provide equivalent functionality.

For both devices, patient alignment is manually managed by the physician. As discussed below, the physician is expected to realign the device relative to the patient if a gross misalignment is observed during treatment. In both the UVX and KXL devices, realignment is performed by physical movement of the beam relative to the cornea.

The KXL and UVX instructions for use contain equivalent directions for establishing patient fixation, maintaining fixation during the treatment, and manually correcting for fixation drift as necessary. During the procedures, patients are directed to align their eyes to the nominal center of the treatment beam. As stated in the UVX Operator’s Manual, physicians were instructed as follows:

In the case of the UVX, maintenance of alignment by physical movement of the beam is achieved by manual manipulation of the device on its table mount.

The KXL device employs equivalent physician instructions regarding eye movement. Table 6 from the Type A meeting briefing package (SN0027) includes alignment instructions for the physician, abstracted from the proposed KXL Operator’s manual:

In the case of the KXL, maintenance of alignment by physical movement of the beam is achieved by manual manipulation of the wireless remote, which in turn actuates an internal motion controller. The physician-controlled physical movement of the beam in the KXL is therefore functionally equivalent to the physician-controlled physical movement of the beam in the UVX. No explicit fail-safe provisions against excessive eye motion existed in the clinical trial protocol, in the UVX instructions for use, or in the KXL instructions for use.

Comment: The above KXL instructions are not equivalent to the UVX instructions. The instructions in the labeling should be revised to accurately describe the fixation task.
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 Response to Deficiency 2d: 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).

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 Response to Deficiency 2e: 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).

Comment: The evaluation of the responses to deficiencies 2d and 2e is deferred pending review of the responses to the two deficiencies below, which are to be sent interactively to Avedro to facilitate the review process.
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/s/

JACQUELYN E SMITH
01/13/2016
Memorandum

Date: December 2, 2015

From: Senior Electronics Engineer (Jeffrey L. Silberberg), CDRH/OSEL/DBP

Subject: EMC and wireless consult for NDA203324 Avedro (b)(4) KXL UV irradiation system

To: Jacqueline Smith, CDER/OND/OAP/DTOP
To: Brad Cunningham, CDRH/ODE/DOED/DSDB
To: Damia Jackson, CDRH/ODE/DOED/DSDB

Scope

This is in response to your request for a review of the EMC and wireless issues in the sponsor’s responses dated November 18, 2015.

Recommendations

I have reviewed the sponsor's latest responses regarding one potentially significant and one minor EMC issue.

The sponsor claims that the March EMC testing was performed after modifications (b)(4) were completed. This response is acceptable.

Regarding the one remaining numerical value that is still shown with the European decimal separator (the comma), the sponsor does not appear to have submitted evidence of the change; however, the sponsor promises that the change will be made. Because this is a minor issue, I will trust the sponsor on it.

There were no remaining wireless technology issues in this file.

Therefore, there are no remaining EMC issues that would prevent approval of this device and thus this drug/device combination product.

Jeffrey L. Silberberg - S
2015.12.02 10:48:19 -05'00'
Jeffrey L. Silberberg
Senior Electronics Engineer
Division of Biomedical Physics
OSEL/CDRH/FDA

Reference ID: 3856424

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Date: 2015.12.07
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/s/

JACQUELYN E SMITH
12/07/2015
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Clinical Inspection Summary

DATE: March 26, 2015

TO: Jacquelyn Smith, Regulatory Project Manager
    William Boyd, M.D., Clinical Team Leader
    Division of Transplantation and Ophthalmology Products

FROM: Good Clinical Practice Assessment Branch
      Division of Clinical Compliance Evaluation
      Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
         Branch Chief
         Good Clinical Practice Assessment Branch
         Division of Clinical Compliance Evaluation
         Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections (Addendum 2)

NDA: 203324

APPLICANT: Avedro, Inc.

DRUG: Riboflavin ophthalmic solution/KXL system (combination product
NME: Yes

THERAPEUTIC CLASSIFICATION: Resubmission (6-month review clock)

INDICATIONS: (proposed)

DIVISION ACTION GOAL DATE: March 27, 2015
PDUFA DATE: March 29, 2015
I. BACKGROUND:

NDA 203324 was originally submitted by Avedro, Inc. on March 8, 2012, but received a Refuse to File letter on May 4, 2012, because the proposed commercial formulation differed from the formulation studied in Phase 3 trials and there was insufficient CMC data to perform a substantial review. A complete response submission was received September 16, 2013. Five clinical site inspections covering three Phase 3 clinical studies and a sponsor inspection of Avedro, Inc. were conducted during this review cycle. See Clinical Inspection Summary of February 22, 2014 and Clinical Inspection Summary Addendum of March 14, 2014 in DARRTS for findings. A Complete Response letter was issued on March 14, 2014 citing numerous deficiencies including CMC, device, clinical/statistical, and bioresearch monitoring related issues. See Complete Response letter of March 14, 2014 in DARRTS for details. The sponsor submitted a complete response on September 29, 2014.

As part of a complete response submission, Avedro, Inc. was asked to provide an independent third party assessment of Dr. R. Doyle Stulting’s conduct as sponsor-investigator of Study UVX-001 at Emory Vision in Atlanta. Dr. Stulting had conducted the study at Emory Vision, 875 Johnson Ferry Road, Atlanta, GA 30343 but had retired from Emory Vision in March 2010 and was unable to personally access the records at that location. Therefore, the initial FDA inspection was conducted January 27 to March 20, 2014, at the site of his current clinical practice, Woolfson Eye Institute, 800 Mt. Vernon Highway, Suite 120, Atlanta, GA 30328, using copies of source records provided to him by Emory Vision. The inspection duration was prolonged due to weather-related events in Atlanta and Dr. Stulting’s health and further complicated by incomplete receipt of copies of records from Emory Vision. The inspection was formally closed on March 20, 2014 and classified as Voluntary Action Indicated by the FDA field inspector. See Clinical Inspection Summary Addendum of March 14, 2014 in DARRTS for details regarding preliminary inspection observations.

The independent third party audit report submitted by Avedro, Inc. at FDA’s request, 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.

A decision was made by FDA to conduct a follow-on inspection of Study UVX-001 original source records at Emory Vision because of the concerns raised about the adequacy or quality of adverse event reporting at the study site by the independent third party audit report. Emory Vision had relocated from Johnson Ferry Road to Doctors Office Building #3, 5671 Peachtree Dunwoody Rd., Suite 400, Atlanta, GA 30342 in December 2014. The primary objective of the follow-on inspection of Study UVX-001 was to investigate 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 [redacted] to the IRB) and Avedro Inc.’s third party audit
II. RESULTS (by Site): A single follow-on inspection of Study UVX-001 was conducted during this review cycle.

<table>
<thead>
<tr>
<th>Name of CI/Location</th>
<th>Protocol # and # of Subjects</th>
<th>Inspection Date</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. R. Doyle Stulting, M.D. Emory Vision (source)</td>
<td>UVX-001 107 primary eyes</td>
<td>January 20 - 22, 2015</td>
<td>Pending Preliminary VAI</td>
</tr>
<tr>
<td>Doctors Office Building #3 5671 Peachtree Dunwoody Rd., Suite 400 Atlanta, GA 30342</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woolfson Eye Institute (copies of source documents) 800 Mt. Vernon Highway, Suite 120 Atlanta, GA 30328</td>
<td></td>
<td>January 27 – March 20, 2014</td>
<td></td>
</tr>
</tbody>
</table>

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 (original issued March 20, 2014, amended version issued December 18, 2014), review of EIR from 2014 inspection, Dr. Stulting’s April 10, 2014 written response to the Form FDA 483, and observations from the January 2015 inspection; EIR from the January 2015 inspection is pending. A final classification of the inspection of Dr. Stulting will be made once the January 2015 EIR is received by OSI and a letter of correspondence is issued to Dr. Stulting.

III. INSPECTIONAL OBSERVATIONS

Dr. R. Doyle Stulting, M.D.
Atlanta, GA 30342

a. What was inspected:
During the follow-on inspection conducted from January 20-22, 2015, 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.

Reference ID: 3722429
b. **General observations/commentary:**
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, and assessment of measured refraction and visual acuity.

AE logs were created retrospectively (entries appearing in AE log predated earlier appearing entries in the list) and contained information extracted from source documents. The regulatory binder for Study UVX-001 contains a “Delegation of Study Data Entry” form from Avedro (Applicant) to Dr. J. Bradley Randleman (designated as Principal Investigator on this form). This form was signed by Dr. Randleman on July 2, 2010, Avedro on July 16, 2010, and [vendor contracted by NDA Applicant Avedro] on August 19, 2010. This form authorizes staff to enter site-generated and maintained source documentation relevant to subjects enrolled in the study into the official study database. The regulatory binder also contains a follow-up monitoring visit letter dated September 14, 2010, to Dr. J. Bradley Randleman. During the monitoring site visit August 10-13, 2010, a request was made to add Concomitant Medication and AE logs for each study subject as necessary. These documents indicate that data was extracted from source documentation and entered into the study database after Dr. Stulting had left Emory Eye Clinic/Emory Vision.

There was no under-reporting of AEs (source documents for select subjects (Subjects 050, 054, 233, and 239) were scanned and events/reporting were discussed with the review division during inspection). Source document notations match data listings, but do not include assessment of relatedness or severity.

The source records, including study worksheets, progress notes, AE logs, and NDA data listings were reviewed for four specific subjects (Subjects 050, 054, 233, and 239) identified in the third party audit report. Three of those subjects (Subjects 054, 233, and 239) had AE discrepancies reported by the auditor and source records were scanned, shared, and discussed with the clinical review team. There was no under-reporting of AEs. Source document notations match data listings, but do not include assessment of relatedness or severity.

Additional subject source records for keratoconus subjects (02, 04, 16, 28) and corneal ectasia subjects (205, 219, 233) were compared with AE data listings and found to be consistent (related to subject visual complaints, slit lamp findings, and significant diagnoses listed on study worksheets and/or progress notes).

One observation on the Form FDA 483 issued to Dr. Stulting following the January 27 – March 20, 2014 inspection by Investigator Bell was “failure to report promptly
to the IRB all unanticipated problems involving risk to human subjects or others.” This was specifically related to lack of documentation of SAEs for two suicide attempts by Subject following sham treatment procedure performed on the right eye. Source documents located in the subject’s chart at Emory Vision were reviewed and indicate that the suicide attempts did occur during the three month follow-up of the sham procedure. This event was reported to the IRB after Dr. Stulting left Emory Vision. Of note, Subject was documented to have a history of epilepsy, right temporal lobectomy, and significant psychiatric problems (depression, bipolar disorder, anxiety, and past suicide attempts) at study screening per Attachment to Dr. Stulting’s April 10, 2014 written response to the March 2014 Form FDA 483.

c. Assessment of data integrity:

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 and can be relied upon. The source documents did not include assessment of severity or relatedness to study treatment, nor were these defined in the protocol. Extraction of study data, including assessment of severity or relatedness to study treatment of AE, by site personnel and monitors contracted by the sponsor (Avedro, Inc.), 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. Interpretation regarding severity and attribution of AEs is left to the discretion of the review division.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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

Note: A final inspection classification will be made upon receipt of the January 2015 EIR from ORA and written correspondence is issued by OSI to the inspected entity.
Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANICE K POHLMAN
03/27/2015

KASSA AYALEW
03/27/2015
Memorandum

Date: March 27, 2015

2015.03.27 15:56:43 -04'00'

To: Bradley Cunningham, MSE, RAC, LCDR, Branch Chief, DOED/DSDB
Maryam Mokhtarzadeh, MD, Medical Officer, DOED
Malvina Eydelman, MD, DOED Division Director

From: Dexiu Shi, Ph.D., Physicist and Vision Scientist, CDRH/ODE/DOED/DSDB

Doc# NDA203324 - Riboflavin Ophthalmic Solution/KXL System
Drug: Riboflavin Ophthalmic Solution
Device: KXL System
Sponsor: Avedro

Subject: Intercenter/Combination Products Consult on Device Safety
Requested by Jacquelyn Smith, M.A., CDER/OND/OAP/DTOP, Senior Regulatory
Health Project Manager

INTRODUCTION:

Proposed Indications for Use:

Avedro is submitting an Initial New Drug Application for (riboflavin ophthalmic solution) / KXL® System.

The KXL® System is a UVA irradiation system whereby an electronic medical device with a light emitting diode (LED) is used to deliver a dose of UVA light to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Corneal collagen cross-linking improves the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma. Exposure of the cornea to UVA after topical administration of riboflavin induces cross-linking of the corneal collagen fibrils with a resultant increase in tensile strength of the collagen fibrils.
DEVICE OVERVIEW - 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 Photrex™ or Photrex™ Viscous (riboflavin ophthalmic solution). UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System.

Figure 1 Overview Illustration of the KXL System

Figure 2. Wireless Remote
The Optics Head houses the UVA irradiation mechanism. UVA radiation is generated by a UV LED. 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.

The LED is manufactured to emit UVA radiation at a wavelength of 365 nm.

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.

Alignment lasers are used to aid the user in focusing the beam on the patient’s cornea. To correctly position the UV beam onto the cornea, two targeting lasers are used. Both lasers are controlled. Fine alignment of the UV beam through observation of the alignment lasers is controlled through a wireless remote and an internal drive system. Treatment parameters are entered using a touch screen user interface.

Both lasers are controlled. Figure 3 provides an illustration of the X,Y &Z alignment.

The KXL System includes a Radio Frequency Identification (RFID) reader and RFID activation card. The RFID activation cards are supplied with Photrexa or Photrexa Viscous (riboflavin ophthalmic solution) and determine the allowable ranges for user-selectable treatment parameters for the system. 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 to be marketed in the

Page 3 – NDA 203324 – Engineering/Physics Review

Reference ID: 3722870
United States, the maximum allowable treatment parameters will be limited to 3mW/cm² for 30 minutes and a maximum energy density of 5.4 J/cm².

The sponsor modified the software of the to-be-marketed device to implement a software lock-out of the irradiated power above 3 mW/cm². 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.

The following treatment parameters provided by the RFID activation card

- Induction Period: 60 minutes
- Irradiated intensity: 3 mW/cm²
- Total Energy: 5.4 J/cm²
- Exposure Time: 30 minutes

Table 1 shows excerpts from the KXL System specifications.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical</strong></td>
<td>Battery Powered: 12V 35 Ah SLA</td>
</tr>
<tr>
<td></td>
<td>Line voltages 100-240 volts AC, Current</td>
</tr>
<tr>
<td></td>
<td>Single Phase</td>
</tr>
<tr>
<td></td>
<td>RMS, 50/60 Hz, Remote 2x AAA batteries</td>
</tr>
<tr>
<td><strong>User accessible Fuses</strong></td>
<td>250 V~</td>
</tr>
<tr>
<td><strong>Energy Delivery</strong></td>
<td>UV Radiation</td>
</tr>
<tr>
<td></td>
<td>3 mW/cm²</td>
</tr>
<tr>
<td></td>
<td>365 nm</td>
</tr>
<tr>
<td><strong>External Interfaces</strong></td>
<td>USB 2.0</td>
</tr>
<tr>
<td><strong>Battery Life</strong></td>
<td>16 hours</td>
</tr>
<tr>
<td><strong>(normal operating conditions)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**INITIAL REVIEW OF ORIGINAL SUBMISSION**

The sponsor states that:

- The (riboflavin ophthalmic solution) KXL® System was granted orphan drug designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.
- The (riboflavin ophthalmic solution) / KXL® System was granted orphan drug designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.

- There is no FDA approved therapy in the US for the treatment of keratoconus or corneal ectasia following refractive surgery, two orphan indications for which patients are eagerly awaiting a therapeutic treatment option. The (riboflavin ophthalmic solution)/KXL® System addresses a significant unmet medical need in these two orphan patient populations.

- The (riboflavin ophthalmic solution) / KXL® System received CE mark as a commercial medical device in November 2010 and is commercially available throughout Europe.

Reviewer Comment: Clinical Reviewer, Maryam Mokhtarzadeh, MD, identified that:

- Although the NDA was initially submitted for a drug product with the proprietary name [REDACTED], in the most recent submission the sponsor appears to be requesting the following proprietary names for their Riboflavin product: Photrex and Photextra [REDACTED]. This request is being made since “At a teleconference held on 22 May 2012 between Avedro and the Division of Medication Error Prevention and Analysis (DMEPA), Avedro was notified of DMEPA’s preliminary findings that the proposed proprietary name, [REDACTED], was unacceptable [REDACTED].

- The proposed IFU includes 2 orphan drug designations (keratoconus and postrefractive ectasia), however, CDRH has approved at least one product for keratoconus (i.e., Intacs) and therefore it is unclear whether this will present a conflict due to the status of the current submission as a combination product.

REVIEW SUMMARY:

Devices Information

In section 3.2 Regional Information of Device-Information, the following information is provided:

The 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 Photrex or Photrex (riboflavin ophthalmic solution). Irradiating the Photrex or Photrex (riboflavin ophthalmic solution) creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System.
The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient’s cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with Photrex or Photrex (riboflavin ophthalmic solution) and a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

**UVA treatment**

This clinical study is to assess the efficacy and safety of the UV-X™ Illumination System for performing corneal collagen cross-linking (CCCL) for the treatment of corneal ectasia after refractive surgery and progressive keratoconus. The UV-X™ system is a combination product consisting of a UVA 365 nm wavelength light source and Riboflavin 0.1% ophthalmic solution, administered in conjunction with the UVA light as a photosensitizer.

For all listed three studies, irradiance at 3 mW/cm² is applied for 30 minutes while maintaining the total dose at 5.4 J/cm² at the corneal surface. The following are the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA.

- **Induction Period:** 30 minutes
- **Irradiance:** 3 mW/cm²
- **Total Energy:** 5.4 J/cm²
- **Exposure Time:** 30 minutes

➢ **Regarding UVA radiation safety:**

The sponsor states the KXL System complies with IEC 60601-1 and IEC 60825-1 (Safety of laser products) and the IEC 62471 (Photobiological safety of lamps and lamp systems) (page 83). However, the UVA light is for treatment, thus these IEC and/or ISO standards are not applicable. Since UVA light is for treatment, thus the IEC and/or ISO standards (e.g., IEC 60825-1, and Iso15004-2) for laser safety and light hazard protection are not applicable. Scientific literatures are used in my review of the evaluation of UVA eye safety.

- **UVA treatment parameters**

The UVA total energy is the product of the intensity of the UVA beam (irradiance) and the UVA irradiation time. A number of research studies demonstrate that the overall cross-linking effect depends upon the total UVA radiant exposure (i.e. photobiological dose or total energy delivered). Researches for corneal collagen cross-linking has been to use 0.1% riboflavin solution and 365/370 nm UVA at 3 mW/cm² irradiance for 30 minutes, which is equivalent to 5.4 J/cm² radiant exposure were supported by many
literatures that it is below the damage thresholds of UVA for the corneal endothelium, lens, and retina. Therefore, the UVA dose density of 5.4 J/cm² has been used as a kind of “gold standard” for safety assessment for the similar cross-link study (i.e., 365 nm, 0.1% riboflavin). The total UVA energy in excess of 5.4 J/cm² will be potentially risk.

The sponsor stated that the KXL Systems sold commercially in the United States uses a UVA light (365 nm) at an intensity of 3 mW/cm² for maximum exposure up to 30 minutes, thus the total energy will be within 5.4 J/cm². Accordingly, the proposed UVA treatment parameters are considered to be safe. In addition, I found from Avedro webpage, it’s claimed that:

“The KXL® System achieves Accelerated Cross-Linking in just minutes by increasing the UVA power and reducing the exposure time while maintaining the same total energy on the eye as standard cross-linking. It is the first and only cross-linking system manufactured with Accelerated Cross-Linking with continuous wave illumination.”

In recent times, there has been a noticeable increase in studies for developing the accelerated treatment protocols over a significantly shorter exposure period. However, there have been multiple reports that suggest that the overall cross-linking effect depends on the UVA irradiance (i.e., intensity (W/cm²)). There is the safety concern that higher irradiance (> 3 mW/cm²) may induce potential radiation hazard to the eyes.

References:


Reviewer Comment: The KXL Systems sold commercially in the United States uses a UVA light (365 nm) at an intensity of 3 mW/cm² for maximum exposure up to 30 minutes, thus the total energy will be within 5.4 J/cm². Accordingly, the proposed UVA treatment parameters are considered to be safe. There is the safety concern that UVA exposure at higher irradiance (>3 mW/cm²) and/or higher total energy (>5.4 J/cm²) may induce potential radiation hazard to the eyes. The sponsor indicates a Radio Frequency Identification (RFID) activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The detailed discussion on RFID is present at following section.
The Radio Frequency Identification (RFID)

The RFID reader reads RFID activation cards which are supplied with Photrex or Photrex a (riboflavin ophthalmic solution) and determine the allowable ranges for user-selectable treatment parameters for the system. 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 to be marketed in the United States, the maximum allowable treatment parameters will be limited to 3 mW/cm² for 30 minutes and a maximum energy density of 5.4 J/cm².

The sponsor claims that the RFID activation card to be used in the United States is a (RFID) card (a specialized treatment card that contains a set of treatment parameters which provide limits for the allowable power density (mW/cm²) and maximum energy density (J/cm²)). Both Power and Energy parameters have lower, upper and incremental limits that will be customized for sales in the United States. Once the RFID activation card is scanned, the treatment parameters entered by the user (power and energy) are verified against the parameters stored in the RFID activation card. Only if all entered parameters are within the respective ranges allowed on the RFID activation card, the user is allowed to proceed with the treatment.

On Page 21, 3.2.R, it states:

![KXL System UV Treatment Parameters Screen](image)

**Figure 13: KXL System UV Treatment Parameters Screen**

- **Enter UV Treatment Parameters**
  - **Total Energy**
    - **J/cm²**: 5.40
  - **UV Power**
    - **mW/cm²**: 0.3
- **Time left**: 30:00
- **Back** button
- **Submit** button
The user confirms the entered treatment parameters as shown in below figure:

![Enter UV Treatment Parameters](image)

**Reviewer Comment**: The sponsor states that the RFID activation cards supplied in the United States will not allow treatment unless the Total Energy is set to 5.4J/cm² and the UV. The sponsor needs to clarify whether UV radiation intensity of the US version KXL system is locked at the lowest setting (i.e. 3mw/cm²). If so, please describe the method, such as, software control and/or hardware safeguard to shut down or black the UVA beam once the UV radiation intensity is greater than 3mw/cm² (see deficiency#1).

**Figure 44**: KXL System Crate Label

![KXL System Crate Label](image)
• Homogeneity of the UVA irradiance

Spoerl, et al. [1] pointed that for UVA exposure, if hot spots are present, the damage thresholds may be exceeded locally, leading to localized endothelial damage, although the average irradiance may be less than damage thresholds. Therefore, clinically used light sources should be homogeneous of the irradiance across the beam area.

Reference:


Device Description (page 9) indicates that KXL UVA radiation is generated by UV LED (365 nm).

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. The sponsor states the UV Homogeneity Measurement is performed in accordance to KXL System Optical Assembly Calibration (WI-01102-01) to verify that the UV Beam has been properly focused. The acceptance criteria is defined as that the homogeneity (flatness) of the beam at the focal plane shall be % RMS. The KXL System Optical Assembly UV Homogeneity Measurement Master Validation (VAL-00005) is provided in Appendix 2.24.

Reviewer Comment:

- The proposed Homogeneity Measurement Master Validation plan (VAL-00005) is acceptable. However, no test result was presented. The sponsor needs to provide the test results/evidence demonstrating the UVA treatment beam is homogeneous over entire cornea area.

- The sponsor states that “UVA radiation is generated by UV LED (365nm).” The may be hazard to the device operator. The sponsor should explain any mitigation(s) used for protecting the eye safety for operators (deficiency#2).
• **UV beam align system**

The sponsor states that to correctly position the UV beam onto the cornea, two targeting lasers are used:

**Reviewer Comment:** The KXL system used two targeting lasers for illumination. The sponsor claimed that both targeting lasers are eye-safe (Class I laser) based on IEC 60825-1:2007. They do not provide the technical characteristics of the two lasers (laser name/model, maximum output power). This basic information is necessary for the review of the laser safety (deficiency #3).

**Equivalency of UVX and KXL Systems**

The sponsor states that:

The UV-X Illumination System was utilized during the Phase III clinical study reported in the NDA. Avedro, Inc. believes that the KXL System for which commercial approval is being requested is equivalent to the UV-X Illumination System which was used during the Phase III clinical study. Table 8 compares the specifications of the UV-X Illumination System with the KXL System.
### Table 8: Comparison of UV-X Illumination System (Phase III) Specifications with the KXL System (Commercial) Specifications.

<table>
<thead>
<tr>
<th></th>
<th>Phase III (UV-X)</th>
<th>Commercial (KXL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UVA System</strong></td>
<td>UV-X Illumination System</td>
<td>KXL System</td>
</tr>
<tr>
<td><strong>Device Type (Classification)</strong></td>
<td>LED illumination device (Class II)</td>
<td>LED illumination device (Class II)</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>Wavelength: 365 nm</td>
<td>LED: Wavelength: 365 nm</td>
</tr>
<tr>
<td><strong>Device Configuration</strong></td>
<td>Illumination system at end of an arm, attached to a floor stand or a patient bed</td>
<td>Illumination system at end of an articulated arm on top of floor stand, wireless remote control and a system console</td>
</tr>
<tr>
<td><strong>Light Emission</strong></td>
<td>Continuous wave (CW)</td>
<td>Continuous wave (CW)</td>
</tr>
<tr>
<td><strong>Illumination Intensity</strong></td>
<td>3.0 mW/cm²</td>
<td>3.0 mW/cm²</td>
</tr>
<tr>
<td><strong>Illumination Diameter(s)</strong></td>
<td>Variable steps 7.0, 9.0 and 11.0 mm</td>
<td>Fixed at 9.0 mm</td>
</tr>
<tr>
<td><strong>Treatment Time</strong></td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td><strong>Patient Positioning</strong></td>
<td>On bed</td>
<td>On bed</td>
</tr>
<tr>
<td><strong>Targeting System</strong></td>
<td>N/A</td>
<td>Laser crosshairs</td>
</tr>
<tr>
<td><strong>Focal Plane Setting</strong></td>
<td>Subjective (homogeneity of UV pattern)</td>
<td>Objective (crossed laser beams)</td>
</tr>
<tr>
<td><strong>Electric Power</strong></td>
<td>100V to 240 V</td>
<td>100 V to 240 V</td>
</tr>
<tr>
<td><strong>Intensity Check</strong></td>
<td>UV light meter delivered with UV-X System</td>
<td>Integrated UV light meter</td>
</tr>
<tr>
<td><strong>Laser and LED Safety Compliance</strong></td>
<td>IEC 60825-1</td>
<td>IEC 60825-1</td>
</tr>
<tr>
<td></td>
<td>IEC 62471</td>
<td>IEC 60601-1</td>
</tr>
</tbody>
</table>

Major differences are follows:

<table>
<thead>
<tr>
<th></th>
<th><strong>Phase III (UV-X)</strong></th>
<th>Commercial (KXL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Illumination Diameter(s)</td>
<td>Variable steps 7.0, 9.0 and 11.0 mm</td>
</tr>
<tr>
<td></td>
<td>Fixed at 9.0* mm</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Targeting System</td>
<td>No target laser (aligned subjectively by the user)</td>
</tr>
<tr>
<td></td>
<td>Use two targeting lasers</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Focal Plane Setting</td>
<td>Subjective (homogeneity of UV pattern)</td>
</tr>
<tr>
<td></td>
<td>Objective (crossed laser beams)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Intensity Check</td>
<td>UV light meter delivered with UV-X System</td>
</tr>
<tr>
<td></td>
<td>Integrated UV light meter</td>
<td></td>
</tr>
</tbody>
</table>

*Reviewer Note: The sponsor changed the beam diameter to 9.5 mm in the middle of review process.*
On page 83, 3.2.R Regional Information, the sponsor states:

Both systems are LED based illumination systems with a wavelength of 365 nm. Both systems are continuous wave systems with an illumination intensity of 3.0 mW/cm² and a treatment time of 30 minutes. The illumination diameter is 9.0 mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm steps. The patient is positioned on a bed for treatment in a supine position with both systems. The KXL System includes an alignment focusing beam that allows for alignment of the treatment area. The UV-X System was aligned subjectively by the user. The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used an external light meter. Both systems comply with IEC 60601-1 and IEC 60825-1, and the KXL System also complies with IEC 62471.

**Reviewer Comment:** How those differences may affect the SE is discussed at below:

1. The illumination diameters: The illumination diameter is 9.0 mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm. The illumination intensity is given in 3 mJ/cm² which is the same value for UV-X and KXL system.

2. Target system: KXL uses two targeting lasers source with crosshairs. The UV-X System was aligned subjectively by the user. The target system used in KXL system was improved.

3. Focus plane setting: KXL uses crossed laser beam. The UV-X was set focus plane by observe the homogeneity of UV pattern to determine focus plan subjectively.

4. Intensity Check: The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used a light meter.

Clinical reviewer has the concern with the potential illumination diameters used in the trial include “Variable steps 7.0, 9.0 and 11.0 mm” while the device proposed to be marketed has an illumination diameter “Fixed at 9.0 mm”. For KXL, the device functionality has been limited compared to what was used in the clinical study. It is not clear what the repercussions of a fixed illumination beam diameter might be and how the labeling might need to instruct users regarding this difference between the device available and the device studied. Please see Dr. Mokhtarzadeh’s deficiency.
Non-Clinical Laboratory Studies

The following testing and validation materials are provided as appendices:

Appendix 1.1 - Product Requirements Specification
Appendix 1.2 - System Validation Test Plan (PSPEC-00032-NDA)
Appendix 1.3 - System Validation Test Report (PSPEC-00051-NDA)
Appendix 1.5 - System Verification Test Plan (PSPEC-00033-NDA)
Appendix 1.6 - System Verification Test Report (PSPEC-00052-NDA)

**Review Comment:** Additional information of test results is required.

On Page 4, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), it specified that:

6.2.6.4 *Output power shall be controlled to* \( \pm \) %.
6.2.6.8 *Power uniformity over the illuminated area shall be* \( \pm \) % RMS.

a. A tolerance range \( \pm \) % is given for UVA output. Please provide your rationale for why this tolerance range is selected and/or the justification that the % illumination fluctuation will be safe for proposed treatment.

b. Please provide the test result to demonstrate power uniformity over the illuminated area is % RMS for KXL system (deficiency#4).

**LABELING (KXL Operator’s Manual)**

The sponsor provided two versions of KXL Operator’s Manual (i.e., ML-00002, 2011 and ML-00006, 2012) in Appendix 5.1. (device-info-appendices) We found there are discrepancies between these two versions, especially the Indications for Use/Intended Use are not identical. In version ML-00002, 2011 (page 3-1), is included:
DEFIENCIES:

Based on my review, the following engineering and laser and optical radiation safety deficiencies have been identified:

1. The sponsor states a Radio Frequency Identification (RFID) activation card will be used to determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²) and the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA are as follows:

   Induction Period: 30 minutes
   Irradiance: 3 mW/cm²
   Total Energy: 5.4 J/cm²
   Exposure Time: 30 minutes

   Please clarify whether UV radiation intensity of the US version KXL system is locked at the lowest setting (i.e. 3mw/cm²). If yes, please describer the method, such as, any software control and/or hardware safeguards to shut down or block the UVA beam once the UV radiation intensity is greater than 3mw/cm².

2. On Page 4-5, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), it specified that:

   6.2.6.4. Output power shall be controlled to %
   6.2.6.8. Power uniformity over the illuminated area shall be % RMS.

   Please address the following concerns:

   c. A tolerance range (%) is given for UVA output. Please provide your rationale for why this tolerance range is selected and/or the justification that the % illumination fluctuation will be safe for proposed treatment.

   d. Please provide the test result to demonstrate power uniformity over the illuminated area is % RMS for KXL system.

3. You states that “UVA radiation is generated by UV LED (365nm).” Please address the following concerns:

   a. You only provided the Homogeneity Measurement Master Validation plan (VAL-00005) However, no test result was presented. Please explain the criteria of the homogeneity
and provide the test results to demonstrate the UVA treatment beam is homogeneous over entire cornea area.

b. Please be advised that...may be hazard to the device operator. The sponsor should explain any mitigation(s) used for protecting the eye safety for operators.

4. You state that the KXL system used two targeting lasers for illumination, and both targeting lasers are eye-safe (Class I laser) based on IEC 60825-1:2007. However, you do not provide the technical characteristics of the two lasers (laser name/model, maximum output power). Please provide this information. This basic information is necessary for the review of the laser safety.

In addition, it is unclear from your submission how the lasers and LEDs classification was determined; please provide detailed information for determination of laser/LEDs classification. This information will assist us in evaluating the laser and optical radiation safety analyses.

5. You provided two versions of KXL Operator’s Manual (i.e., ML-00002, 2011 and ML-00006, 2012) in Appendix 5.1. We found there are discrepancies between these two versions, especially the Indications for Use/Intended Use are not identical.
Please provide your explanation on the discrepancies and provide your final version of KXL Operator’s Manual for this study.

**REVIEW OF AVEDRO’S RESPONSE (dated 2-21-14) TO CDRH INFORMATION REQUEST (dated 2-11-14)**

The above deficiencies were conveyed to the sponsor in an additional information request on Feb. 11, 2014. Each final version of device deficiency is copied below and followed by the sponsor’s response and reviewer’s comment.

**Agency Request 2:**

The sponsor states a Radio Frequency Identification (RFID) activation card will be used to determine the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage. The proposed treatment parameters that will be allowed by the RFID activation card in KXL Systems for the United States are:

- Induction Period: 30 minutes
- Irradiance: 3 mW/cm²
- Total Energy: 5.4 J/cm²
- Exposure Time: 30 minutes

However, [redacted] a RFID card may not be sufficient to lockout elevated power output that was not adequately studied in the clinical trials provided to support this marketing approval application. Please provide justification for how a RFID can appropriately limit the power output to safer levels.
Avedro Response:

RFID activation cards are a well-known security device used in many applications because of their robustness and inherent data protection capabilities. Avedro uses these same capabilities to ensure the system is used as intended. This is a three-part strategy:

1. The KXL system cannot be run without an authenticated Avedro RFID card inserted.
2. The cards use [redacted] Therefore cards can be neither cloned nor altered.
3. At the Avedro facility, each card is [redacted]

Details:

a. Programming:

The process used to program RFID activation cards dictates that the operator performs 100% verification of the treatment parameters on all programmed cards. In addition, a second operator performs 100% verification of the treatment parameters on all RFID cards.

b. Authentication

1. Each RFID activation card [redacted] cannot be changed or modified.
2. Since the RFID activation card [redacted] modifying the content in any way will fail the authentication process of the KXL system. Any modified or altered card will thus be detected and rejected.

Reviewer Comment: Sponsor’s justification for how a RFID can appropriately limit the power output to safer levels is acceptable. However, they need to clarify that, for US user, the maximum UVA output intensity will be lock at 3 mW/cm². This deficiency has not been addressed satisfactorily.
**Agency Request 3:**

On Page 4-5, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), you specify that:

- 6.2.6.4. Output power shall be controlled to \( (0\%) \%
- 6.2.6.8. Power uniformity over the illuminated area shall be \( (0\%) \%

RMS.

Please address the following concerns:

a. A tolerance range \( (0\%) \% \) is given for UV-A output. Please provide your rationale for why this tolerance range is selected and/or the justification that the \( (0\%) \% \) illumination fluctuation will be safe for proposed treatment.

b. Please provide the test result to demonstrate power uniformity over the illuminated area is \( (0\%) \% \) RMS for KXL system.

**Avedro Response:**
Reviewer Comment: This response is partially acceptable.

The proposed beam diameter is 9.0 mm for KXL system. We believe the beam homogeneity should be tested and ensured within 9 mm, otherwise, larger or less than 3 mW/cm² will result in an over or less UV dosage. Particularly, a hot spot (>3 mW/cm² irradiance) could cause local damage to the endothelium. Please provide your justification on why you believe the size employed to verify beam uniformity is sufficient compared to the 9 mm proposed treatment size.

Agency Request 4:

You state that “UVA radiation is generated by UV LED (365nm).” Please address the following concerns:

a. You only provided the Homogeneity Measurement Master Validation plan (VAL-00005). However, you did not provide any test results. Please provide this information and ensure you explain the homogeneity criteria and provide the test results to demonstrate the UV-A treatment beam is homogeneous over entire treatment area.

Reviewer Comment: The sponsor states that” The validation activities are ongoing. The estimated time frame for the completion of VAL-00005 is March 2014.” This question is pending for response.

b. Please be advised that [redacted] may be hazardous to the device operator. Therefore, please provide information regarding any mitigation method(s) used to address eye safety concerns for operators.

Avedro Response:

The validation activities are ongoing. The estimated time frame for the completion of VAL-00005 is March 2014.
Agency Request 5:

You state that the KXL system used two targeting lasers for illumination, and both targeting lasers are considered as a Class I laser based on IEC 60825-1:2007. However, you do not provide the basic technical characteristics of the two lasers. Please provide this information. In addition, it is unclear how you determined the classification of the lasers and LEDs. Please provide detailed information for how this determination was made so we may fully evaluate the laser and optical radiation safety analyses.

Avedro Response:

This response is satisfactory.
Reviewer Comment: The sponsor states that test reports indicate each targeting laser met class 1 limits and sufficient safety margin is provided. *This response is satisfactory.*

**REVIEW OF AVEDRO’S RESPONSE TO FDA CR (COMPLETE RESPONSE) LETTER DATED MARCH 14, 2014**

The outstanding device issues identified from Avedro’s response (dated 2-21-14) have included in FDA’s Complete Response letter (dated 14 March 2014). Each final version of device deficiency is copied below and followed by the sponsor’s response and reviewer’s comments.

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 postmarket 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.

**Avedro Response: (in briefing-meeting-typea-20140806 submission)**

The differences stated in Table 8 do not encompass all differences between the device studied and the device that is intended to be marketed. As described in the NDA, the original sponsor of IND 77,882 under which the clinical studies were conducted was Peschke Meditrade. Per the original IND 77,882 submitted by Peschke Meditrade, the UVA illumination device utilized in the clinical studies was IROC’s UV-X Illumination System. In an IND amendment dated 7 May 2010, Avedro informed FDA of the change in sponsorship for IND 77,882 from Peschke Meditrade to Avedro, Inc. Also, Avedro’s UV-A device (the KXL System) was submitted to both IND 77,882 for investigational use and NDA 203-324 for proposed commercial use.

Table 5 and Table 6 present the device description, treatment settings, software and instructions for use for each of the systems and an assessment of equivalence. Avedro asserts that the differences between the systems do not impact the safety or effectiveness of the device because the UV treatment parameters that directly impact the dose of UV light between the systems are identical. As shown in Module 3.2.R Device Information Appendices, Appendix 3.1, the spectral output of the KXL System is equivalent to the spectral output of the UV-X Illumination System. Therefore, all specifications that directly impact dose are equivalent between the two systems.

**Reviewer Comment:** Avedro asserted that the differences between the systems do not impact the safety or effectiveness of the device because the UV treatment parameters that directly impact the dose of UV light between the systems are identical. However, they did not provide sufficient information to support. For example, the focal alignment differences raised the concern with substantial equivalency between UVX and KXL.

UV focal alignment differences between the IROC UVX and Avedro KXL Devices (cited from Table 5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IROC UV-X (used in UVX-001, UVX-002 and UVX-003)</th>
<th>Avedro KXL System (device to be marketed)</th>
<th>Sponsor’s Equivalence Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV Focal Alignment</td>
<td>User observes the riboflavin fluorescence to gauge beam shape to determine proper alignment.</td>
<td>Two visible aiming lasers provide direct alignment confirmation in x, y, and z directions.</td>
<td>The KXL System alignment system should be easier for users to correctly align the system compared to the more subjective process with the UV-X system, however, this difference should not impact the safety or effectiveness of the treatment delivered with the devices.</td>
</tr>
</tbody>
</table>
Avedro Response: (in mult-mod-info-amend.pdf)

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. In the agency’s 01 August 2014 preliminary comments, CDRH stated the following:

*The information provided addresses our concern. The following additional concerns were raised: The instructions for use of the device studied differ from those you intend to market therefore we recommend that you revise your instructions for use to be consistent with the device studied. Otherwise, please explain the rationale for this difference. Please be advised that our labeling review is still ongoing, concurrent with our review of the file.*

At the 06 August 2014 Type A Meeting, Avedro explained that 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.

**Reviewer Comment:** The KXL System alignment system objectively aligns the system. The procedure is independent of the riboflavin application and user’s observing capacity and experience. However, with UVX, the user observes the riboflavin fluorescence to gauge beam shape to determine proper alignment. This subjective method is NOT independent of the riboflavin application (diffusion) and user’s observing capacity and experience. Additional information on why the differences in focusing will not affect device performance was requested on 2/4/15.

**Avedro Response to Question 2.d.i.2: Regarding system alignment**

As described in Avedro’s response to Complete Response Item #5 (SN0027), the UVX system alignment is achieved by the user observing the riboflavin fluorescence to gauge beam shape to determine proper alignment while the KXL System utilizes two visible aiming lasers to provide direct alignment confirmation in the x, y and z directions. Both systems have a correct focal plane for treatment and a method for the user to identify the correct treatment plane.

The UVX device relies on a trained physician to find the best focus on the eye, recognizing that proper alignment results in a UVA beam with circular pattern and relatively sharp edges. The KXL System assists the trained physician, using two, class I,
laser crosses to assist in alignment. At proper focus (overlapped crosses) the KXL UVA beam results in a circular pattern with relatively sharp edges. Other than ease of use, differences in focusing procedure have no effect on device performance.

**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.*

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/cm².

**Avedro Response: (in briefing-meeting-typea-20140806 submission.pdf)**

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/cm². 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 is in process and will be completed by July 2014.

**Avedro Respons: (in mult-mod-info-amend.pdf)**

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.6 (SN 0027, Module 1.6.2), where we committed to modifying the software of the to-be-marketed device to implement the software lock-out of the irradiated power above 3 mW/cm².

Validation of the software lock-out has been completed. Enclosed is the validation and verification test reports (PSPEC-00053-NDA and PSPEC-00054-NDA, respectively). As a result of this change, the following additional supportive documents have been revised:

- PSPEC-00027-NDA
- PSPEC-00030-NDA
- PSPEC-00031-NDA
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.*

7. You indicate that

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

Avedro Response: *(in briefing-meeting-typea-20140806 submission.pdf)*
The validation activities for the Homogeneity Measurement Master Validation plan have been completed and results are provided in Final Report VAL-0005-RPT.

Reviewer Comment: The Homogeneity measurement master validation test was based on the following acceptance criteria:

The acceptance criteria given in VAL-0005 Rev B is:

1) Gage R&R
   - meet the UV beam Homogeneity specification
2) All UV beam Homogeneity results were %.

Reviewer note: Basic Definitions of Gage R&R *(http://www.dmaictools.com/dmaic-measure/grr)*

Gage R&R (Gage Repeatability and Reproducibility) is the amount of measurement variation introduced by a measurement system, which consists of the measuring instrument itself and the individuals using the instrument. A Gage R&R study is a critical step in manufacturing Six Sigma projects, and it quantifies three things:

1. Repeatability – variation from the measurement instrument
2. Reproducibility – variation from the individuals using the instrument
3. Overall Gage R&R, which is the combined effect of (1) and (2)

The overall Gage R&R is normally expressed as a percentage of the tolerance for the CTQ (Critical-to-Quality) being studied, and a value of 20% Gage R&R or less is considered acceptable in most cases.
Test results: The sponsor stated that because all UV beam Homogeneity results were \( % \) and the resulting Gage R&R met all of the predetermined acceptance criteria.

Data analysis

Reviewer Comment: The test report demonstrates that UV beam homogeneity measurement results were \( % \) which met the predetermined acceptance criteria (i.e., \( % \)). Deficiency#7 has been adequately addressed.
RECOMMENDATION: Additional information is required.

There are unresolved issues regarding whether and how the device differences between the UV-X System and the KXL System will affect the safety and performance throughout the course of review. We also observed additional differences in sponsor’s presentation at the advisory committee meeting and from interactive review correspondence received March 16, 2015. Bruce Drum, Ph.D., vision scientist of DOED, has joined in the discussion on the device related deficiencies for this CR letter. Based on discussion with DOED management, we have following non-clinical deficiencies:

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.

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

/s/

JACQUELYN E SMITH  
03/27/2015
Date: March 10, 2014

From: Senior Electronics Engineer (Jeffrey L. Silberberg), CDRH/OSEL/DESE

Subject: Consult - Review of responses to EMC information requests for NDA203324 Avedro KXL UV irradiation system

To: Brad Cunningham, CDRH/ODE/DOED/DSDB

Scope

This is in response to your request for a review of the sponsor’s responses dated February 21, 2014 to EMC information requested in a letter from FDA dated February 11, 2014.

Conclusions

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

Recommendations

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.

1. In Request 6, we noted that on page 60 and 61 of the device-information document, there was a table of “recognized standards” with which the KXL System is claimed to comply. However, 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 important. Also, 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.

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

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, while the FDA Forms 3654 specify the version and date of publication, Table 6 does not, and this information should be added.

2. In Request 7, we noted that 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’s 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/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

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. Your promise to include the Essential Performance statement in the operator’s manual is conditionally acceptable, pending our receipt of the revised operator’s manual and confirmation of inclusion of the Essential Performance statement.

3. In Request 8, we noted that there are 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 110 VAC 60 Hz. We noted that the AC input specifications of the KXL System are 100-240 VAC. We asked the sponsor to perform these tests as specified by IEC 60601-1-2, i.e. repeat them at 100 VAC.

You responded that Avedro commits to conducting additional testing as requested and will submit information as soon as it is available. This response is conditionally acceptable, pending our receipt and review of test reports for the additional testing.

4. In Request 10, we noted that IEC 60601-1-2:2007 specifies requirements for testing and for labeling. 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. 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; and

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

You said that you commit to updating the operators manual to include all the items above. Your promise to include these items in the operator’s manual is conditionally acceptable, pending our receipt of the revised operator’s manual and review of these items.

5. In Request 11, we noted that the KXL System incorporates wireless remote control and RFID, yet we were not able to find information on the effective radiated power of either wireless device, nor were we able to find information on the communication service or protocol used by the wireless remote control. We asked you to provide this information and also address all the issues raised in the 2013 FDA guidance Radio Frequency Wireless Technology in Medical Devices (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm077210.htm), including performing wireless coexistence testing or submitting a justification as to why wireless coexistence testing is not needed.

You responded as follows:
a. RFID reader ENG-00754
   • 13.56 MHz Reader/Writer
   • Integral Antenna: Maximum 4” Read Range
   • US/FCC number SX90RFID1
   • Max output power is 200 mW
   • Meets: ISO18000-3, ISO15693

You noted that measured emissions from the RFID were considerably below CISPR 11 and FCC limits. You said that coexistence testing is not needed.

You submitted some of the information needed to assess this wireless function of the device, and this is (partially) acceptable. However, your implication is not valid. Medical equipment that has a radiated RF immunity of 3 V/m would need to be kept at least 0.54 m (almost 2’) from the device. Furthermore, both implantable and non-implantable medical devices have been shown to be susceptible to RFID readers operating at 13.56 MHz. Please explain how interference to implantable and non-implantable medical devices in the vicinity of the RFID reader will be mitigated.

b. Wireless remote control: ENG-01085
   • FCC ID SXJ87027-T
   • Frequency Range 2402 MHz to 2476 MHz
   • Max Effective Power: 0.501 mW

You said 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 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.

6. In Request 12 we noted that 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, mistakes and accidents do happen. We said that 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. Your promise to include these items in the operator’s manual is conditionally acceptable, pending our receipt of the revised operator’s manual and a reproduction of the device label and review of these items.

Background

The KXL System is an electronic medical device intended to deliver ultraviolet light (365 nm wavelength) in a circular
pattern onto the cornea after application of (riboflavin ophthalmic solution). According to the sponsor, irradiating creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The KXL System is shown in Figure 1.

While the sponsor does not specify the intended use environments explicitly, it can be assumed that the system will be used in hospitals, clinics, and doctors’ offices.

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 exposure time, and UV intensity) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with (riboflavin ophthalmic solution) and a radio-frequency identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user selectable power density levels and the maximum allowable dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

**Figure 1 - The KXL System**

The UV irradiance dose is the product of the intensity of the irradiance and the exposure time. The following are the treatment parameters that the sponsor claims will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction Period</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>
Irradiance: 3 mW/cm²
Exposure Time: 30 minutes

Although the submission might include appendices that describe wider treatment parameters that are available on devices sold outside of the United States, the sponsor claims that all devices sold commercially in the United States will have treatment specifications limited by the RFID activation card to those listed here.

Table 1 shows excerpts from the KXL System specifications.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical</strong></td>
<td>Battery Powered: 12V 35 Ah SLA Line voltages 100-240 volts AC Single Phase</td>
</tr>
<tr>
<td></td>
<td>RMS, 50/60 Hz % Current</td>
</tr>
<tr>
<td><strong>User accessible Fuses</strong></td>
<td>250 V~</td>
</tr>
<tr>
<td><strong>Energy Delivery</strong></td>
<td>UV Radiation 3 mW/cm² 365 nm</td>
</tr>
<tr>
<td><strong>External Interfaces</strong></td>
<td>USB 2.0</td>
</tr>
<tr>
<td><strong>Battery Life</strong></td>
<td>16 hours</td>
</tr>
<tr>
<td>(normal operating conditions)</td>
<td></td>
</tr>
</tbody>
</table>

The KXL System is a portable system with an articulating arm that houses the illumination system at the end. The articulating arm allows movement of the system for alignment of the UV Beam to the patient’s cornea. The articulating arm sits on top of a floor stand that houses an internal battery that powers the system. The battery is recharged by a system internal charger from a standard AC outlet. The complete optics assembly can be moved in x, y, and z. A wireless remote controls all system movements.

A system console houses the user interface and the RFID reader. The user interface controls all treatment parameters that are set through a touch screen PC running Windows Embedded Standard. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable dosage (in J/cm²) for the system. According to the sponsor, the software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console and there are more than zero treatments remaining.

The Optics Head houses the UVA irradiation mechanism. UVA radiation is generated by UV LED. The LED is manufactured to emit UVA radiation at a wavelength of 365 nm. 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. Both lasers are controlled.

Reference ID: 3722902
Treatment parameters entered by the user (power, time and energy) are verified against the parameters stored in the RFID activation card. Only if all three entered parameters are within the respective ranges allowed on the RFID activation card, the user is allowed to proceed with the treatment.

The RFID activation card is programmed with an initial number of treatments for which it may be used. When scanned, the number of treatments remaining is decremented by one until the card is empty. An RFID activation card can only be used if it is identified by the system’s cryptography software module as a certified Avedro-created tag and if its country code matches that of the KXL System. A given multi-use RFID activation card will be accepted only if it contains at least one remaining treatment. Once a multi-use RFID activation card has been scanned, the user is given a visual indication of the number of treatments remaining on the card.

Therefore, it is not possible to simply store and re-write the current number of treatments remaining on a given multi-use disposable RFID activation card.

Since cards cannot be written by the KXL System, when a multi-use card is scanned, a previously unlocked memory block on the card is irreversibly locked. Since blocks can never be unlocked, this method prevents a malicious user from “rolling back” the number of treatments remaining on a given card. Since there are 64 blocks on a given tag, the number of treatments per card is limited to 64.

The position of the KXL System head can be manually adjusted and located appropriately over the patient’s eye by the
The position can then be fine-tuned using the wireless remote control, in an X, Y and Z direction. (See Figure 2.)

The joystick controls X and Y directions; the two buttons control the movement along the Z axis.

**Figure 2 - Wireless remote control**

The approximate sequence of operation is as follows:

- Device power is turned on by the user. The system then checks for startup errors and if the system is starting up correctly, a system calibration is performed. The system checks whether a partial treatment has been detected. If not, the system prepares for a new treatment.

- To begin preparing for treatment, the user enters the induction period for the instillation of the \( \text{(8)(6) riboflavin ophthalmic solution) } \) in minutes and seconds.

- The user sets the UV treatment time in minutes and seconds and the UV power.

- The user is instructed to scan an RFID treatment activation card using the RFID reader.

- The user is prompted to sync the alignment remote with the KXL System and does so by pressing the sync button on the alignment remote.

- The patient’s eye is prepared for treatment by the physician removing the epithelium. The KXL System then instructs the doctor to apply the \( \text{(8)(6) riboflavin ophthalmic solution) } \).

- The KXL System tracks the induction time and notifies the user that the induction is complete.

- The UV treatment is then performed.

- The KXL System tracks the treatment time, turns off the UV and notifies the user when the treatment has been completed.

- Once the treatment has been completed, the system may be powered off.
Responses to information requests

1. In Request 6, we noted that on page 60 and 61 of the device-information document, there was a table of “recognized standards” with which the KXL System is claimed to comply. However, 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 important. Also, 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 the sponsor to be consistent in the claims of conformity. Finally, we asked the sponsor to submit an FDA Form 3654 for each standard to which conformity was claimed.

The sponsor 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. The sponsor should be asked to 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.


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

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.

Reference ID: 3722902
If the sponsor decides to keep these declarations, while the FDA Forms 3654 specify the version and date of publication, Table 6 does not, and this information should be added.

2. In Request 7, we noted that 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, the sponsor had not specified the performance that was determined to be the Essential Performance of the KXL System. It’s possible that this could be derived from the specification of Criterion A; however, we asked the sponsor to specify the Essential Performance explicitly. We recommended that any future EMC testing to IEC 60601-1-2 submitted by the sponsor 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.

The sponsor 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/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

The sponsor 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, the sponsor committed to updating the operators manual to include the Essential Performance statement.

The Essential Performance statement is acceptable. The sponsor’s promise to conform to the immunity pass/fail requirements of IEC 60601-1-2 is also acceptable. The sponsor’s promise to include the Essential Performance statement in the operator’s manual is conditionally acceptable, pending our receipt of the revised operator’s manual and confirmation of inclusion of the Essential Performance statement.

3. In Request 8, we noted that there are 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 100 VAC Hz. We noted that the AC input specifications of the KXL System are 100-240 VAC. We asked the sponsor to perform these tests as specified by IEC 60601-1-2, i.e. repeat them at 100 VAC.

The sponsor responded that Avedro commits to conducting additional testing as requested and will submit information as soon as it is available. This response is conditionally acceptable, pending our receipt and review of test reports for the additional testing.

4. In Request 9, we noted that the EMC test reports identified the modifications below that were made to the KXL System in order to pass the tests. We asked the sponsor to affirm that all of these modifications will be included in all production units.

We said that if these features will not be included in the marketed version of the device, the sponsor should submit an explanation for why [how] the testing that was completed is appropriate to support an EMC evaluation of the device or re-test the device without the additional modification[s] that would not be included in a marketed
device.

The sponsor replied that items 2-8 in the list above are to be included in the marketed version of the product exactly as they were during the testing. Regarding item 1, has been implemented compared to the one that was used during the original testing. The sponsor said that this will be used during the additional IEC 60601-1-2 testing that was to be performed. This response is acceptable.

5. In Request 10, we noted that IEC 60601-1-2:2007 specifies requirements for testing and for labeling. 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. This includes the items listed below. We were not able to find any of these items in the Operator’s Manual.

a. We asked the sponsor 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 the sponsor 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; and

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

The sponsor said that they commit to updating the operators manual to include all the items above. The sponsor’s promise to include these items in the operator’s manual is conditionally acceptable, pending our receipt of the revised operator’s manual and review of these items.

6. In Request 11, we noted that the KXL System incorporates wireless remote control and RFID, yet we were not able to find information on the effective radiated power of either wireless device, nor were we able to find information on the communication service or protocol used by the wireless remote control. We asked the sponsor to provide this information and also address all the issues raised in the 2013 FDA guidance Radio Frequency Wireless Technology in Medical Devices (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/tcm077210.htm), including performing wireless coexistence testing or submitting a justification as to why wireless coexistence testing is not needed.

The sponsor responded as follows:

a. RFID reader ENG-00754
• 13.56 MHz Reader/Writer
• Integral Antenna: Maximum 4” Read Range
• US/FCC number SX90RFID1
• Max output power is 200 mW
• Meets: ISO18000-3, ISO15693

The sponsor noted that measured emissions from the RFID were considerably below CISPR 11 and FCC limits. According to the sponsor, coexistence testing is not needed.

The sponsor submitted some of the information needed to assess this wireless function of the device, and this is (partially) acceptable. However, the sponsor’s implication is not valid.

Medical equipment that has a radiated RF immunity of 3 V/m would need to be kept at least 0.54 m (almost 2’) from the device. Furthermore, both implantable and non-implantable medical devices have been shown to be susceptible to RFID readers operating at 13.56 MHz. The sponsor should be asked to explain how interference to implantable and non-implantable medical devices in the vicinity of the RFID reader will be mitigated.

b. Wireless remote control: ENG-01085
• FCC ID SXJ87027-T
• Frequency Range 2402 MHz to 2476 MHz
• Max Effective power: 0.501 mW

According to the sponsor, 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 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 the sponsor discussed the low duty cycle of the receiver, the sponsor did not mention a duty cycle for the transmitter, so the assumption is that it is on continuously. The sponsor should be asked to submit wireless coexistence test results for this service or a valid rationale for not performing wireless coexistence testing.

7. In Request 12 we noted that 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, mistakes and accidents do happen. We said that 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 the sponsor 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”.

The sponsor said that they commit to updating the operators manual and device label to include these items. The sponsor’s promise to include these items in the operator’s manual is conditionally acceptable, pending our receipt of the revised operator’s manual and a reproduction of the device label and review of these items.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
03/27/2015
Memorandum

Date: March 6, 2015

From: Senior Electronics Engineer (Jeffrey L. Silberberg), CDRH/OSEL/DBP

Subject: EMC consult for NDA203324 Avedro KXL UV irradiation system

To: Brad Cunningham, CDRH/ODE/DOED/DSDB

To: Dexiu Shi, CDRH/ODE/DOED/DSDB

cc: Maritze Ortega, CDRH/ODE/DOED/DSDB

Scope

This is in confirmation of changes in EMC labeling that the sponsor promised to make and further additional EMC information that, in response letter dated February 12, 2015, the sponsor promised to submit.

Recommendations

We are waiting on the sponsor for the following:

- Retesting to be completed and the report to be received from the test lab to verify EMC following a change in design.

Meanwhile, more (additional) 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.

1. In Agency Request 12, we asked you to add MRI warnings to the Operator’s Manual and the device label. You submitted evidence that the “MR Unsafe” warning and symbol have been added to the Operator’s Manual. This is acceptable. However, you have not yet submitted evidence that the “MR Unsafe” symbol has been added to the device label. Please submit this evidence.

2. In Agency Request 10, we asked that you evidence of meeting the labeling requirements of IEC 60601-1-2:2007. You submitted a revised Operator’s Manual that included the needed information. For the most part it was complete and accurate. However, we noted some very minor errors, as follows:

   - 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.

   - In Table 5-4, the “Rated maximum output power” heading cell, the “W” should be in parentheses: “(W)”.

Analysis (review of AI responses)

1. In Agency Request 7, we said that 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, the sponsor had not specified the performance that was determined to be the Essential Performance of the KXL System. It’s possible that this could be derived from the specification of Criterion A; however, we asked the sponsor to specify the Essential Performance explicitly. We said that any future EMC testing to IEC 60601-1-2 submitted by the sponsor 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.

The sponsor replied 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/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

Avedro commits that future EMC testing will include testing to IEC 60601-1-2:2007, including immunity pass/fail criteria that conform to the requirements of the standard.

In addition, Avedro commits to updating the operators manual to include the essential performance statement.

These responses were conditionally acceptable, pending verification of addition of the Essential Performance statement to the Operator’s Manual.

The sponsor has submitted evidence that the Essential Performance statement has been added to the Operator’s Manual. This response is acceptable.

2. In Agency Request 8, we said that regarding immunity tests, IEC 60601-1-2:2007 indicates that for ME EQUIPMENT and ME SYSTEMS that have multiple voltage settings or autoranging voltage capability (for voltage input), 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 100-240 VAC/50 Hz. We noted that the AC input specifications of the KXL System are 100-240 VAC. We asked the sponsor to perform these tests as specified by IEC 60601-1-2 (i.e. repeat them at 100 VAC) and provide the results of this testing for review.

The sponsor replied that Avedro commits to conducting additional testing as requested and will submit [the] information as soon as it is available.

This response was conditionally acceptable, pending examination of the applicable EMC test report.

I made this request in a review memo dated February 2014. The sponsor has this month submitted an EMC test report dated May 2014 regarding testing of the KXL System that was performed in March 2014. The test report shows conformance with the requirements of IEC 60601-1-2:2007 discussed above. This response is acceptable.

3. In Agency Request 9, we said that the EMC test reports that the sponsor provided identified the modifications (listed below) 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 these modifications (listed below) will be included in all units to be marketed:

We said that if these features will not be included in the marketed version of the device, the sponsor should provide an explanation for why the testing that was completed is appropriate to support an EMC evaluation of the device or re-test the device without the additional modification that would not be included in a marketed device.

The sponsor replied that items b-h will be included in the marketed version of the product and that item a has been revised. According to the sponsor, this will be used during the additional IEC 60601-1-2 testing that is "currently being performed".

Reference ID: 3722908
This response was conditionally acceptable, pending examination of the test report of the additional EMC testing.

See the note above that the sponsor might need until March 12 for the retesting to be completed and the report to be received from the test lab.

4. 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. This includes the items listed below. We were not able to find any of these items in the Operator’s Manual.

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

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

      The sponsor has submitted evidence that the Essential Performance statement has been added to the Operator’s Manual. This response is acceptable.

   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.

      The sponsor has submitted evidence that this warning has been added to the Operator’s Manual. This response is acceptable.

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

      The sponsor has submitted evidence that these tables have been added to the Operator’s Manual. There are two very minor errors in the tables. The sponsor should be asked to correct them; however, they should not prevent approval of the KXL UV Illumination System.

      • 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.

      • In Table 5-4, the “Rated maximum output power” heading cell, the “W” should be in parentheses: “(W)”.

   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.

      The sponsor has submitted evidence that this information has been added to the Operator’s Manual. This response is acceptable.

   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.

      The sponsor has submitted evidence that the warning required by the FCC has been added to the Operator’s Manual. This warning adequately covers receiver issues. Therefore, this response is acceptable.

b. We asked the sponsor 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.

The sponsor has submitted evidence that this statement has been added to the Operator’s Manual. This response is acceptable.

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

The sponsor has submitted evidence that this statement has been added to the Operator’s Manual. This response is acceptable.

5. 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 has submitted evidence that the “MR Unsafe” warning and symbol have been added to the Operator’s Manual. This is acceptable. However, the sponsor has not yet submitted evidence that the “MR Unsafe” symbol has been added to the device label. The sponsor should be asked to submit this evidence.

Jeffrey L. Silberberg
16:12:06 -04’00’

Jeffrey L. Silberberg
Senior Electronics Engineer
Division of Biomedical Physics
OSLE/CDRH/FDA
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
03/27/2015
Date: January 6, 2015

From: Senior Electronics Engineer (Jeffrey L. Silberberg), CDRH/OSEL/DBP

Subject: Consult - Review of responses to EMC and wireless information requests for NDA203324 Avedro KXL UV irradiation system

To: Brad Cunningham, CDRH/ODE/DOED/DSDB
To: Maritze Ortega, CDRH/ODE/DOED/DSDB
To: Dexiu Shi, CDRH/ODE/DOED/DSDB

Scope

This is in response to your request for a review of the sponsor’s responses 1.11.4 to EMC and wireless information requested in a letter from FDA.

Recommendations

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.

3.5. Complete Response Item #9 (Type A Meeting Briefing Package Section 3.9)

We told you that 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/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

You then responded with a new EMC test report and a revised draft KXL System Operator’s Manual. The EMC test report VAL-00095-RPT dated May 13, 2014 shows that the EMC testing was repeated and used Essential Performance as the immunity pass/fail criteria. It also shows that the three immunity tests for which the tests are required to be performed at minimum and maximum line voltage were performed correctly. These aspects of your response are acceptable. However, a revised Essential Performance statement (see below) was used in the new EMC testing, the old Essential Performance statement appears in the Operator’s Manual, and the IEC 60601-1 test report (VAL-00091-RPT) states for subclause 4.3 that...

The Essential Performance statement in VAL-00095-RPT is as follows:

Essential Performance Defined by Operating Mode

During testing the KXL System was operating as follows: The KXL shall deliver UV-A energy over a non-adjustable fixed circular area (nominally 9 mm diameter) at a controlled intensity (within % of the user-
selected value) and user-selected time (within \textit{(b)(4)} \%, whichever is larger) to deliver the total fluence (J/cm\(^2\), \textit{(b)(4)} \%) chosen by the user. The total fluence may be delivered in a continuous single exposure, a series of pulsed (on/off) exposures, or in multiple sessions.

Please reconcile the Essential Performance statement among the EMC (60601-1-2) test report, the 60601-1 test report, and the Operator’s Manual or, alternatively, explain how these can be different. This information is needed so that we can determine if the KXL System is in conformity with IEC 60601-1-2:2007.

3.7. Complete Response Item #11 (Type A Meeting Briefing Package Section 3.11)

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, it is necessary to submit evidence of meeting the labeling requirements. This includes the items listed below. We were able to find most of these items in the draft revised Operator’s Manual. However, there are some errors, as discussed below. This information is needed so that we can determine if the KXL System is in conformity with IEC 60601-1-2:2007.

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

a) A statement of the performance that was determined to be Essential Performance;

As discussed above, you did include a statement of Essential Performance in the Operator’s Manual. However, it no longer agrees with what is in EMC test report VAL-00095-RPT. As stated above, please reconcile the Essential Performance statement among the EMC (60601-1-2) test report, the 60601-1 test report, and the Operator’s Manual or, alternatively, explain how these can be different.

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

While you did include the four required tables, there are numerous errors in Table 5-3 and Table 5-4. These errors are discussed below.

Additional and extended items

1. The EMC test report VAL-00095-RPT dated May 13, 2014, identified the modifications below that were made to the KXL System in order to pass the \textit{(b)(4)} tests. Please affirm that all of these modifications will be included in all production units.

<table>
<thead>
<tr>
<th>Modifications Required for Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modifications were required for the following tests:</td>
</tr>
<tr>
<td>In order to be compliant \textit{(b)(4)}, the following modifications were implemented.</td>
</tr>
</tbody>
</table>

Reference ID: 3722913
Prior to these modifications, 

2. There are errors in EMC guidance tables 5-3 and 5-4 in the Operator’s Manual, as discussed below. Please correct them. This information is needed so that we can determine if the KXL System is in conformity with IEC 60601-1-2:2007.

3. In the Operator’s Manual, the Symbol Table, the text shown for the non-ionizing symbol (#17) is confusing and misleading. Please change to something like “this device includes RF transmitters”. This information is needed to help assure the safety and effectiveness of the KXL System.

**Intended use**

The KXL System is an electronic medical device intended to deliver ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of (riboflavin ophthalmic solution). According to the sponsor, irradiating creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The KXL System is shown in Figure 1.

While the sponsor does not specify the intended use environments explicitly, it can be assumed that the system will be used in hospitals, clinics, and doctors’ offices.

**Device description**

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 exposure time, and UV intensity) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with (riboflavin ophthalmic solution) and a radio-frequency identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user selectable power density levels and the maximum allowable dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the
The UV irradiance dose is the product of the intensity of the irradiance and the exposure time. The following are the treatment parameters that the sponsor claims will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA.

Induction Period: 30 minutes
Irradiance: 3 mW/cm²
Exposure Time: 30 minutes

Although the submission might include appendices that describe wider treatment parameters that are available on devices sold outside of the United States, the sponsor claims that all devices sold commercially in the United States will have treatment specifications limited by the RFID activation card to those listed here.

The KXL System is a portable system with an articulating arm that houses the illumination system at the end. The articulating arm allows movement of the system for alignment of the UV Beam to the patient’s cornea. The articulating arm sits on top of a floor stand that houses an internal battery that powers the system. The battery is recharged by a system internal charger from a standard AC outlet. The complete optics assembly can be moved in x, y, and z. A wireless remote controls all system movements.

Table 1 shows excerpts from the KXL System specifications.

<table>
<thead>
<tr>
<th>Table 1: KXL System Specifications (excerpts)</th>
</tr>
</thead>
</table>

Reference ID: 3722913
A system console houses the user interface and the RFID reader. The user interface controls all treatment parameters that are set through a touch screen PC running Windows Embedded Standard. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable dosage (in J/cm²) for the system. According to the sponsor, the software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console and there are more than zero treatments remaining.

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

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. Both lasers are controlled.
Treatment parameters entered by the user (power, time and energy) are verified against the parameters stored in the RFID activation card. Only if all three entered parameters are within the respective ranges allowed on the RFID activation card, the user is allowed to proceed with the treatment.

The RFID activation card is programmed with an initial number of treatments for which it may be used. When scanned, the number of treatments remaining is decremented by one until the card is empty. An RFID activation card can only be used if it is identified by the system’s cryptography software module as a certified Avedro-created tag and if its country code matches that of the KXL System. A given multi-use RFID activation card will be accepted only if it contains at least one remaining treatment. Once a multi-use RFID activation card has been scanned, the user is given a visual indication of the number of treatments remaining on the card.

Therefore, it is not possible to simply store and re-write the current number of treatments remaining on a given multi-use disposable RFID activation card.

Since cards cannot be written by the KXL System, when a multi-use card is scanned, a previously unlocked memory block on the card is irreversibly locked. Since blocks can never be unlocked, this method prevents a malicious user from “rolling back” the number of treatments remaining on a given card. Since there are 64 blocks on a given tag, the number of treatments per card is limited to 64.

The position of the KXL System head can be manually adjusted and located appropriately over the patient’s eye by the physician. The position can then be fine-tuned using the wireless remote control, in an X, Y and Z direction. (See Figure 2.)

The joystick controls X and Y directions; the two buttons control the movement along the Z axis.
The approximate sequence of operation is as follows:

- Device power is turned on by the user. The system then checks for startup errors and if the system is starting up correctly, a system calibration is performed. The system checks whether a partial treatment has been detected. If not, the system prepares for a new treatment.

- To begin preparing for treatment, the user enters the induction period for the instillation of the (riboflavin ophthalmic solution) in minutes and seconds.

- The user sets the UV treatment time in minutes and seconds and the UV power.

- The user is instructed to scan an RFID treatment activation card using the RFID reader.

- The user is prompted to sync the alignment remote with the KXL System and does so by pressing the sync button on the alignment remote.

- The patient’s eye is prepared for treatment by the physician removing the epithelium. The KXL System then instructs the doctor to apply the (riboflavin ophthalmic solution).

- The KXL System tracks the induction time and notifies the user that the induction is complete.

- The UV treatment is then performed.

- The KXL System tracks the treatment time, turns off the UV and notifies the user when the treatment has been completed.

- Once the treatment has been completed, the system may be powered off.

**Analysis (review of responses to information requests)**

3.2. Complete Response Item #6 (Type A Meeting Briefing Package Section 3.6)

The sponsor indicated that they intended 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 the device, we asked the sponsor to modify the software of the device to implement a software lock-out of irradiated power above
3 mW/cm².

The sponsor replied that validation of the software lock-out has been completed. The sponsor submitted validation and verification test reports (PSPEC-00053-NDA and PSPEC-00054-NDA, respectively) and drafts of the following supportive documents modified accordingly:

• PSPEC-00027-NDA
• PSPEC-00030-NDA
• PSPEC-00031-NDA
• PSPEC-00034-NDA
• PSPEC-00036-NDA
• PSPEC-00037-NDA
• PSPEC-00039-NDA
• PSPEC-00040-NDA

While I defer to the software reviewer regarding the software aspects of this change and the documentation, from an EMC standpoint, this response appears to be acceptable.

3.3. Complete Response Item #7 (Type A Meeting Briefing Package Section 3.7)

The sponsor indicated

The sponsor indicated that validation activities for the Homogeneity Measurement Master Validation plan (VAL-0005) were ongoing. We asked the sponsor to provide the results of these validation activities.

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

I am addressing this item because it is in with the EMC items. In my opinion, it appears that the sponsor has submitted evidence of the validation promised and the test report appears to show that the device passed the tests. Thus, it appears to me that this response is acceptable.

3.4. Complete Response Item #8 (Type A Meeting Briefing Package Section 3.8)

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

In the sponsor’s 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. We asked the sponsor to 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 the sponsor to be consistent in their claims of conformity. Finally, we asked the sponsor to submit an FDA Form 3654 for each standard to which conformity was claimed.

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

a. In Table 6, ISO 14971:2007/(R)2010 was 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.


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

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. We told the sponsor that if they decided to keep these declarations, [FDA Forms 3654 specify the version and date of publication], we would like them to add this information to Table 6 of the application.

The sponsor replied that 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 does indeed correct the errors in former Table 6. This response is acceptable.
### Table 7: List of Recognized Consensus Standards

<table>
<thead>
<tr>
<th>STANDARD</th>
<th>FDA RECOGNITION NUMBER</th>
<th>TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAMI/ANSI/ISO 14971:2007/(R)2010</td>
<td>5-70</td>
<td>Medical devices – Application of risk management to medical devices</td>
</tr>
<tr>
<td>ISO 13485:2003</td>
<td>--</td>
<td>Medical devices – Quality management systems – Requirements for regulatory purposes</td>
</tr>
<tr>
<td>IEC 60601-1-6:2006 ED 2.0</td>
<td>--</td>
<td>Medical Electrical Equipment – Part 1-6: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Usability</td>
</tr>
<tr>
<td>IEC 62471:2006 ED 1.0</td>
<td>12-249</td>
<td>Photobiological safety of lamps and lamp systems</td>
</tr>
<tr>
<td>ISO 15223-1:2012</td>
<td>5-73</td>
<td>Medical Devices. Symbols to be used with Medical Device Labels, Labeling and Information to be supplied. General Requirements.</td>
</tr>
<tr>
<td>IEC 62366:2008</td>
<td>5-50</td>
<td>Medical Devices-Application of usability engineering to medical devices</td>
</tr>
</tbody>
</table>

The sponsor replied that to address item #e, FDA Form 3654 for IEC 60601-1-6 has been updated and is consistent with the testing performed in the attached 60601-1 Test Report. The revised FDA Form 3654 that the sponsor submitted is correct. This response is acceptable.

The sponsor replied that to address item #g, FDA Form 3654 for IEC 60601-1-2 has been updated and is consistent with the testing performed in the attached VAL-00095-RPT. The revised FDA Form 3654 that the sponsor submitted is correct. This response is acceptable.

The sponsor also submitted a revised FDA Form 3654 for IEC 60601-1:2005 that has been updated to be consistent with the testing performed in the attached VAL-00091-RPT. The revised FDA Form 3654 that the sponsor submitted is correct. This response is acceptable.

#### 3.5. Complete Response Item #9 (Type A Meeting Briefing Package Section 3.9)

We told the sponsor that 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, the sponsor 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 the sponsor to specify the Essential Performance explicitly. We recommended that any future EMC testing to IEC 60601-1-2 that the sponsor 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.

Reference ID: 3722913
The sponsor 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/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

The sponsor then responded with a new EMC test report and a revised draft KXL System Operator’s Manual. The EMC test report VAL-00095-RPT dated May 13, 2014 shows that the EMC testing was repeated and used Essential Performance as the immunity pass/fail criteria. It also shows that the three immunity tests for which the tests are required to be performed at minimum and maximum line voltage (see 3.6/3.10 below) were performed correctly. These aspects of the sponsor’s response are acceptable. However, a revised Essential Performance statement (see below) was used in the new EMC testing, the old Essential Performance statement appears in the Operator’s Manual, and the IEC 60601-1 test report (VAL-00091-RPT) states for subclause 4.3 that

The Essential Performance statement in VAL-00095-RPT is as follows:

**Essential Performance Defined by Operating Mode**

During testing the KXL System was operating as follows: The KXL shall deliver UV-A energy over a non-adjustable fixed circular area (nominally 9 mm diameter) at a controlled intensity (within \( \text{\%} \) of the user-selected value) and user-selected time (within \( \text{\%} \), whichever is larger) to deliver the total fluence (J/cm², \( \text{\%} \)) chosen by the user. The total fluence may be delivered in a continuous single exposure, a series of pulsed (on/off) exposures, or in multiple sessions.

The sponsor should be asked to reconcile the Essential Performance statement among the EMC (60601-1-2) test report, the 60601-1 test report, and the Operator’s Manual or, alternatively, explain how these can be different. This information is needed so that we can determine if the KXL System is in conformity with IEC 60601-1-2:2007.

### 3.6. Complete Response Item #10 (Type A Meeting Briefing Package Section 3.10)

There are 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 original EMC test report showed that the testing was performed only at VAC/Hz. We noted that the AC input specifications of the KXL System are 100-240 VAC. We asked the sponsor to perform these tests as specified by IEC 60601-1-2, i.e. repeat them at 100 VAC and submit the results of the testing.

The sponsor replied that these tests were performed correctly as evidenced by new EMC test report VAL-00095-RPT dated May 13, 2014. The report shows that these three tests were performed at the minimum and maximum power input line voltages. This response is acceptable.

### 3.7. Complete Response Item #11 (Type A Meeting Briefing Package Section 3.11)

IEC 60601-1-2:2007 specifies requirements for testing and for labeling. In order to demonstrate conformity with the standard (which the sponsor claimed), in addition to evidence of meeting the testing requirements of the standard, it is necessary 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. The sponsor then submitted a revised Operator’s Manual. The acceptability of the EMC labeling items is discussed below. This information is needed so that we can determine if the KXL System is in conformity with IEC 60601-1-2:2007.

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

i) A statement of the performance that was determined to be Essential Performance;
As discussed above, the sponsor did include a statement of Essential Performance in the Operator’s Manual. However, it no longer agrees with what is in EMC test report VAL-00095-RPT. As stated above, the sponsor should be asked to reconcile the Essential Performance statement among the EMC (60601-1-2) test report, the 60601-1 test report, and the Operator’s Manual or, alternatively, explain how these can be different.

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.

This warning has been included in the Operator’s Manual. This response is acceptable.

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

While the sponsor did include the four required tables, there are numerous errors in Table 5-3 and Table 5-4. These errors are discussed below.

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.

The Operator’s Manual now includes this information for both transmitters. This response is acceptable.

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.

The Operator’s Manual now includes this information for both transmitters. This response is acceptable.

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

1. 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.

The FCC warning includes a similar statement. This is acceptable.

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

The Operator’s Manual now includes this statement. This response is acceptable.

This should have been a separate item:

The KXL System incorporates a wireless remote control and radio frequency identification (RFID) capabilities. As noted above, requested that the sponsor you provide a software lockout of powers in excess of 3mW/cm². Thus, RFID concerns will no longer be applicable in the absence of a RFID mechanism. However, we did still have remaining concerns regarding the effective radiated power of the wireless device. The sponsor 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 the wireless technology used is the 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 the sponsor discussed the low duty cycle of the receiver, the sponsor did not mention a duty cycle for the transmitter, so the
assumption is that it is on continuously. We asked the sponsor to submit wireless coexistence test results for this service or a valid rationale for not performing wireless coexistence testing.

The sponsor’s response is as follows:

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 that is ISO/IEC 17025 accredited. As outlined in the attached 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.

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.

Based on the results of the coexistence test 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 conclusion of the coexistence testing was “There were no issues during the testing process. This response is acceptable.

3.8. Complete Response Item #12 (Type A Meeting Briefing Package Section 3.12)

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, we advised proper precautions for inclusion in the sponsor’s labeling. Thus, we recommended that 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 the sponsor 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. We noted that 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 submitted a revised KXL Operator’s Manual, including a reproduction of the device label, showing that the ASTM MRI terminology has been included in the warning and the ASTM symbol has been included in the manual and on the device label. This response is acceptable.

Additional and extended items

1. The EMC test report VAL-00095-RPT dated May 13, 2014, identified the modifications below that were made to the KXL System in order to pass the tests. The sponsor should be asked to affirm that all of these modifications will be included in all production units.

Modifications Required for Compliance
Modifications were required for the following tests:

In order to be compliant the following modifications were implemented.

Prior to these modifications,

We said the following paragraph the last time the device required modifications in order to pass EMC testing, but the new EMC test report clearly states that without the modifications listed above, the device would fail tests. So I don’t think the paragraph is valid this time.

[If these features will not be included in the marketed version of the device, the sponsor should submit an explanation for why [how] the testing that was completed is appropriate to support an EMC evaluation of the device or re-test the device without the additional modification[s] that would not be included in a marketed device.]

2. There are errors in EMC guidance tables 5-3 and 5-4 in the Operator’s Manual, as discussed below. The sponsor should be asked to correct them. This information is needed so that we can determine if the KXL System is in conformity with IEC 60601-1-2:2007.
3. In the Operator's Manual, the Symbol Table, the text shown for the non-ionizing symbol (#17) is confusing and misleading. The sponsor should be asked to change to something like “this device includes RF transmitters”. This information is needed to help assure the safety and effectiveness of the KXL System.

Jeffrey L. Silberberg
2015.03.27
16:17:05 -04'00'

Jeffrey L. Silberberg
Senior Electronics Engineer
Division of Biomedical Physics
OSD/CDRH/FDA
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
03/27/2015
Memorandum

Date: March 24, 2015

To: Bradley Cunningham, MSE, RAC, LCDR, Branch Chief, DOED/DSDB
Maryam Mokhtarzadeh, MD, Medical Officer, DOED
Malvina Eydelman, MD, DOED Division Director

From: Dexiu Shi, Ph.D., Physicist and Vision Scientist, CDRH/ODE/DOED/DSDB

Doc# NDA203324 - Riboflavin Ophthalmic Solution/KXL System
Drug: Riboflavin Ophthalmic Solution
Device: KXL System
Sponsor: Avedro

Subject: Intercenter/Combination Products Consult on Device Safety
Requested by Jacquelyn Smith, M.A., CDER/OND/OAP/DTOP, Senior Regulatory Health Project Manager

INTRODUCTION:

Proposed Indications for Use:

Avedro is submitting an Initial New Drug Application for riboflavin ophthalmic solution / KXL® System.

The KXL® System is a UVA irradiation system whereby an electronic medical device with a light emitting diode (LED) is used to deliver a dose of UVA light to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Corneal collagen cross-linking improves the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma. Exposure of the cornea to UVA after topical administration of riboflavin induces cross-linking of the corneal collagen fibrils with a resultant increase in tensile strength of the collagen fibrils.
DEVICE OVERVIEW - 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 Photrex or Photrex Viscous (riboflavin ophthalmic solution). UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System.

Figure 1 Overview Illustration of the KXL System

Figure 2. Wireless Remote
The Optics Head houses the UVA irradiation mechanism. UVA radiation is generated by a UV LED. 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.

The LED is manufactured to emit UVA radiation at a wavelength of 365 nm.

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.

Alignment lasers are used to aid the user in focusing the beam on the patient’s cornea. To correctly position the UV beam onto the cornea, two targeting lasers are used.

Both lasers are controlled. Fine alignment of the UV beam through observation of the alignment lasers is controlled through a wireless remote and an internal drive system. Treatment parameters are entered using a touch screen user interface.

Both lasers are controlled.

Figure 3 provides an illustration of the X, Y & Z alignment.

The KXL System includes a Radio Frequency Identification (RFID) reader and RFID activation card. The RFID activation cards are supplied with Photrexa or Photrexa Viscous (riboflavin ophthalmic solution) and determine the allowable ranges for user-selectable treatment parameters for the system. 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 to be marketed in the

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Reference ID: 3722080
United States, the maximum allowable treatment parameters will be limited to 3 mW/cm² for 30 minutes and a maximum energy density of 5.4 J/cm².

The sponsor modified the software of the to-be-marketed device to implement a software lock-out of the irradiated power above 3 mW/cm². 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.

The following treatment parameters provided by the RFID activation card

- **Induction Period:** 30 minutes
- **Irradiated intensity:** 3 mW/cm²
- **Total Energy:** 5.4 J/cm²
- **Exposure Time:** 30 minutes

Table 1 shows excerpts from the KXL System specifications.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical</strong></td>
<td>Battery Powered: 12V 35 Ah SLA</td>
</tr>
<tr>
<td></td>
<td>Line voltages 100-240 volts AC</td>
</tr>
<tr>
<td></td>
<td>Single Phase RMS, 50/60 Hz</td>
</tr>
<tr>
<td></td>
<td>User accessible Fuses: 250 V~</td>
</tr>
<tr>
<td><strong>Energy Delivery</strong></td>
<td>UV Radiation</td>
</tr>
<tr>
<td></td>
<td>3 mW/cm²</td>
</tr>
<tr>
<td></td>
<td>365 nm</td>
</tr>
<tr>
<td><strong>External Interfaces</strong></td>
<td>USB 2.0</td>
</tr>
<tr>
<td><strong>Battery Life</strong></td>
<td>16 hours</td>
</tr>
<tr>
<td><strong>(normal operating conditions)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**INITIAL REVIEW OF ORIGINAL SUBMISSION**

The sponsor states that:

- The (riboflavin ophthalmic solution) / KXL® System was granted orphan drug designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.
- The (riboflavin ophthalmic solution) / KXL® System was granted orphan drug designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.

- There is no FDA approved therapy in the US for the treatment of keratoconus or corneal ectasia following refractive surgery, two orphan indications for which patients are eagerly awaiting a therapeutic treatment option. The (riboflavin ophthalmic solution) / KXL® System addresses a significant unmet medical need in these two orphan patient populations.

- The (riboflavin ophthalmic solution) / KXL® System received CE mark as a commercial medical device in November 2010 and is commercially available throughout Europe.

**Reviewer Comment:** Clinical Reviewer, Maryam Mokhtarzadeh, MD, identified that:

- Although the NDA was initially submitted for a drug product with the proprietary name in the most recent submission the sponsor appears to be requesting the following proprietary names for their Riboflavin product: Photrexa and Photextra This request is being made since “At a teleconference held on 22 May 2012 between Avedro and the Division of Medication Error Prevention and Analysis (DMEPA), Avedro was notified of DMEPA’s preliminary findings that the proposed proprietary name, was unacceptable

- The proposed IFU includes 2 orphan drug designations (keratoconus and postrefractive ectasia), however, CDRH has approved at least one product for keratoconus (i.e., Intacs) and therefore it is unclear whether this will present a conflict due to the status of the current submission as a combination product.

**REVIEW SUMMARY:**

**Devices Information**

In section 3.2 Regional Information of Device-Information, the following information is provided:

**The 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 (riboflavin ophthalmic solution). Irradiating the Photrexa or Photrexa creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System.
The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient’s cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with Photrexa or Photrexa (riboflavin ophthalmic solution) and a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

UVA treatment

This clinical study is to assess the efficacy and safety of the UV-X™ Illumination System for performing corneal collagen cross-linking (CCCL) for the treatment of corneal ectasia after refractive surgery and progressive keratoconus. The UV-X™ system is a combination product consisting of a UVA 365 nm wavelength light source and Riboflavin 0.1% ophthalmic solution, administered in conjunction with the UVA light as a photosensitizer.

For all listed three studies, irradiance at 3 mW/cm² is applied for 30 minutes while maintaining the total dose at 5.4 J/cm² at the corneal surface. The following are the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA.

- Induction Period: 30 minutes
- Irradiance: 3 mW/cm²
- Total Energy: 5.4 J/cm²
- Exposure Time: 30 minutes

Regarding UVA radiation safety:

The sponsor states the KXL System complies with IEC 60601-1 and IEC 60825-1 (Safety of laser products) and the IEC 62471 (Photobiological safety of lamps and lamp systems) (page 83). However, the UVA light is for treatment, thus these IEC and/or ISO standards are not applicable. Since UVA light is for treatment, thus the IEC and/or ISO standards (e.g., IEC 60825-1, and Iso15004-2) for laser safety and light hazard protection are not applicable. Scientific literatures are used in my review of the evaluation of UVA eye safety.

- UVA treatment parameters

The UVA total energy is the product of the intensity of the UVA beam (irradiance) and the UVA irradiation time. A number of research studies demonstrate that the overall cross-linking effect depends upon the total UVA radiant exposure (i.e. photobiological dose or total energy delivered). Researches for corneal collagen cross-linking has been to use 0.1% riboflavin solution and 365/370 nm UVA at 3 mW/cm2 irradiance for 30 minutes, which is equivalent to 5.4 J/cm² radiant exposure were supported by many
literatures that it is below the damage thresholds of UVA for the corneal endothelium, lens, and retina \[1, 2, 3\]. Therefore, the UVA dose density of 5.4 J/cm² has been used as a kind of “gold standard” for safety assessment for the similar cross-link study (i.e., 365 nm, 0.1% riboflavin). The total UVA energy in excess of 5.4 J/cm² will be potentially risk.

The sponsor stated that the KXL Systems sold commercially in the United States uses a UVA light (365 nm) at an intensity of 3 mW/cm² for maximum exposure up to 30 minutes, thus the total energy will be within 5.4 J/cm². Accordingly, the proposed UVA treatment parameters are considered to be safe. In addition, I found from Avedro webpage, it’s claimed that:

“The KXL® System achieves Accelerated Cross-Linking in just minutes by increasing the UVA power and reducing the exposure time while maintaining the same total energy on the eye as standard cross-linking. It is the first and only cross-linking system manufactured with Accelerated Cross-Linking with continuous wave illumination.”

In recent times, there has been a noticeable increase in studies for developing the accelerated treatment protocols over a significantly shorter exposure period. However, there have been multiple reports that suggest that the overall cross-linking effect depends on the UVA irradiance (i.e., Intensity (W/cm²)). There is the safety concern that higher irradiance (> 3 mW/cm²) may induce potential radiation hazard to the eyes.

References:


Reviewer Comment: The KXL Systems sold commercially in the United States uses a UVA light (365 nm) at an intensity of 3 mW/cm² for maximum exposure up to 30 minutes, thus the total energy will be within 5.4 J/cm². Accordingly, the proposed UVA treatment parameters are considered to be safe. There is the safety concern that UVA exposure at higher irradiance (>3 mW/cm2) and/or higher total energy (>5.4 J/cm²) may induce potential radiation hazard to the eyes. The sponsor indicates a Radio Frequency Identification (RFID) activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The detailed discussion on RFID is present at following section.
• The Radio Frequency Identification (RFID)

The RFID reader reads RFID activation cards which are supplied with Photrex or Photrex (riboflavin ophthalmic solution) and determine the allowable ranges for user-selectable treatment parameters for the system. 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 to be marketed in the United States, the maximum allowable treatment parameters will be limited to 3 mW/cm^2 for 30 minutes and a maximum energy density of 5.4 J/cm^2.

The sponsor claims that the RFID activation card to be used in the United States is a card (a specialized treatment card that contains a set of treatment parameters which provide limits for the allowable power density (mW/cm^2) and maximum energy density (J/cm^2)). Both Power and Energy parameters have lower, upper and incremental limits that will be customized for sales in the United States. Once the RFID activation card is scanned, the treatment parameters entered by the user (power and energy) are verified against the parameters stored in the RFID activation card. Only if all entered parameters are within the respective ranges allowed on the RFID activation card, the user is allowed to proceed with the treatment.

On Page 21, 3.2.R it states:

![Figure 13: KXL System UV Treatment Parameters Screen](image)

Reference ID: 3722080
The user confirms the entered treatment parameters as shown in below figure:

**Reviewer Comment:** The sponsor states that the RFID activation cards supplied in the United States will not allow treatment unless the Total Energy is set to 5.4J/cm² and the UV.

The sponsor needs to clarify whether UV radiation intensity of the US version KXL system is locked at the lowest setting (i.e. 3mw/cm²). If so, please describe the method, such as, software control and/or hardware safeguard to shut down or black the UVA beam once the UV radiation intensity is greater than 3mw/cm² (see deficiency#1).

**Figure 44:** KXL System Crate Label
- **Homogeneity of the UVA irradiance**

Spoerl, et al. [1] pointed that for UVA exposure, if hot spots are present, the damage thresholds may be exceeded locally, leading to localized endothelial damage, although the average irradiance may be less than damage thresholds. Therefore, clinically used light sources should be homogeneous of the irradiance across the beam area.

Reference:


Device Description (page 9) indicates that KXL UVA radiation is generated by [LED (365 nm)].

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. The sponsor states the UV Homogeneity Measurement is performed in accordance to KXL System Optical Assembly Calibration (WI-01102-01) to verify that the UV Beam has been properly focused. The acceptance criteria is defined as that the homogeneity (flatness) of the beam at the focal plane shall be [6%] RMS. The KXL System Optical Assembly UV Homogeneity Measurement Master Validation (VAL-00005) is provided in Appendix 2.24.

**Reviewer Comment:**

- The proposed Homogeneity Measurement Master Validation plan (VAL-00005) is acceptable. However, no test result was presented. The sponsor needs to provide the test results/evidence demonstrating the UVA treatment beam is homogeneous over entire cornea area.

- The sponsor states that “UVA radiation is generated by [UV LED (365nm)].” The [may be hazard to the device operator. The sponsor should explain any mitigation(s) used for protecting the eye safety for operators (deficiency#2).
• UV beam align system

The sponsor states that to correctly position the UV beam onto the cornea, two targeting lasers are used:

Both lasers are controlled

Reviewer Comment: The KXL system used two targeting lasers for illumination. The sponsor claimed that both targeting lasers are eye-safe (Class I laser) based on IEC 60825-1:2007. They do not provide the technical characteristics of the two lasers (laser name/model, maximum output power). This basic information is necessary for the review of the laser safety (deficiency #3).

Equivalency of UVX and KXL Systems

The sponsor states that:

The UV-X Illumination System was utilized during the Phase III clinical study reported in the NDA. Avedro, Inc. believes that the KXL System for which commercial approval is being requested is equivalent to the UV-X Illumination System which was used during the Phase III clinical study. Table 8 compares the specifications of the UV-X Illumination System with the KXL System.
Table 8: Comparison of UV-X Illumination System (Phase III) Specifications with the KXL System (Commercial) Specifications.

<table>
<thead>
<tr>
<th></th>
<th>Phase III (UV-X)</th>
<th>Commercial (KXL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UVA System</strong></td>
<td>UV-X Illumination System</td>
<td>KXL System</td>
</tr>
<tr>
<td><strong>Device Type (Classification)</strong></td>
<td>LED illumination device (Class II)</td>
<td>LED illumination device (Class II)</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>Wavelength: 365 (^{0}\text{nm})</td>
<td>LED: Wavelength: 365 (^{0}\text{nm})</td>
</tr>
<tr>
<td><strong>Device Configuration</strong></td>
<td>Illumination system at end of an arm, attached to a floor stand or a patient bed</td>
<td>Illumination system at end of an articulated arm on top of floor stand, wireless remote control and a system console</td>
</tr>
<tr>
<td><strong>Light Emission</strong></td>
<td>Continuous wave (CW)</td>
<td>Continuous wave (CW)</td>
</tr>
<tr>
<td><strong>Illumination Intensity</strong></td>
<td>3.0 mW/cm(^2)</td>
<td>3.0 mW/cm(^2)</td>
</tr>
<tr>
<td><strong>Illumination Diameter(s)</strong></td>
<td>Variable steps 7.0, 9.0 and 11.0 (^{\text{mm}})</td>
<td>Fixed at 9.0 (^{\text{mm}})</td>
</tr>
<tr>
<td><strong>Treatment Time</strong></td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td><strong>Patient Positioning</strong></td>
<td>On bed</td>
<td>On bed</td>
</tr>
<tr>
<td><strong>Targeting System</strong></td>
<td>N/A</td>
<td>Laser crosshairs</td>
</tr>
<tr>
<td><strong>Focal Plane Setting</strong></td>
<td>Subjective (homogeneity of UV pattern)</td>
<td>Objective (crossed laser beams)</td>
</tr>
<tr>
<td><strong>Electric Power</strong></td>
<td>100V to 240 V</td>
<td>100 V to 240 V</td>
</tr>
<tr>
<td><strong>Intensity Check</strong></td>
<td>UV light meter delivered with UV-X System</td>
<td>Integrated UV light meter</td>
</tr>
<tr>
<td><strong>Laser and LED Safety Compliance</strong></td>
<td>IEC 60825-1</td>
<td>IEC 60825-1</td>
</tr>
<tr>
<td><strong>Electrical Safety Compliance</strong></td>
<td>IE 60601-1</td>
<td>IE 60601-1</td>
</tr>
</tbody>
</table>

Major differences are as follows:

| 1 | **Illumination Diameter(s)** | Variable steps 7.0, 9.0 and 11.0 \(^{\text{mm}}\) | Fixed at 9.0 \(^{\text{mm}}\) |
| 2 | **Targeting System**          | No target laser (aligned subjectively by the user) | Use two targeting lasers |
| 3 | **Focal Plane Setting**        | Subjective (homogeneity of UV pattern)              | Objective (crossed laser beams) |
| 4 | **Intensity Check**            | UV light meter delivered with UV-X System           | Integrated UV light meter |

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Reference ID: 3722080
On page 83, 3.2.R Regional Information, the sponsor states:

Both systems are LED based illumination systems with a wavelength of 365 nm. Both systems are continuous wave systems with an illumination intensity of 3.0 mW/cm² and a treatment time of 30 minutes. The illumination diameter is 9.0 mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm steps. The patient is positioned on a bed for treatment in a supine position with both systems. The KXL System includes an alignment focusing beam that allows for alignment of the treatment area. The UV-X System was aligned subjectively by the user. The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used an external light meter. Both systems comply with IEC 60601-1 and IEC 60825-1, and the KXL System also complies with IEC 62471.

**Reviewer Comment:** How those differences may affect the SE is discussed at below:

1. **The illumination diameters:** The illumination diameter is 9.0 mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm. The illumination intensity is given in 3 mJ/cm² which is the same value for UV-X and KXL system.

2. **Target system:** KXL uses two targeting lasers source with crosshairs. The UV-X System was aligned subjectively by the user. The target system used in KXL system was improved.

3. **Focus plane setting:** KXL uses crossed laser beam. The UV-X was set focus plane by observe the homogeneity of UV pattern to determine focus plan subjectively.

4. **Intensity Check:** The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used a light meter.

Clinical reviewer has the concern with the potential illumination diameters used in the trial include “Variable steps 7.0, 9.0 and 11.0 mm” while the device proposed to be marketed has an illumination diameter “Fixed at 9.0 mm”. For KXL, the device functionality has been limited compared to what was used in the clinical study. It is not clear what the repercussions of a fixed illumination beam diameter might be and how the labeling might need to instruct users regarding this difference between the device available and the device studied. Please see Dr. Mokhtarzadeh’s deficiency.
Non-Clinical Laboratory Studies

The following testing and validation materials are provided as appendices:

Appendix 1.1 - Product Requirements Specification
Appendix 1.2 - System Validation Test Plan (PSPEC-00032-NDA)
Appendix 1.3 - System Validation Test Report (PSPEC-00051-NDA)
Appendix 1.5 - System Verification Test Plan (PSPEC-00033-NDA)
Appendix 1.6 - System Verification Test Report (PSPEC-00052-NDA)

**Review Comment:** Additional information of test results is required.

On Page 4, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), it specified that:

6.2.6.4   Output power shall be controlled to \( \text{[redacted]} \)\%.
6.2.6.8   Power uniformity over the illuminated area shall be \( \text{[redacted]} \)\% RMS.

a. A tolerance range \( \text{[redacted]} \)\% is given for UVA output. Please provide your rationale for why this tolerance range is selected and/or the justification that the \( \text{[redacted]} \)\% illumination fluctuation will be safe for proposed treatment.

b. Please provide the test result to demonstrate power uniformity over the illuminated area is \( \text{[redacted]} \)\% RMS for KXL system (deficiency #4).

**LABELING (KXL Operator’s Manual)**

The sponsor provided two versions of KXL Operator’s Manual (i.e., ML-00002, 2011 and ML-00006, 2012) in Appendix 5.1. (device-info-appendices) We found there are discrepancies between these two versions, especially the Indications for Use/Intended Use are not identical. In version ML-00002, 2011 (page 3-1),\( \text{[redacted]} \) is included:

Page 14 – NDA 203324 – Engineering/Physics Review

Reference ID: 3722080
DEFIENCIES:

Based on my review, the following engineering and laser and optical radiation safety deficiencies have been identified:

1. The sponsor states a Radio Frequency Identification (RFID) activation card will be used to determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²) and the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA are as follows:

   Induction Period: 60 minutes
   Irradiance: 3 mW/cm²
   Total Energy: 5.4 J/cm²
   Exposure Time: 30 minutes

   Please clarify whether UV radiation intensity of the US version KXL system is locked at the lowest setting (i.e. 3mW/cm²). If yes, please descriptor the method, such as, any software control and/or hardware safeguard to shut down or black the UVA beam once the UV radiation intensity is great than 3mW/cm².

2. On Page 4-5, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), it specified that:

   6.2.6.4. Output power shall be controlled to %.
   6.2.6.8. Power uniformity over the illuminated area shall be % RMS.

   Please address the following concerns:

   c. A tolerance range (%) is given for UVA output. Please provide your rationale for why this tolerance range is selected and/or the justification that the % illumination fluctuation will be safe for proposed treatment.

   d. Please provide the test result to demonstrate power uniformity over the illuminated area is % RMS for KXL system.

3. You states that “UVA radiation is generated by UV LED (365nm).” Please address the following concerns:

   a. You only provided the Homogeneity Measurement Master Validation plan (VAL-00005) However, no test result was presented. Please explain the criteria of the homogeneity
and provide the test results to demonstrate the UVA treatment beam is homogeneous over entire cornea area.

b. Please be advised that [redacted] may be hazard to the device operator. The sponsor should explain any mitigation(s) used for protecting the eye safety for operators.

4. You state that the KXL system used two targeting lasers for illumination, and both targeting lasers are eye-safe (Class I laser) based on IEC 60825-1:2007. However, you do not provide the technical characteristics of the two lasers (laser name/model, maximum output power). Please provide this information. This basic information is necessary for the review of the laser safety.

In addition, it is unclear from your submission how the lasers and LEDs classification was determined; please provide detailed information for determination of laser/LEDs classification. This information will assist us in evaluating the laser and optical radiation safety analyses.

5. You provided two versions of KXL Operator’s Manual (i.e., ML-00002, 2011 and ML-00006, 2012) in Appendix 5.1. We found there are discrepancies between these two versions, especially the Indications for Use/Intended Use are not identical.
Please provide your explanation on the discrepancies and provide your final version of KXL Operator’s Manual for this study.

**REVIEWER OF AVEDRO’S RESPONSE (dated 2-21-14) TO CDRH INFORMATION REQUEST (dated 2-11-14)**

The above deficiencies were conveyed to the sponsor in an additional information request on Feb. 11, 2014. Each final version of device deficiency is copied below and followed by the sponsor’s response and reviewer’s comment.

**Agency Request 2:**

The sponsor states a Radio Frequency Identification (RFID) activation card will be used to determine the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage. The proposed treatment parameters that will be allowed by the RFID activation card in KXL Systems for the United States on are:

- Induction Period: 30 minutes
- Irradiance: 3 mW/cm²
- Total Energy: 5.4 J/cm²
- Exposure Time: 30 minutes

However, a RFID card may not be sufficient to lockout elevated power output that was not adequately studied in the clinical trials provided to support this marketing approval application. Please provide justification for how a RFID can appropriately limit the power output to safer levels.
Avedro Response:

RFID activation cards are a well-known security device used in many applications because of their robustness and inherent data protection capabilities. Avedro uses these same capabilities to ensure the system is used as intended. This is a three-part strategy:

1. The KXL system cannot be run without an authenticated Avedro RFID card inserted.
2. The cards use Therefore cards can be neither cloned nor altered.
3. At the Avedro facility, each card is

Details:

a. Programming:

The process used to program RFID activation cards dictates that the operator performs 100% verification of the treatment parameters on all programmed cards. In addition, a second operator performs 100% verification of the treatment parameters on all RFID cards.

b. Authentication

1. Each RFID activation card cannot be changed or modified.
2. Since the RFID activation card modifying the content in any way will fail the authentication process of the KXL system. Any modified or altered card will thus be detected and rejected.

Reviewer Comment: Sponsor’s justification for how a RFID can appropriately limit the power output to safer levels is acceptable. However, they need to clarify that, for US user, the maximum UVA output intensity will be lock at 3 mW/cm2. This deficiency has not been addressed satisfactorily.
Agency Request 3:

On Page 4-5, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), you specify that:

- 6.2.6.4. Output power shall be controlled to [REDACTED] %.
- 6.2.6.8. Power uniformity over the illuminated area shall be [REDACTED] % RMS.

Please address the following concerns:

a. A tolerance range [REDACTED] is given for UV-A output. Please provide your rationale for why this tolerance range is selected and/or the justification that the [REDACTED] % illumination fluctuation will be safe for proposed treatment.
b. Please provide the test result to demonstrate power uniformity over the illuminated area is [REDACTED] % RMS for KXL system.

Avedro Response:
Reviewer Comment: This response is partially acceptable.

The proposed beam diameter is 9.0 mm for KXL system. We believe the beam homogeneity should be tested and ensured within 9 mm, otherwise, larger or less than 3mw/cm² will result in an over or less UV dosage. Particularly, a hot spot (>3 mW/cm² irradiance) could cause local damage to the endothelium. Please provide your justification on why you believe the size employed to verify beam uniformity is sufficient compared to the 9 mm proposed treatment size.

Agency Request 4:

You state that “UVA radiation is generated by UV LED (365nm).” Please address the following concerns:

a. You only provided the Homogeneity Measurement Master Validation plan (VAL-00005). However, you did not provide any test results. Please provide this information and ensure you explain the homogeneity criteria and provide the test results to demonstrate the UV-A treatment beam is homogeneous over entire treatment area.

Reviewer Comment: The sponsor states that “The validation activities are ongoing. The estimated time frame for the completion of VAL-00005 is March 2014.” This question is pending for response.

b. Please be advised that [redacted] may be hazardous to the device operator. Therefore, please provide information regarding any mitigation method(s) used to address eye safety concerns for operators.

Avedro Response:

The validation activities are ongoing. The estimated time frame for the completion of VAL-00005 is March 2014.
Agency Request 5:

You state that the KXL system used two targeting lasers for illumination, and both targeting lasers are considered as a Class I laser based on IEC 60825-1:2007. However, you do not provide the basic technical characteristics of the two lasers. Please provide this information. In addition, it is unclear how you determined the classification of the lasers and LEDs. Please provide detailed information for how this determination was made so we may fully evaluate the laser and optical radiation safety analyses.

Avedro Response:
Reviewer Comment: The sponsor states that Test reports indicate each targeting laser met class 1 limits and sufficient safety margin is provided. This response is satisfactory.

REVIEWEW OF AVEDRO’S RESPONSE TO FDA CR (COMPLETE RESPONSE) LETTER DATED MARCH 14, 2014

The outstanding device issues identified from Avedro’s response (dated 2-21-14) have included in FDA’s Complete Response letter (dated 14 March 2014). Each final version of device deficiency is copied below and followed by the sponsor’s response and reviewer’s comments.

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 postmarket 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.

Avedro Response: [in briefing-meeting-typea-20140806 submission]

The differences stated in Table 8 do not encompass all differences between the device studied and the device that is intended to be marketed. As described in the NDA, the original sponsor of IND 77,882 under which the clinical studies were conducted was Peschke Medittrade. Per the original IND 77,882 submitted by Peschke Medittrade, the UVA illumination device utilized in the clinical studies was IROC’s UV-X Illumination System. In an IND amendment dated 7 May 2010, Avedro informed FDA of the change in sponsorship for IND 77,882 from Peschke Medittrade to Avedro, Inc. Also, Avedro’s UV-A device (the KXL System) was submitted to both IND 77,882 for investigational use and NDA 203-324 for proposed commercial use.

Table 5 and Table 6 present the device description, treatment settings, software and instructions for use for each of the systems and an assessment of equivalence. Avedro asserts that the differences between the systems do not impact the safety or effectiveness of the device because the UV treatment parameters that directly impact the dose of UV light between the systems are identical. As shown in Module 3.2.R Device Information Appendices, Appendix 3.1, the spectral output of the KXL System is equivalent to the spectral output of the UV-X Illumination System. Therefore, all specifications that directly impact dose are equivalent between the two systems.

**Reviewer Comment:** Avedro asserted that the differences between the systems do not impact the safety or effectiveness of the device because the UV treatment parameters that directly impact the dose of UV light between the systems are identical. However, they did not provide sufficient information to support. For example, the focal alignment differences raised the concern with substantial equivalency between UVX and KXL.

UV focal alignment differences between the IROC UVX and Avedro KXL Devices (cited from Table 5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IROC UV-X (used in UVX-001, UVX-002 and UVX-003)</th>
<th>Avedro KXL System (device to be marketed)</th>
<th>Sponsor’s Equivalence Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV Focal Alignment</td>
<td>User observes the riboflavin fluorescence to gauge beam shape to determine proper alignment.</td>
<td>Two visible aiming lasers provide direct alignment confirmation in x, y, and z directions.</td>
<td>The KXL System alignment system should be easier for users to correctly align the system compared to the more subjective process with the UV-X system, however, this difference should not impact the safety or effectiveness of the treatment delivered with the devices.</td>
</tr>
</tbody>
</table>
Avedro Response: (in mult-mod-info-amend.pdf)

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 in the clinical studies compared to the device proposed for marketing approval. In the agency’s 01 August 2014 preliminary comments, CDRH stated the following:

The information provided addresses our concern. The following additional concerns were raised: The instructions for use of the device studied differ from those you intend to market therefore we recommend that you revise your instructions for use to be consistent with the device studied. Otherwise, please explain the rationale for this difference. Please be advised that our labeling review is still ongoing, concurrent with our review of the file.

At the 06 August 2014 Type A Meeting, Avedro explained that 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.

Reviewer Comment: The KXL System alignment system objectively aligns the system. The procedure is independent of the riboflavin application and user’s observing capacity and experience. However, with UVX, the user observes the riboflavin fluorescence to gauge beam shape to determine proper alignment. This subjective method is NOT independent of the riboflavin application (diffusion) and user’s observing capacity and experience. Additional information on why the differences in focusing will not affect device performance was requested on 2/4/15.

Avedro Response to Question 2.d.i.2: Regarding system alignment

As described in Avedro’s response to Complete Response Item #5 (SN0027), the UVX system alignment is achieved by the user observing the riboflavin fluorescence to gauge beam shape to determine proper alignment while the KXL System utilizes two visible aiming lasers to provide direct alignment confirmation in the x, y and z directions. Both systems have a correct focal plane for treatment and a method for the user to identify the correct treatment plane.

The UVX device relies on a trained physician to find the best focus on the eye, recognizing that proper alignment results in a UVA beam with circular pattern and relatively sharp edges. The KXL System assists the trained physician, using two, class I,
laser crosses to assist in alignment. At proper focus (overlapped crosses) the KXL UVA beam results in a circular pattern with relatively sharp edges. Other than ease of use, differences in focusing procedure have no effect on device performance.

**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.

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/cm².

**Avedro Response: (in briefing-meeting-typea-20140806 submission.pdf)**

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/cm². 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 is in process and will be completed by July 2014.

**Avedro Respons: (in mult-mod-info-amend.pdf)**

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.6 (SN 0027, Module 1.6.2), where we committed to modifying the software of the to-be-marketed device to implement the software lock-out of the irradiated power above 3 mW/cm².

Validation of the software lock-out has been completed. Enclosed is the validation and verification test reports (PSPEC-00053-NDA and PSPEC-00054-NDA, respectively). As a result of this change, the following additional supportive documents have been revised:

- PSPEC-00027-NDA
- PSPEC-00030-NDA
- PSPEC-00031-NDA
**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.*

7. You indicate that

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

**Avedro Response:** (in briefing-meeting-typea-20140806 submission.pdf)

The validation activities for the Homogeneity Measurement Master Validation plan have been completed and results are provided in Final Report VAL-0005-RPT.

**Reviewer Comment:** The Homogeneity measurement master validation test was based on the following acceptance criteria:

The acceptance criteria given in VAL-0005 Rev B is:

1) Gage R&R

   meet the UV beam Homogeneity specification

2) All UV beam Homogeneity results were

**Reviewer note:** Basic Definitions of Gage R&R ([http://www.dmaictools.com/dmaic-measure/grr](http://www.dmaictools.com/dmaic-measure/grr))

Gage R&R (Gage Repeatability and Reproducibility) is the amount of measurement variation introduced by a measurement system, which consists of the measuring instrument itself and the individuals using the instrument. A Gage R&R study is a critical step in manufacturing Six Sigma projects, and it quantifies three things:

1. Repeatability – variation from the measurement instrument
2. Reproducibility – variation from the individuals using the instrument
3. Overall Gage R&R, which is the combined effect of (1) and (2)

The overall Gage R&R is normally expressed as a percentage of the tolerance for the CTQ (Critical-to-Quality) being studied, and a value of 20% Gage R&R or less is considered acceptable in most cases.
**Test results:** The sponsor stated that because all UV beam Homogeneity results were $^{(b)}(4)\%$ and the resulting Gage R&R met all of the predetermined acceptance criteria.

**Reviewer Comment:** The test report demonstrates that UV beam homogeneity measurement results were $^{(b)}(4)\%$ which met the predetermined acceptance criteria (i.e., $^{(b)}(4)\%$). *Deficiency#7 has been adequately addressed.*
RECOMMENDATION: Additional information is required.

There are unresolved issues regarding whether and how the device differences between the UV-X System and the KXL System will affect the safety and performance throughout the course of review. We also observed additional differences in sponsor’s presentation at the advisory committee meeting and from interactive review correspondence received March 16, 2015. Bruce Drum, Ph.D., vision scientist of DOED, has joined in the discussion on the device related deficiencies for this CR letter. Based on discussion with DOED management, we have following non-clinical deficiencies:

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 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.

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

/s/

JACQUELYN E SMITH
03/26/2015
From: Maryam Mokhtarzadeh, MD
ICIB/DOED/ODE

To: Bradley Cunningham, DSDB Branch Chief
Dexiu Shi, Physicist and Laser Reviewer
Tieuvi Nguyen, ICIB Branch Chief
Malvina Eydelman, DOED Division Director

Re: NDA 203324 (Response to Complete Response Letter – Initial Review provided 2/7/14)
Photrex, Photrex Viscous, KXL Device
riboflavin ophthalmic solution (20% dextran),
riboflavin ophthalmic solution (0% dextran),
UV-A Irradiation
(Previously: Riboflavin ophthalmic solution 0.12% (KXL system)
Avedro, Inc.

Proposed Indications for Use:
• For the treatment of progressive keratoconus
• For the treatment of corneal ectasia following refractive surgery

per device labeling:

Date: March 24, 2015

Recommendation: Additional Information Needed Prior to Making a Determination
(NDA terminology: Complete Response)

Introduction/Summary of Review Course:
This review encompasses the complete response and any additional information requested/reviewed
since the complete response (e.g. requested over the course of advisory committee meeting
preparations but sometimes received after the 2/24/2015 meeting).

I provided an initial review on February 7, 2014 for this file prior to a Complete Response action taken by
CDER. A meeting was held on August 6, 2014 with the Applicant to discuss the upcoming complete
response submission that the Applicant intended to submit (prior to official review). These responses were received by the agency September 29, 2014 and preparations for an advisory committee began shortly thereafter. The joint advisory committee met on February 24, 2015.

As the CDRH clinical reviewer on this NDA, I began this clinical review by providing deficiencies specific only to the device (ex., differences between the device to be studied and that to be marketed) - without resolution, these issues would preclude relevance of the entire dataset from a CDRH perspective. To date, neither my initial review nor the current review outlines the complete outcomes reported in the study reports. This is due to the fact that there were significant concerns with regard to the data that precluded a complete review on the last round of review (for example, differences between the device studied and the device to be marketed) and the fact that additional analyses are now needed (following the advisory committee’s recommendations) that will significantly impact the organization and presentation of the data. For example, poolability of data was a critical issue and the advisory committee recommended removal of subjects who were treated with a larger illumination diameter from the data sets. The committee furthermore stated that pediatric and adult corneas are different and that extrapolation across these populations is inappropriate. Therefore, in the absence of an organized presentation of data to review based on our current understanding of the critical issues in this file, a complete and final review of all outcomes will be deferred until corrected/revised datasets have been provided.

The review of this file has been complicated by many factors including the flaws and weaknesses of the study protocols (and resulting dataset) and differences of opinion between CDER and CDRH (particularly regarding the limitations and weaknesses of the studies and how these may have impacted the study and study results and how/whether these could be conveyed to the advisory committee).

**Overview:**

Pages 3-76 of this review describe the complete response.

Pages 77-112 of this review describes the interactive review performed on this round. This includes differences in the prespecified endpoints and analyses in the protocols and the endpoints and analyses in the final SAP and information requested interactively during review of the complete response and preparation for the advisory committee.

Page 111-113 describes the literature review conducted by CDRH’s DEPI group in OSB which is a separate CDRH review for this file. Note that due to time constraints imposed by the upcoming advisory committee meeting and the confusion generated regarding the use of literature on this file, I requested a very focused (limited) literature review from DEPI which they graciously provided under extremely tight deadlines.

Pages 113-115 briefly describes (1) the discussion at the advisory committee and alludes to the additional analyses recommended, (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 my Recommendation, significant concerns and major deficiencies to be communicated to the Applicant

Page 120 lists attachments to this review
REVIEW OF COMPLETE RESPONSE Received 9/29/2014:

From file 0028 submitted 9/29/2014: “mult-mod-info-amend” – Note that the deficiencies and Sponsor’s responses have been cut and paste into this review for the purpose of ensuring the accuracy of the information reported by the Applicant. The images cut and paste do not reflect this reviewer’s opinion but rather the Applicant’s statements. The reviewer comments and impressions appear as text in this document (rather than an image with a border) and therefore can be distinguished from the Applicant’s language.

Items #1 (DRUG CONSTITUENT PART) and #2 (DRUG FACILITY INSPECTION) pertain to CDER drug component/review items.

Item #3: DEVICE CONSTITUENT PART

3.1. Complete Response Item #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 postmarket 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.
Avedro Response:

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. In the agency's 01 August 2014 preliminary comments, CDRH stated the following:

The information provided addresses our concern. The following additional concerns were raised: The instructions for use of the device studied differ from those you intend to market. The instructions you intend to market advise the user [redacted]. Therefore we recommend that you revise your instructions for use to be consistent with the device studied [redacted]. Otherwise, please explain the rationale for this difference. Please be advised that our labeling review is still ongoing, concurrent with our review of the file.

At the 06 August 2014 Type A Meeting, Avedro explained [redacted] 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.

Reviewer Comments: The Applicant provided additional information regarding the devices and stated a rationale by which they provided us adequate information for our review to continue. As stated at the meeting in August, based on the information provided our preclinical and clinical review of the submission could continue. The differences between devices would continue to be assessed over the course of the resulting review.

I defer to other relevant members of the CDRH review team (i.e., software, engineering) to review the Applicant's response, as per their expertise. From a clinical perspective, the following were noted as significant differences requiring discussion at the advisory committee meeting (excerpts from CDRH slides and script appear below):

While the KXL System is the device proposed for marketing, all clinical data submitted in this NDA was obtained in studies using a different device, the UV-X. The applicant provided a comparison between the two devices. Both devices are non-contacting, UV light sources utilizing light emitting diodes (or LEDs) to deliver UV light at a wavelength of 365 nm. However, there are numerous differences between the UV device studied, and the one proposed for marketing.
Among many differences between the UV-X system studied and the KXL system proposed to be marketed which are listed in FDA’s backgrounder, we note the following:

First, the dimensions are very different. The KXL system is much larger and heavier than the UV-X system. The UV-X system requires mounting on a table top stand by the user while the KXL system is a standalone system on an independent wheeled console. (This alludes to the fact that these devices are not mere modifications of one another nor different versions along a development line but fundamentally different products with very different size and appearance. Therefore, there must be MANY differences between the devices and we are somewhat limited by what the Applicant provides us with regard to understanding the significant differences between the machines.)

The UV-X has the capability to be rotated and therefore to allow horizontal UV delivery to treat subjects in a sitting or supine position while the KXL system limits the patient position to the supine position. (The Applicant has stated that all patients were supine in the study, however, the protocol allows for positioning in a surgical chair or table with the subject reclining comfortably).

The UV-X system had three available beam diameters for investigators to choose between (7.5 mm, 9.5 mm, and 11.5 mm) while the KXL System only includes a 9.0 mm fixed diameter. These will be discussed in greater detail on the next slide.

Finally, for the UV-X system, UV focal alignment was subjective: the user observed the riboflavin fluorescence to gauge beam shape to determine proper alignment.
For the KXL system, the alignment is objective: Two visible aiming lasers provide direct alignment confirmation in x, y, and z Directions as will be discussed on a later slide.

Selection of Illumination Diameter (Aperture)

- Protocol:
  “The correct aperture setting (Small/ 7.5 mm, Medium/ 9.5 mm, Large/ 11.5 mm) will be selected for the size of the eye...”

- Site start-up and training:
  “…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.”

While the protocol directed investigators to select the correct illumination diameter setting based on the size of the eye, when asked how investigators were instructed to choose the appropriate illumination diameter for use, the applicant provided additional information, stating that “As part of site start-up and training, 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.”
Of subjects who were crosslinked in the ITT population:

According to the Applicant, no subjects received the small diameter (which was 7.5 mm)

All UVX-001 subjects received the medium diameter (which was 9.5 mm)

As listed in this table, 10 subjects in UVX-002 received the Large (11.5 mm) while 61 subjects are identified to have received the medium diameter. 7 subjects in UVX-003 received the Large (11.5 mm) while 56 subjects are identified to have received the medium diameter.

While the majority of subjects in the clinical studies were treated with the medium or 9.5 mm setting of the UV-X system, please note that no subjects studied were treated with an illumination diameter less than 9.5 mm, while the device proposed for marketing would only include a 9.0 mm illumination diameter. Therefore, use of the KXL system would result in a smaller corneal diameter treated.
With respect to another difference between the devices, for UV focal alignment, the UV-X device studied used a subjective focal alignment: the user observed the riboflavin fluorescence to gauge beam shape to determine proper alignment.

For the KXL system to be marketed, the alignment is objective: Two visible aiming lasers provide direct alignment confirmation in x, y, and z directions as seen in the image on this slide.

Therefore, we note 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.

While an objective method may improve consistency of the plane at which treatment is delivered, it is unclear how that treatment plane may differ from the one studied and the resulting impact on safety and effectiveness.

Additional preclinical concerns have been raised over the course of this review. Additional differences between the devices (beam shape, focal length, etc.) and concerns with the lack of clarity with regard to the Applicant’s description of key device features (optical system issues, collimation of the beams, etc.) which could affect the impact of differences such as working distance and focal length, have been raised by the preclinical review team and management. My impression is that many of these differences MAY impact performance and resulting safety and effectiveness outcomes. Many
differences have been described by the sponsor as “improvements” – however, I note that improvements still have the potential to impact outcomes, and often there is a tradeoff. Until the preclinical review is complete, I cannot comment on all the potential reasons why performance of the UV-X may not accurately represent safety and effectiveness of the KXL System. The preclinical review team is aware of a number of clinical phenomenon that may differ between devices and cannot be adequately studied at the bench (for example, eye drift, which may be significant over a 30 minute exposure time and is even more of a potential concern in a pediatric population – and could impact outcomes with different laser focusing methods/instructions). My preliminary comment is that any labeling (if approved) should be clear that the device proposed for approval was not studied - and definitive plans for a rigorous postapproval study must be made prior to any potential approvable decision since real data with the device will be needed to generate meaningful and accurate labeling in the future.

3.2. Complete Response Item #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/cm².

Avedro Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.6 (SN 0027, Module 1.6.2), where we committed to modifying the software of the to-be-marketed device to implement the software lock-out of the irradiated power above 3 mW/cm².

Validation of the software lock-out has been completed. Enclosed is the validation and verification test reports (PSPEC-00053-NDA and PSPEC-00054-NDA, respectively). As a result of this change, the following additional supportive documents have been revised:

- PSPEC-00027-NDA
- PSPEC-00030-NDA
- PSPEC-00031-NDA
- PSPEC-00034-NDA
- PSPEC-00036-NDA
- PSPEC-00037-NDA
- PSPEC-00039-NDA
- PSPEC-00040-NDA
Reviewer Comments: Proposal is adequate from a clinical perspective. I defer to other relevant members of the CDRH review team (i.e., software, engineering) to review the response, as per their expertise. Labeling should identify additional specific treatment parameter recommendations, as were studied (for example, induction time, zone of epithelial debridement, etc.)

3.3. Complete Response Item #7
You indicate that validation activities for the Homogeneity Measurement Master Validation plan (VAL-0005) are ongoing. Please provide the results of your validation activities.

Avedro Response:
Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.7 (SN 0027, Module 1.6.2).

Reviewer Comments: I defer to other relevant members of the CDRH review team (i.e., software, engineering) to review the response, as per their expertise. The engineering reviewer mentioned in an email to me that homogeneity testing may have been performed with a different illumination diameter than the one proposed for marketing. The engineering review will address such issues, if necessary.
3.4. Complete Response Item #8

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

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.


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

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
Reviewer Comments: I defer to other relevant members of the CDRH review team (i.e., software, engineering, etc.) to review the response, as per their expertise.

3.5. Complete Response Item #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/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

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 Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.9 (SN 0027, Module 1.6.2).

Reviewer Comments: I defer to other relevant members of the CDRH review team (i.e., software, engineering, etc.) to review the response, as per their expertise.

3.6. Complete Response Item #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 100-240 VAC, 50 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 Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.10 (SN 0027, Module 1.6.2).

Reviewer Comments: I defer to other relevant members of the CDRH review team (i.e., software, engineering, etc.) to review the response, as per their expertise.
3.7. Complete Response Item #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 you provide a software lockout of powers in excess of 3mW/cm². 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-I shows that the wireless technology used is the Bluetooth 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 Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.11 (SN 0027, Module 1.6.2).

Reviewer Comments: Labeling is still under review from a clinical perspective. I defer to other relevant members of the CDRH review team (i.e., software, engineering, etc.) to review the response, as per their expertise.

3.8. Complete Response Item #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 Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.12 (SN 0027, Module 1.6.2).

Reviewer Comments: Labeling is still under review from a clinical perspective. I defer to other relevant
members of the CDRH review team (i.e., software, engineering, etc.) to review the response, as per their expertise.

Section #4: CLINICAL/STATISTICAL DEFICIENCIES

4.1. Complete Response Item #13a

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.

In the Type A Meeting Briefing Package, Section 3.13 (SN 0027, Module 1.6.2), Avedro provided a summary of the number of subjects by illumination diameter that was included in efficacy and safety analysis by study. In the agency’s 01 August 2014 preliminary comments, CDRH requested the following:

CDRH Comment #1a:

The response to item 13a (i.e. aperture/illumination diameter) clarified the total number of subjects treated under the large diameter setting. However, in light of the number of subjects affected, we request the following additional data in order to evaluate the distribution of this event across study eyes and subpopulations:

a. Please list the total number of eyes treated with the medium vs. large aperture settings by study (i.e. UVX-001, UVX-002, UVX-003). Please subdivide this group into the number of eyes in subjects with keratoconus and the number of eyes in subjects with postrefractive corneal ectasia treated with each aperture setting. Please subdivide this last group (post refractive corneal ectasia) based on the specific refractive treatment after which ectasia developed (i.e. subjects s/p LASIK, s/p PRK, s/p epi-LASIK, etc.) Finally, please separately list the number of eyes treated with the large aperture setting in pediatric subjects, which CDRH identifies as individuals from birth to 21 years of age (see “premarket Assessment of Pediatric Medical Devices: Guidance for Industry and Food and Drug Administration Staff” issued on March 24, 2014, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf). Please subdivide the pediatric data to separately list subjects between 14-18 years of age (up to their 18th birthday) and subjects between 18-21 years of age for each study.

Avedro Response to CDRH Request #1a:

The total number of eyes treated with the medium versus large aperture settings by study and by indication was provided in NDA 203-324 Sequence 0021 (dated 21 February 2014) and is provided in Table 2 for ease of reference. No subjects received treatment using the small aperture setting and subjects in UVX-001 received treatment using the medium aperture setting only.
Reviewer Comments: Response is adequate. The use of other illumination diameter beams in a small number of subjects in the studies does not appear to have been preferentially chosen for specific subpopulations. We note that the number of subjects reported in Table 2 does not appear to reflect the actual number in studies UVX-002 and UVX-003, therefore, when additional analyses are requested (as per the advisory committee recommendations below) this will be clarified as I believe this discrepancy reflects a small number of subjects in whom the diameter used was not specified.
**CDRH Request #1b:**

Please review the demographic and baseline data from the eyes which were treated under the large aperture setting in order to determine if there were any common features which may be relevant to the investigator’s choice to use the largest aperture setting as opposed to the medium or small settings. If common features are identified, please provide additional information to support whether adequate data exists in the subjects treated with the medium aperture setting to ensure that absence of the large aperture setting in the device you intend to market does not compromise the safety and effectiveness of your device for any identifiable subpopulation that was studied.

**Avedro Response to CDRH Request #1b:**

In order to identify any additional common features that may have been relevant to the investigator’s choice of aperture, available baseline and demographic data including gender, age, baseline $K_{max}$ and corneal thickness at the thinnest point were reviewed. These data are presented in Table 5 and Table 6, respectively for the pooled keratoconus and pooled ectasia populations. There do not appear to be any differences between the groups treated with the medium aperture and those treated with the large aperture in any of the demographic or baseline variables. Given the small number of patients treated with the large aperture in each of the two indications, no formal analyses were conducted.

**Reviewer Comments:** Response is adequate. The use of other illumination diameter beams in a small number of subjects in the studies does not appear to have been preferentially chosen for specific subpopulations nor for particular demographic characteristics.

**CDRH Request #2:**

You previously stated (in your February 2014 submission regarding this issue) that “As part of site start-up and training, 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.” In order to better characterize variations in study procedures which occurred based on investigator discretion and variations which were identified as protocol deviations please provide the following:

a. An organized listing of the number of protocol deviations in each study by category (for example, deviations pertaining to enrollment criteria, out of window visits, device settings, etc.) with subcategories where relevant.

b. A discussion regarding any additional events pertaining to device settings or use that were varied based on “investigator discretion”.

c. A discussion regarding if (and how) variations in study procedures based on investigator discretion were distinguished from protocol deviations.
Avedro Response to CDRH Request #2:
Detailed listings and counts of protocol deviations by category in the keratoconus (UVX-002 pooled) and ectasia (UVX-003 pooled) populations are provided in Table 7 and Table 8, respectively.

Per the study protocols, the only device settings that the Investigators had the ability to change were the working distance and the illumination aperture. The UV intensity was fixed at 3 mW/cm² and could not be changed by the user. The duration of the UV illumination was set at 30 minutes. After 30 minutes, the UV light source would automatically switch off. The operators were instructed to keep track of the irradiation time independently to confirm actual treatment time.

Details of the treatment procedure were captured in the subjects’ source documents and in the electronic case report forms (eCRFs). Procedure details included the actual number and dosing times of riboflavin as well as UV illumination aperture and time. Thus any variations in the treatment procedure, whether based on investigator discretion or not, were collected in the eCRF. Variations in the study procedures that were not consistent with the protocol, such as not following the riboflavin dosing regimen or continuing with the procedure despite a corneal thickness of <400 μm, were categorized and collected as protocol deviations.
<table>
<thead>
<tr>
<th>Violation/Deviation Reason</th>
<th>Subcategory</th>
<th>Number of Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not meet inclusion/exclusion</td>
<td>Exclusion #06: Pregnancy (including plan to become pregnant) or lactation the course of the study.</td>
<td>CXL Group (N = 162)</td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td>Control Group (N = 113)</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion</td>
<td>Exclusion #10: Taking Vitamin C (ascorbic acid) within 1 week of treatment.</td>
<td></td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion</td>
<td>Inclusion #02: Having a diagnosis of progressive keratoconus defined as one or more of the following changes over a period of 24 months or less before randomization.</td>
<td></td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion</td>
<td>Inclusion #07: 1-5 ratio &gt; 1.5 on the Pentacam map or topography map</td>
<td></td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion</td>
<td>Inclusion #08: BSCVA worse than 20/20 (&lt;53 letters on ETDRS chart)</td>
<td></td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion</td>
<td>Inclusion #09: Contact Lens Wearers Only: Removal of contact lenses for the required period of time prior to the screening refraction.</td>
<td></td>
</tr>
<tr>
<td>criteria</td>
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<td>1</td>
</tr>
<tr>
<td>Did not obtain proper consent</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>prior to performing study procedure</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Not treated per randomization</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>assignment</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>BSCVA not done</td>
<td>--</td>
<td>11</td>
</tr>
<tr>
<td>UCVA not done</td>
<td>--</td>
<td>2</td>
</tr>
<tr>
<td>Manifest refraction not done</td>
<td>--</td>
<td>5</td>
</tr>
<tr>
<td>IOP measurement not done</td>
<td>--</td>
<td>113</td>
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<tr>
<td>Slit lamp exam not done</td>
<td>--</td>
<td>4</td>
</tr>
</tbody>
</table>
### Table 7: UVX-002 Pooled (Keratoconus) - Counts of Protocol Deviations by Category (Continued)

<table>
<thead>
<tr>
<th>Violation/Deviation Reason</th>
<th>Subcategory</th>
<th>Number of Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CXL Group (N = 102)</td>
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<tr>
<td>Endothelial cell count not done</td>
<td>--</td>
<td>33</td>
</tr>
<tr>
<td>Dilated fundus exam not done</td>
<td>--</td>
<td>5</td>
</tr>
<tr>
<td>Pentacam pachymetry, keratometry not done</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>Ultrasound pachymetry not done</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>Manual keratometry not done</td>
<td>--</td>
<td>14</td>
</tr>
<tr>
<td>RSVP questionnaire not done</td>
<td>--</td>
<td>11</td>
</tr>
<tr>
<td>Patients questionnaire not done</td>
<td>--</td>
<td>19</td>
</tr>
<tr>
<td>Other (Specify)</td>
<td>Artificial Tears/BSS/water used instead of protocol specified hypotonic saline.</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Contact Lens Wearer - Refraction not stable/stability check not done</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Crossover eye/ Fellow eye not treated within 6 months of study eye treatment</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Data point not available/reported</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Exam done on different date</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Exam not done</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Fellow eye did not qualify for treatment</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ICF documentation improper/incomplete</td>
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</tr>
<tr>
<td></td>
<td>Keratoconus progression time period too long</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Keratoconus severity incorrect.</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 7: UVX-002 Pooled (Keratoconus) - Counts of Protocol Deviations by Category (Continued)

<table>
<thead>
<tr>
<th>Violation/Deviation Reason</th>
<th>Subcategory</th>
<th>Number of Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CXL Group (N = 102)</td>
</tr>
<tr>
<td>Other (Specify) Cont’d.</td>
<td>RSVP done at treatment visit, rather than screening.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Riboflavin dosing not per protocol</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Screening exams not repeated when treatment &gt; 30 days after screening</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Treatment and screening on same day</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Treatment not within 30 days of screening</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Visit not done</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Visit out of protocol specified window</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Wrong eye randomized</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 8: UVX-003 Pooled (Ectasia) - Counts of Protocol Deviations by Category

<table>
<thead>
<tr>
<th>Violation/Deviation Reason</th>
<th>Subcategory</th>
<th>Number of Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>CXL Group (N = 91)</strong></td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion criteria</td>
<td>Exclusion #08: Taking Vitamin C (ascorbic acid) supplements within 1 week of the cross-linking treatment.</td>
<td>1</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion criteria</td>
<td>Inclusion #04: BSCVA worse than 20/20 (&lt;55 letters on ETDRS chart).</td>
<td>2</td>
</tr>
<tr>
<td>Did not meet inclusion/exclusion criteria</td>
<td>Inclusion #05: Contact Lens Wearers Only: Removal of contact lenses for the required period of time prior to the screening refraction.</td>
<td>2</td>
</tr>
<tr>
<td>Did not obtain proper consent prior to performing study procedure</td>
<td>--</td>
<td>12</td>
</tr>
<tr>
<td>BSCVA not done</td>
<td>--</td>
<td>8</td>
</tr>
<tr>
<td>UCVA not done</td>
<td>--</td>
<td>8</td>
</tr>
<tr>
<td>Manifest refraction not done</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>IOP measurement not done</td>
<td>--</td>
<td>66</td>
</tr>
<tr>
<td>Slit lamp exam not done</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>Endothelial cell count not done</td>
<td>--</td>
<td>26</td>
</tr>
<tr>
<td>Pentacam pachymetry, keratometry not done</td>
<td>--</td>
<td>7</td>
</tr>
<tr>
<td>Ultrasound pachymetry not done</td>
<td>--</td>
<td>4</td>
</tr>
<tr>
<td>Corneal topography not done</td>
<td>--</td>
<td>1</td>
</tr>
<tr>
<td>Manual keratometry not done</td>
<td>--</td>
<td>42</td>
</tr>
<tr>
<td>RSVP questionnaire not done</td>
<td>--</td>
<td>24</td>
</tr>
<tr>
<td>Patients questionnaire not done</td>
<td>--</td>
<td>15</td>
</tr>
</tbody>
</table>

### Table 8: UVX-003 Pooled (Ectasia) - Counts of Protocol Deviations by Category (Continued)

<table>
<thead>
<tr>
<th>Violation/Deviation Reason</th>
<th>Subcategory</th>
<th>Number of Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>CXL Group (N = 91)</strong></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td>Artificial Tears/BSS/water used instead of protocol specified hypotonic saline.</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Contact Lens Wearer - Refraction not stable/stability check not done</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Crossover eye/ Fellow eye not treated within 6 months of study eye treatment</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Data point not available/reported</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Exam not done</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>ICF documentation improper/incomplete</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Pachymetry under 400 microns</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>RSVP done at treatment visit, rather than screening.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Riboflavin dosing not per protocol</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Screening exams not repeated when treatment &gt; 30 days after screening</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>Treatment and screening on same day</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Treatment not within 30 days of screening</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>UV Light illumination time &lt; 30 mins</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Visit not done.</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Visit out of protocol specified window</td>
<td>39</td>
</tr>
</tbody>
</table>
Reviewer Comments: While the response provides the requested information, we note the following –

Table 7 reports 20 protocol deviations related to enrollment criteria and 59 instances where endothelial cell count was not done in addition to 129 out of window visits and 41 visits “not done”. Violations in the enrollment criteria and visit schedule occurred more frequently in the control arm. Limitations in the interpretation of the control data (due to study design, for example) have been noted on prior rounds of review and these deviations may represent additional limitations/weaknesses. No additional interaction with the sponsor is necessary, but a discussion and summary of these deviations were felt to be may be important to include in written/verbal presentation to the advisory committee.

Table 8 reports on similar data for ectasia subjects. Presentation of protocol deviations were relevant to panel presentation, as mentioned above.

Note that deviations related to corneal thickness may have a significant impact on results and the advisory committee recommended stratification of data based on such parameters, as discussed below. Note that in my original review, a number of such instances were identified by the Applicant in the study reports – these and other protocol deviations may have had significant clinical impact (due to the importance of the 400 micron minimum thickness to establish adequate riboflavin shielding for posterior ocular structures): (excerpt from my original review copied below as an image)
From section 3.14:

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 III 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.

Reviewer Comments: Response is adequate, however, additional risk mitigation including labeling recommendation related to maintaining a beam centered on the cornea may be necessary (if not already included). From a device perspective, this is an important treatment parameter.

Response to Item #13C (which is referenced by the sponsor) is reviewed below.
4.3. Complete Response Item #13c

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.

In the Type A Meeting Briefing Package, Section 3.15 (SN 0027, Module 1.6.2). Avedro provided an analysis of the safety data by visit for each study. In the agency’s 01 August 2014 preliminary comments, CDRH requested the following:

The response to item 13c (i.e. new analyses of safety data by study visit) appears to be complete, however additional review on this subject will continue – for example stratified safety analyses by subpopulations as requested below.

CDRH Request #1:

You provide additional safety analyses in the current submission. However, it is unclear whether how many subjects required ocular surgery over the course of the trial (e.g., laser interventions, cataract surgery, corneal transplant, etc.). Please provide a discussion regarding the incidence and etiology of surgical interventions and the distribution between the treatment arms and subpopulations (pediatric subjects, patients s/p LASIK, etc.)

Avedro Response to CDRH Request #1:

No subjects required ocular surgery in any CXL eye over the course of the UVX clinical trials.

CDRH Request #2:

In order to better characterize the data available and the risk/benefit profile of this combination product in potentially vulnerable subpopulations we request the following information:

a) Please provide an accountability table for the following subpopulations, including details regarding availability at each study visit in addition to randomized arm and whether or not the subject had “crossed over” or had the fellow eye treated:

   i) Subjects between 14-18 years of age (up to their 18th birthday)

   ii) Subjects between 18-21 years of age

   iii) Subjects treated for postrefractive corneal ectasia subdivided by the specific refractive treatment after which ectasia developed (i.e. s/p LASIK, s/p PRK, s/p epi-LASIK, etc.)

Avedro Response to CDRH Request #2.a.i and 2.a.ii:

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. The analysis of the pediatric population by years of age (14-18 [up to their 18th birthday] and 18-21) is included in Table 9.
### Table 9: Pediatric Population

<table>
<thead>
<tr>
<th>Age 14-18</th>
<th>UVX-001 (Keratoconus)</th>
<th>UVX-002</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXL Group</td>
<td>Control Group</td>
<td>CXL Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Age 14-18</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Age 18-21</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Details regarding availability at each study visit and whether or not subjects had “crossed over” or had the fellow eye treated for the pediatric subpopulations (14 – 18 years of age; 18 – 21 years of age) in UVX-001 are provided in Table 10 and Table 11, respectively.

One subject 14 – 18 years of age was randomized into the control group and remained in this group until their six month visit, at which time they crossed over and their sham eye was treated. The subject’s fellow eye was also treated. Details of subject availability at each study visit are provided in Table 10.

### Table 10: Pediatric Subjects (14 – 18 Years of Age) in UVX-001: Availability by Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=0)</td>
<td># Subjects with Fellow Eye Treated (n=0)</td>
</tr>
<tr>
<td>Month 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Month 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Month 6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Month 12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Five subjects 18 – 21 years of age were randomized to treatment: two in the CXL group and three in the control group. Of the two subjects randomized in the CXL group, one had their fellow eye treated. Of the three subjects randomized to the control group, two had their sham eye treated and one had their fellow eye treated. Details of subject availability at each study visit are provided in Table 11.
Table 11: Pediatric Subjects (18 – 21 Years of Age) in UVX-001: Availability by Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=2)</td>
<td># Subjects with Fellow Eye Treated (n=1)</td>
</tr>
<tr>
<td>Month 1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Month 3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Month 6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Month 12</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Details regarding availability at each study visit and whether or not subjects had “crossed over” or had their fellow eye treated for the pediatric subpopulations in UVX-002 are provided in Table 12 and Table 13, respectively.

Ten (10) subjects 14 – 18 years of age were randomized to treatment: seven in the CXL group and three in the 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 control group, all had their sham eyes treated and two had their fellow eye treated. Details of subject availability at each study visit are provided in Table 12.

Table 12: Pediatric Subjects (14 – 18 Years of Age) in UVX-002: Availability by Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=7)</td>
<td># Subjects with Fellow Eye Treated (n=5)</td>
</tr>
<tr>
<td>Month 1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Month 3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Month 6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Month 12</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Seventeen (17) subjects 18 – 21 years of age were randomized to treatment: ten in the CXL group and seven in the 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 control group, all had their sham eyes treated and six had their fellow eye treated. Details of subject availability at each study visit are provided in Table 13.
Table 13: Pediatric Subjects (18 – 21 Years of Age) in UVX-002: Availability by Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment</td>
<td># Subjects with Fellow Eye Treated</td>
</tr>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Month 1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Month 3</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Month 6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Month 12</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Avedro Response to CDRH Request #2.a.iii:

The number of ectasia subjects based on the type of refractive surgery received (LASIK Only, LASIK and PRK, and PRK Only) prior to the development of ectasia in UVX-001 and UVX-003 is provided in Table 14. The majority of subjects enrolled developed ectasia following LASIK only (pooled, 91% in CXL Group; 94% in Control Group).

Table 14: Ectasia Subjects Based on Refractive Surgery

<table>
<thead>
<tr>
<th></th>
<th>UVX-001</th>
<th>UVX-003</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL Group</td>
<td>Control Group</td>
<td>CXL Group</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>LASIK Only</td>
<td>23 (96%)</td>
<td>25 (100%)</td>
<td>60 (90%)</td>
</tr>
<tr>
<td>LASIK and PRK</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>PRK Only</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>

In UVX-001, forty-eight (48) subjects who developed ectasia following LASIK only were randomized to treatment: twenty-three (23) in the CXL group and twenty-five (25) in the control group. Of the 23 subjects randomized in the CXL Group, five elected to have their fellow eye treated. Of the 25 subjects randomized to the Control Group, 21 had their sham eyes treated and seven had their fellow eye treated. Details of subject availability at each study visit are provided in Table 15.
**Table 15: Ectasia Subjects (LASIK Only) in UVX-001: Availability by Study Visit**

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=23)</td>
<td># Subjects with Fellow Eye Treated (n=5)</td>
</tr>
<tr>
<td>Month 1</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Month 3</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Month 6</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Month 12</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

Only one subject randomized to the CXL group in UVX-001 developed ectasia following LASIK and PRK and no subjects randomized had developed ectasia following PRK only. The one subject who developed ectasia following LASIK and PRK had visits at Month 1 and Month 3 and did not have his fellow eye treated.

Details regarding availability at each study visit and whether or not subjects had “crossed over” or had the fellow eye treated for subjects who developed ectasia following LASIK only, LASIK and PRK, and PRK only in UVX-003 are provided in Table 16, Table 17, and Table 18 respectively.

118 subjects who developed ectasia following LASIK only were randomized to treatment: sixty (60) in the CXL group and fifty-eight (58) in the control group. Of the sixty (60) subjects randomized in the CXL group, twenty (20) elected to have their fellow eye treated. Of the fifty-eight (58) subjects randomized to the control group, fifty-four (54) had their sham eyes treated and fourteen (14) had their fellow eye treated. Details of subject availability at each study visit are provided in Table 16.

**Table 16: Ectasia Subjects (LASIK Only) in UVX-003: Availability by Study Visit**

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=60)</td>
<td># Subjects with Fellow Eye Treated (n=20)</td>
</tr>
<tr>
<td>Month 1</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td>Month 3</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>Month 6</td>
<td>56</td>
<td>18</td>
</tr>
<tr>
<td>Month 12</td>
<td>51</td>
<td>18</td>
</tr>
</tbody>
</table>

Seven (7) subjects who developed ectasia following LASIK and PRK were randomized to treatment: three (3) in the CXL group and four (4) in the control group. Of the three (3) subjects randomized in the CXL group, none elected to have their fellow eye treated. Of the four (4) subjects randomized to the Control Group, four (4) had their sham eyes treated and none had their fellow eye treated. Details of subject availability at each study visit are provided in Table 17.
Table 17: Ectasia Subjects (LASIK and PRK) in UVX-003: Availability by Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=5)</td>
<td># Subjects with Fellow Eye Treated (n=0)</td>
</tr>
<tr>
<td>Month 1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Month 3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Month 6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Month 12</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Five (5) subjects who developed ectasia following PRK only were randomized to treatment: four (4) in the CXL group and one (1) in the control group. Of the four (4) subjects randomized in the CXL group, one elected to have their fellow eye treated. The one subject randomized to the control group elected to have their sham eyes treated and their fellow eye treated. Details of subject availability at each study visit are provided in Table 18.

Table 18: Ectasia Subjects (PRK Only) in UVX-003: Availability by Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CXL Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects Randomized to Treatment (n=4)</td>
<td># Subjects with Fellow Eye Treated (n=1)</td>
</tr>
<tr>
<td>Month 1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Month 3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Month 6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Month 12</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**CDRH Request #2b:**

*Your enrollment criteria regarding subjects with “postrefractive corneal ectasia” are broad. Please provide a discussion characterizing the population actually studied with regard to ocular history and disease severity, progression, duration, etc.*

**Avedro Response to CDRH Request #2b:**

As summarized in Table 14 above, the majority of enrolled subjects with “postrefractive corneal ectasia” developed ectasia following LASIK only (pooled, 91% in CXL Group; 94% in Control Group). The inclusion criteria did not require documentation of progression and no information on the duration or severity of ectasia was collected.

Mean baseline $K_{max}$ (SD) were $55.4 \pm 6.86$ D in the CXL Group and $54.8 \pm 6.4$ D in the Control Group. Mean baseline corneal thickness at the apex and thinnest points, respectively, were $446$ and $432$ µm in the CXL Group, and $448$ and $432$ µm in the Control Group.
Reviewer Comment: Note that, as in the rest of the study, accountability at the 12 month visit according to randomized treatment is poor in the control arm across all subpopulations. These

The most frequent ocular risk factors for corneal ectasia at baseline were ocular history (92%, CXL: 96%, control) and eye rubbing (33%, CXL: 26%, control) (Table 19). Other ocular risk factors (overall frequencies) at baseline were “other risk history” (9%) and family history (4%). The type of contact lens worn most frequently by subjects in each treatment group was rigid gas permeable contact lenses (40%, CXL: 45%, control). Other types of contact lens that subjects reported using (overall frequencies) were soft lens (39%), soft toric lens (19%), and soft extended wear lens (10%).

Reviewer Comment: The sponsor’s response contained inadequate detail. Therefore, data line listings were reviewed regarding ocular history. Numerous issues were identified due to the lack of specific criteria in the postrefractive corneal ectasia population. First, there were no enrollment criteria to ensure that only a progressive population was enrolled. This is problematic as the population enrolled may not include poolable disease – and risk/benefit profile could be impacted based on whether or not the disease is progressive. In addition, it is noted that many subjects had multiple refractive interventions and enhancements over a diverse range of time. The timing and details of the “refractive procedure” resulting in ectasia was not recorded in all instances – this is problematic as crosslinking a day or a week or even a month after a refractive procedure for presumed “ectasia” may be inappropriate.

In addition, there were no exclusion criteria for prior crosslinking and at least one subject was recorded to have undergone crosslinking (in a fellow eye) previously. However, it is unclear whether such history was elicited in all subjects and since there was no exclusion criteria preventing enrollment of such subjects, this is a significant concern.

These concerns were raised to CDER, however, CDER would not allow discussion of limitations/concerns regarding the enrollment criteria at the advisory committee meeting as they approved the protocol. This limited our ability to discuss issues pertaining to the actual population studied which resulted from the broad nature of the enrollment criteria.
Table 19: Ocular Risk Factors and Contact Lens Wear (ITT: Pooled UVX-001 [Corneal Ectasia Subjects] and UVX-003)

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter</th>
<th>Statistic</th>
<th>CXL Group n (%)</th>
<th>Control Group n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>Eye Rubbing</td>
<td>N</td>
<td>91 (67.0%)</td>
<td>86</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>61 (67.0%)</td>
<td>64 (74.4%)</td>
<td>125 (70.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>30 (33.0%)</td>
<td>22 (25.6%)</td>
<td>52 (29.4%)</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td>N</td>
<td>91 (67.0%)</td>
<td>86</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>89 (97.8%)</td>
<td>81 (94.2%)</td>
<td>170 (96.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>2 (2.2%)</td>
<td>5 (5.8%)</td>
<td>7 (4.0%)</td>
</tr>
<tr>
<td>Ocular History</td>
<td></td>
<td>N</td>
<td>91 (67.0%)</td>
<td>88</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>7 (7.7%)</td>
<td>4 (4.5%)</td>
<td>11 (6.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>84 (92.3%)</td>
<td>84 (95.5%)</td>
<td>168 (93.9%)</td>
</tr>
<tr>
<td>Other Risk History</td>
<td></td>
<td>N</td>
<td>89 (67.0%)</td>
<td>86</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>83 (93.3%)</td>
<td>77 (89.5%)</td>
<td>160 (91.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>6 (6.7%)</td>
<td>9 (10.5%)</td>
<td>15 (8.6%)</td>
</tr>
<tr>
<td>Contact Lens</td>
<td>Soft Lens</td>
<td>N</td>
<td>89 (67.0%)</td>
<td>85</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>54 (60.7%)</td>
<td>53 (62.4%)</td>
<td>107 (61.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>35 (39.3%)</td>
<td>32 (37.6%)</td>
<td>67 (38.5%)</td>
</tr>
<tr>
<td></td>
<td>Soft Toric Lens</td>
<td>N</td>
<td>88 (67.0%)</td>
<td>80</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>74 (84.1%)</td>
<td>63 (78.8%)</td>
<td>137 (81.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>14 (15.9%)</td>
<td>17 (21.3%)</td>
<td>31 (18.5%)</td>
</tr>
<tr>
<td></td>
<td>Soft Extended Wear</td>
<td></td>
<td>89 (67.0%)</td>
<td>80</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>83 (93.3%)</td>
<td>70 (87.5%)</td>
<td>153 (90.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>6 (6.7%)</td>
<td>10 (12.5%)</td>
<td>16 (9.5%)</td>
</tr>
<tr>
<td></td>
<td>Rigid Gas Permeable</td>
<td></td>
<td>90 (67.0%)</td>
<td>87</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>54 (60.0%)</td>
<td>48 (55.2%)</td>
<td>102 (57.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>36 (40.0%)</td>
<td>39 (44.8%)</td>
<td>75 (42.4%)</td>
</tr>
</tbody>
</table>

N = Number of subjects in the ITT population.
Reviewer Comment: Note that in UVX-001, the Applicant reports that in the pediatric subpopulation the difference between treatment groups did not meet the primary efficacy endpoint (based on both LOCF and observed values, as per Table 20-21). It appears the single subject ages 14-18 years of age may have actually had worsening Kmax. In UVX-002, the outcomes were more favorable for pediatric subjects and the efficacy endpoint was reached. Use in the pediatric population with
limited/conflicting evidence of efficacy and a significantly flawed trial raises serious concerns. We also note that the adverse event data in the pediatric population includes suicide attempts.

Seventeen (17) pediatric subjects 18 – 21 years of age were randomized into the study: ten in the CXL group and seven in the control group. The $K_{\text{max}}$ data, LOCF and observed, for these subjects are provided in Table 23. Using LOCF, the difference between treatment groups exceeded 1.0 D at Month 6 (−0.8 D CXL vs. 2.8 D control) and Month 12 (−3.2 D CXL vs. 2.8 D control). For observed values, the difference between treatment groups also exceeded 1.0 D at Month 3 (−1.2 D CXL vs. 0.5 D control) and Month 6 (−1.2 D CXL vs. 5.7 D control); at Month 12, the observed change from baseline in the CXL group was −3.2 D.

Overall, efficacy results from the 33 pediatric subjects aged 14-21 years are consistent with the overall population studied in that the results met the primary efficacy endpoint.

In UVX-001, there was only one subject aged 14-18 years. That subject was randomized to the control group. Of the 5 subjects aged 18-21 years enrolled, 2 were randomized to the CXL group and 3 to control. The difference between treatment groups did not meet the endpoint in this small number of subjects.

In UVX 002, both the 10 subjects aged 14-18 years and the 17 subjects aged 18-21 years met the primary endpoint. Due to the small number of subjects, data from the one subject aged 14-18 years and five subjects aged 18-21 years from the UVX 001 study were pooled with the subjects from the UVX 002 study. For subjects aged 14-18 years, the pooling of data are consistent with the overall subject population in that the primary efficacy endpoint was met with LOCF (−5.9 D CXL vs. 1.4 control) and observed (−6.6 CXL). For subjects aged 18–21 years, the pooling of data are consistent with the overall subject population in that the primary efficacy endpoint was met with LOCF (−2.6 D CXL vs. 2.2 control) and observed (−2.6 CXL).
Table 20: Mean Changes from Baseline $K_{\text{max}}$ in the Randomized Study Eye: Age 14-18 (UVX-001, ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>CXL Group (N=0)</th>
<th>Control Group (N=1)</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>n</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>--</td>
<td>$81.3$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>n</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Mean</td>
<td>$87.4$</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Month 6</td>
<td>n</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td></td>
<td>Observed</td>
<td>Mean</td>
<td>$84.1$</td>
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<td></td>
<td>SD</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>LOCF</td>
<td>Mean</td>
<td>$84.1$</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Mean</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Table 21: Mean Changes from Baseline $K_{\text{max}}$ in the Randomized Study Eye: Age 18-21 (UVX-001, ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>CXL Group (N=2)</th>
<th>Control Group (N=3)</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline</td>
<td>n</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>57.4</td>
<td>66.3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.86</td>
<td>10.00</td>
<td>0.4</td>
</tr>
<tr>
<td>Month 3</td>
<td>n</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>57.8</td>
<td>67.1</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>7.57</td>
<td>9.47</td>
<td>0.71</td>
</tr>
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<td>Month 6</td>
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<td>3</td>
<td>2</td>
</tr>
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<td>Mean</td>
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<td>67.1</td>
<td>0.3</td>
</tr>
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<td></td>
<td>SD</td>
<td>8.34</td>
<td>9.47</td>
<td>1.48</td>
</tr>
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<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>57.7</td>
<td>--</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8.34</td>
<td>--</td>
<td>1.48</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>LOCF</td>
<td>Mean</td>
<td>57.7</td>
<td>67.1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8.13</td>
<td>9.47</td>
<td>1.27</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>57.7</td>
<td>--</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8.13</td>
<td>--</td>
<td>1.27</td>
</tr>
</tbody>
</table>
### Table 22: Mean Changes from Baseline $K_{\text{max}}$ in the Randomized Study Eye: Age 14-18 (UVX-002, ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>CXL Group (N=7)</th>
<th>Control Group (N=3)</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>CXL Group</td>
<td>Control Group</td>
<td>CXL Group (N=7)</td>
</tr>
<tr>
<td>Baseline</td>
<td>n</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>64.6</td>
<td>62.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>15.18</td>
<td>13.44</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>n</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>58.3</td>
<td>60.5</td>
<td>-7.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.51</td>
<td>13.13</td>
<td>12.68</td>
</tr>
<tr>
<td>Month 6</td>
<td>n</td>
<td>7</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>LOCF</td>
<td>Mean</td>
<td>58.5</td>
<td>63.1</td>
<td>-6.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.12</td>
<td>14.59</td>
<td>13.32</td>
</tr>
<tr>
<td>Month 6</td>
<td>n</td>
<td>7</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>58.5</td>
<td>65.7</td>
<td>-6.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.12</td>
<td>19.66</td>
<td>13.32</td>
</tr>
<tr>
<td>Month 12</td>
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<td>3</td>
<td>7</td>
</tr>
<tr>
<td>LOCF</td>
<td>Mean</td>
<td>58.7</td>
<td>63.1</td>
<td>-5.9</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.14</td>
<td>14.59</td>
<td>11.49</td>
</tr>
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<td>Month 12</td>
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<tr>
<td>Observed</td>
<td>Mean</td>
<td>58.9</td>
<td>--</td>
<td>-6.6</td>
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<tr>
<td></td>
<td>SD</td>
<td>5.62</td>
<td>--</td>
<td>12.41</td>
</tr>
</tbody>
</table>
## Table 23: Mean Changes from Baseline $K_{\text{max}}$ in the Randomized Study Eye: Age 18-21 (UVX-002, ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>CXL Group (N=10)</th>
<th>Control Group (N=7)</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (65.8)</td>
<td>Mean (66.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (13.10)</td>
<td>SD (10.35)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>n</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Mean (64.8)</td>
<td>Mean (66.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (13.01)</td>
<td>SD (11.06)</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>n</td>
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<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Mean (64.8)</td>
<td>Mean (66.5)</td>
<td>-1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (13.01)</td>
<td>SD (11.06)</td>
<td>1.70</td>
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<td>7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>LOCF</td>
<td>Mean (65.1)</td>
<td>Mean (68.8)</td>
<td>-0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (12.68)</td>
<td>SD (13.56)</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>n</td>
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<td>8</td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Mean (66.3)</td>
<td>Mean (78.4)</td>
<td>-1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (13.66)</td>
<td>SD (13.72)</td>
<td>2.20</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td>10</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>LOCF</td>
<td>Mean (62.6)</td>
<td>Mean (68.8)</td>
<td>-3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (11.66)</td>
<td>SD (13.56)</td>
<td>5.42</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>n</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Mean (62.6)</td>
<td>Mean (68.8)</td>
<td>-3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (11.66)</td>
<td>SD (13.56)</td>
<td>5.42</td>
</tr>
</tbody>
</table>
Efficacy by Subpopulations – Refractive Surgery

The majority of subjects enrolled in UVX-001 developed ectasia following LASIK only. Only one subject developed ectasia following LASIK and PRK and no subjects enrolled developed ectasia following PRK only.

For subjects who developed ectasia following LASIK only, the $K_{\text{max}}$ data for this subpopulation, both LOCF and observed, are provided in Table 24. Using LOCF, the difference between treatment groups exceeded 1.0 D at Month 6 (0.8 D CXL vs. 1.0 D control) and Month 12 (1.2 D CXL vs. 1.0 D control). For observed values, the difference between treatment groups met or exceeded 1.0 D at Month 3 (0.1 D CXL vs. 0.9 D control) and Month 6 (0.8 D CXL vs. 1.6 D control); at Month 12, the observed change from baseline for the CXL group was −1.4 D.

One subject in the CXL group developed ectasia following LASIK and PRK. The $K_{\text{max}}$ data for this subject, both LOCF and observed, are provided in Table 25. Only observed data up to Month 3 are available.

The majority of subjects enrolled in UVX-003 developed ectasia following LASIK only. Seven subjects developed ectasia following LASIK and PRK and five subjects developed ectasia following PRK only.

The $K_{\text{max}}$ data (LOCF and observed) for the subjects who developed ectasia following LASIK are provided in Table 26. The difference between treatment groups exceeded 1.0 D at Month 6 (0.6 D CXL vs. 0.7 D control) and Month 12 (−0.5 D CXL vs. 0.7 D control) based on LOCF. Using observed data, the difference between treatment groups did not meet the primary efficacy endpoint at Month 3 (0.1 D CXL vs. 0.6 D control) but did at Month 6 (−0.5 D CXL vs. 0.6 D control) and Month 12 (−0.6 D CXL vs. 0.4 D control).

The $K_{\text{max}}$ data (LOCF and observed) for subjects who developed ectasia following LASIK and PRK are provided in Table 27. Using LOCF, the difference between treatment groups did not meet the efficacy endpoint at Month 6 (0.0 D CXL vs. −1.7 D control) or at Month 12 (−0.5 D CXL vs. −1.7 D control). For observed values, the difference between treatment groups exceeded 1.0 D at Month 3 (0.0 D CXL vs. 1.1 D control) but not at Month 6 (−0.3 D CXL vs. −4.1 D control); at Month 12, the change from baseline in the CXL group was −0.8 D.

The $K_{\text{max}}$ data (LOCF and observed) for the subjects who developed ectasia following PRK only are provided in Table 28. Using LOCF, the difference between treatment groups did not exceed 1.0 D at Month 6 (−0.4 D CXL vs. 0.0 D control) or at Month 12 (−0.4 D CXL vs. 0.0 control). For observed values, the difference between treatment groups did not exceed 1.0 D at Month 3 (0.6 D CXL vs. 0.0 control) or Month 6 (−0.4 D CXL vs. 0.0 control); at Month 12, the change from baseline in the CXL group was −0.4 D.

As the majority of subjects in both UVX-001 and UVX-003 studies enrolled developed ectasia following LASIK only, the efficacy results from this group are consistent with the overall study results in that the results met the primary efficacy endpoint.

Data from the seven subjects who developed ectasia following LASIK and PRK and the five subjects who developed ectasia following PRK in Study UVX-003 are not consistent with the overall population in that the results did not meet the primary efficacy endpoint in these small numbers of subjects.
Reviewer Comment: Note that the data from the subjects who had undergone PRK previously (either with or without LASIK) demonstrate that the effectiveness results were not consistent with the overall population and did not meet the primary efficacy endpoint (even at 12 months). While the numbers are small, there is an anatomic reason this may have occurred relating to structural differences in the cornea from prior surgery. Therefore, these results cannot be ignored. This information underscores the importance of considering the broad enrollment criteria for postrefractive corneal ectasia and questions the poolability of the population enrolled based on these criteria. Differences in ocular history and number and type of surgical interventions could have a significant impact – as seen in this example. Ironically, it appears in Table 27 that the control arm may have improved more than the experimental arm – this may be a result of the fact that the control arm received some treatment effect from the riboflavin they received (without epithelial debridement) or it could reflect errors in Kmax measurement, variable disease progression, or other confounding factors, etc..

From a clinical perspective, these findings are potentially significant and very concerning. This data underscores my belief that the postrefractive corneal ectasia population included subjects with such diverse ocular histories and procedures (which would impact the structure of the cornea and potentially the anatomic effects of crosslinking) that I have great concern with the data collected in this population.
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### Table 25: Mean Changes from Baseline $K_{\text{max}}$ in the Randomized Study Eye: LASIK and PRK (UVX-001, ITT Population)

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### Table 26: Mean Changes from Baseline $K_{\text{max}}$ in the Randomized Study Eye: LASIK Only (UVX-003, ITT Population)

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### Table 28: Mean Changes from Baseline \( k_{\text{max}} \) in the Randomized Study Eye: PRK Only (UVX-003, ITT Population)

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Reviewer Comment: The endothelial cell data are noisy and clearly the lack of good methodology and variability due to disease impacted the collection of accurate data. Increases in endothelial cell counts,
for example, are believed to be nonphysiologic. Trends, however, are noted and the sponsor clearly identifies that the data in pediatric subjects 18-21 years of age was different than for the remainder of the population with almost 2-3x the cell loss compared to the control group. This loss could reflect the increased difficulty in obtaining a good measurement in pediatric subjects, but if so, the loss would have been expected to be seen in the control group as well. Since endothelial cell counts are a safety measure, this represents a potential outstanding concern in the pediatric population.

A slightly higher decrease in Endothelial cell counts in subjects who had ectasia following PRK (without history of LASIK) in the experimental arm compared to the control arm was also noted.

While it is hard to draw definitive conclusion from the endothelial cell data for the reasons outlined above, these findings represent outstanding safety concerns. Good quality endothelial cell data collected with appropriately rigorous methodology is needed to address these concerns and cannot be found in the current study. In addition, this issue underscores the need for larger studies – the small number of pediatric subjects and number of post-PRK subjects in the current study make interpretation of these findings a challenge.
Table 29: Endothelial Cell Count (\(\text{cell/mm}^2\)) in the Randomized: Age 14-18
(UVX-001 and UVX-002 Pooled, Safety Population)

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Reviewer Comment: The Applicant has identified trends indicating that in vulnerable subpopulations there may be greater loss of BSCVA soon after crosslinking than would be experienced otherwise (which may be transient?). This may be due to the epithelial defect experienced in the experimental arm or to variations in the natural history of the disease which confounded results between the two arms. The numbers are small and results are difficult to interpret since the control data is limited past 3 months post-procedure.
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### Table 35: Best Spectacle-Corrected Visual Acuity Loss of ≥15 Letters: Age 18-21 (UVX-001 and UVX-002 Pooled, Safety Population)

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Safety Analysis by Subpopulation — Adverse Events

An analysis of the safety data by study visit for the pediatric subgroups (14–18 and 18–21 years of age) and by type of refractive surgery is provided in Table 39 through Table 43. 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 subgroup, 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 TEAE in the 14-18 pediatric subgroup was corneal opacity (haze); other TEAE listed occurred in one subject each in the CXL group. The most commonly reported ocular TEAE occurring in ≥10% of the CXL subjects in the 18-21 pediatric subgroup were corneal opacity, eye pain, punctate keratitis, conjunctival hyperaemia, corneal striae, and foreign body sensation in eyes.

The most common ocular TEAEs, occurring in ≥10% of the CXL subjects, in the LASIK only refractive surgery subgroup were corneal opacity (haze), corneal epithelium defect, eye pain, photophobia, punctate keratitis, vision blurred, and dry eye. The most common ocular TEAEs (reported by more than one subject) in the LASIK and PRK subgroup were eye pain and punctate keratitis, and in the PRK only subgroup was corneal opacity.

The TEAEs observed in the CXL group through Month 12 were generally consistent for both subgroups, indicating that TEAEs generally develop in the short-term with few late-onset complications. These data are consistent with the overall safety profile.
### Table 39: Summary of Adverse Events Reported by ≥2% of Subjects: Age 14-18 (UVX-001 and UVX-002, Pooled, Safety Population)

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<td>0</td>
<td>0</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal opacity</td>
<td>3.2 (28.6%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior chamber flare</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal striae</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal thinning</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Pain</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glare</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halo Vision</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Ocular TEAEs</strong></td>
<td>1.1 (14.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye complication associated with device</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 40: Summary of Adverse Events Reported by ≥2% of Subjects: Age 18-21 (UVX-001 and UVX-002, Pooled, Safety Population)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class/Preferred Term</th>
<th>CXL Group (N=12)</th>
<th>CXL Group (N=12)</th>
<th>CXL Group (N=12)</th>
<th>CXL Group (N=12)</th>
<th>CXL Group (N=12)</th>
<th>Control Group (N=10)</th>
<th>Control Group (N=10)</th>
<th>Control Group (N=10)</th>
<th>Control Group (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (% of Subjects Reporting Any AE</strong>s</td>
<td><strong>Month 3</strong></td>
<td><strong>Month 6</strong></td>
<td><strong>Month 9</strong></td>
<td><strong>Month 12</strong></td>
<td><strong>Month 3</strong></td>
<td><strong>Month 6</strong></td>
<td><strong>Month 9</strong></td>
<td><strong>Month 12</strong></td>
<td></td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>29.10 (83.3%)</td>
<td>9.4 (40.0%)</td>
<td>0</td>
<td>0</td>
<td>2.2 (16.7%)</td>
<td>0</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Corneal Opacity</td>
<td>28.10 (83.3%)</td>
<td>9.4 (40.0%)</td>
<td>0</td>
<td>0</td>
<td>2.2 (16.7%)</td>
<td>0</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Eye Pain</td>
<td>3.3 (25.0%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Punctate Keratitis</td>
<td>3.3 (25.0%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>2.2 (16.7%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Corneal striae</td>
<td>2.2 (16.7%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Foreign Body Sensation in Eyes</td>
<td>2.2 (16.7%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Corneal Epithelium Defect</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Dry Eye</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Eyelid Oedema</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Ocular Hypertension</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissues Disorders</strong></td>
<td><strong>Month 3</strong></td>
<td><strong>Month 6</strong></td>
<td><strong>Month 9</strong></td>
<td><strong>Month 12</strong></td>
<td><strong>Month 3</strong></td>
<td><strong>Month 6</strong></td>
<td><strong>Month 9</strong></td>
<td><strong>Month 12</strong></td>
<td></td>
</tr>
<tr>
<td>Ingrown Nail</td>
<td>1.1 (8.3%)</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

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 41: Summary of Adverse Events Reported by ≥2% of Subjects: LASIK Only (UVX-001 and UVX-003, Pooled, Safety Population)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class/Preferred Term</th>
<th>CXL Group (N=83)</th>
<th>Control Group (N=83)</th>
<th>CXL Group (N=83)</th>
<th>Control Group (N=83)</th>
<th>CXL Group (N=83)</th>
<th>Control Group (N=83)</th>
<th>CXL Group (N=83)</th>
<th>Control Group (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 3</td>
<td>Months 6</td>
<td>Month 9</td>
<td>Month 12</td>
<td>Month 3</td>
<td>Months 6</td>
<td>Month 9</td>
<td>Month 12</td>
</tr>
<tr>
<td>Number (%) of Subjects Reporting Any AE*</td>
<td>290.53(90.4%)</td>
<td>56.30(16.1%)</td>
<td>27.03(31.7%)</td>
<td>8.67(7.2%)</td>
<td>10.76(8.4%)</td>
<td>1.11(1.2%)</td>
<td>15.61(13.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal opacity</td>
<td>270.75(90.4%)</td>
<td>45.27(33%)</td>
<td>22.17(20.5%)</td>
<td>8.97(7.2%)</td>
<td>9.76(8.4%)</td>
<td>1.11(1.2%)</td>
<td>11.9(10.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>68.57(80.7%)</td>
<td>6.67(7.2%)</td>
<td>7.67(7.2%)</td>
<td>1.11(1.2%)</td>
<td>3.36(3.6%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Pain</td>
<td>30.24(28.9%)</td>
<td>2.22(2.4%)</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>17.16(19.3%)</td>
<td>0</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punctate Keratitis</td>
<td>16.16(20.1%)</td>
<td>3.2(2.4%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>14.14(16.9%)</td>
<td>3.36(3.6%)</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Eye</td>
<td>12.12(15.5%)</td>
<td>4.44(4.8%)</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>8.89(10.6%)</td>
<td>1.11(1.2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laceration increased</td>
<td>8.89(10.6%)</td>
<td>1.11(1.2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Discomfort</td>
<td>8.89(10.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal stain</td>
<td>7.78(8.4%)</td>
<td>6.67(7.2%)</td>
<td>5.56(6.0%)</td>
<td>2.22(2.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>7.78(8.4%)</td>
<td>0</td>
<td>5.56(6.0%)</td>
<td>2.22(2.4%)</td>
<td></td>
<td></td>
<td></td>
<td>4.44(4.8%)</td>
</tr>
<tr>
<td>Anterior chamber flare</td>
<td>5.56(6.0%)</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign Body Sensation in Eyes</td>
<td>5.56(6.0%)</td>
<td>1.11(1.2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid Oedema</td>
<td>4.44(4.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>4.44(4.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival Hypeernia</td>
<td>3.36(3.6%)</td>
<td>3.36(3.6%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal Disorder</td>
<td>3.36(3.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal Oedema</td>
<td>3.36(3.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratitis</td>
<td>3.36(3.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meibomian Gland Dysfunction</td>
<td>4.36(3.6%)</td>
<td>1.11(1.2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glare</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halo Vision</td>
<td>2.22(2.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Hypersensitivity</td>
<td>2.22(2.4%)</td>
<td>1.11(1.2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.
Reviewer Comment: Note that data collected from a subjective complaint questionnaire (PRO) appears to be included in the summary of adverse event data (i.e., glare, halo, etc.) However, FDA PRO experts have not formally reviewed the questionnaire nor the data. Therefore, this potentially represents an outstanding safety concern.
Reviewer Comments: The definition of “progressive” as per the enrollment criteria would likely be needed in the IFU as well. However, the advisory committee questioned one or two of the four enrollment criteria specifying the “progression” which would define this population. This requires further analysis as described below under the advisory committee section.

Reviewer Comment: We note that the final SAP created after the study was completed and after some results were published altered the endpoint to evaluate loss of 3 lines or more of BSCVA rather than 2 lines or more of BSCVA. We believe loss of BSCVA is a significant safety concern and requires additional interaction as discussed in the additional deficiencies suggested in the advisory committee section of this review. I do not agree with ignoring the prespecified safety analyses and do not believe adequate justification has been given for the change.
4.5. Complete Response Item #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.

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.

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.

da. 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.

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.

In the Type A Meeting Briefing Package, Section 3.17 (SN 0027, Module 1.6.2), Avedro provided new statistical analyses, reference to peer reviewed published controlled clinical data and confirmation of dataset review to provide substantial evidence of safety and effectiveness of cross-linking for the treatment of keratoconus. In the agency’s 01 August 2014 preliminary comments, the statistical reviewer confirmed that the clinical data coupled with the information provided appeared to address complete response Item #14. CDRH stated the following additional information was needed:

CDRH Request #1:

With regard to the “output printing error” on the Pentacam which occurred in study UVX-001, we are concerned that this may indicate a larger problem with reliability of data generated from this device. Therefore, we recommend the following additional information be submitted:

a. Please review study output from this Pentacam to determine whether any other data generated from this instrument was non physiological (e.g. do not limit “nonphysiologic” Kmax to mean negative or zero values. Please also evaluate pachymetry and any other measurements collected, to the extent possible.) This is requested in order to determine whether the “error” was an isolated event or a more extensive problem.

b. Please provide a discussion regarding whether this “output printing error” could represent a device malfunction that could have impacted accuracy of data in other subjects at this site.

c. Please provide revised analyses after eliminating any erroneous or nonphysiologic study data identified since even a relatively small number of such errors could potentially affect the results.
Avedro Response to CDRH Request #1:

a. Avedro has conducted a thorough review of the Kmax data for Study UVX-001 and has not identified any nonphysiologic Kmax values, other than the Kmax value of -0.3 diopters (D) at Month 1 for Subject 00230 which was previously identified and determined to be an “output printing error”. For the purpose of this review, nonphysiologic Kmax values in this keratoconus and ectasia population were defined as those that were less than 30 D or greater than 100 D. All Kmax values in this study were generated from the same Pentacam and ranged from 42 to 89 D. A review of the pachymetry data generated by this Pentacam was also conducted and did not yield any non-physiologic values; pachymetry values ranged from 123 to 611 μm.

b. The “output printing error” that generated the negative Kmax value (-0.3 D) for Subject 00230 appears to be an isolated event and does not represent a device malfunction. Avedro obtained the source Pentacam file for this event and sent it to [REDACTED] for full investigation. Per their investigation, the issue was a software error. The file was generated using software version 1.16r61 which had a bug such that whenever a negative curvature value appeared anywhere on the corneal surface, it was displayed as Kmax. The bug was fixed with the next released Pentacam software. Per [REDACTED] the error was a rare event and could be clearly identified (by the negative sign) when it did occur. Upon reprinting the Pentacam data for this exam using new software, the new output for Kmax was 64.4 D which is consistent with the K values on the topographic map for this scan. Additionally, Avedro reviewed all available Pentacam printouts from this site and compared the Kmax values to the K readings on the topographic map to ensure that the Kmax values and location were consistent with the maps; no discrepancies were found.

c. Since the only Kmax errors that occurred were at the 1 month timepoint, there is no impact on the primary efficacy analyses.

Reviewer Comment: Response is adequate. The problem appears to have been isolated and adequately investigated. Concern remains regarding the variability of Kmax values in this population and the lack of good methodology (multiple scans per visit with averages, etc.). However, these issues cannot be corrected in the current data set as the study has been completed. It does underscore the importance of considering all data and outcomes since Kmax and endothelial cell data each appear to have serious methodological issues in the trial (i.e., lack of rigorous methodology) and known variability in disease corneas (increased variability compared to performance in “normal” corneas) reported in the published literature (Hashemi K, Guber I, Bergin C, Majo F. Reduced precision of the Pentacam HR in eyes with mild to moderate keratoconus. Ophthalmology. 2015 Jan;122(1):211-2.)
Reviewer Comments: Note that the sponsor found that in both UVX-001 and UVX-002 female subjects showed a greater degree of flattening than male subjects. It is unclear why this would occur and may merit additional follow-up in the postapproval study.

The CDRH statistical review performed poolability analyses for keratoconus age by subgroup (>35 or otherwise) and keratoconus gender subgroup using treatment –by-subgroup interaction effect (as described in Dr. Fang’s review). No statistical significance was found, however, the treatment-by-subgroup effect was statistically significant in the postrefractive corneal ectasia subgroup for age and
gender, but the interaction effect was quantitative rather than qualitative – younger subgroup and female subgroup obtained more reduction of $K_{\text{max}}$ from baseline to Month 12. As there is not an obvious anatomic/physiologic explanation for this I believe this may be something to consider investigating in the postapproval study, if the product is approved. While there were no pediatric subjects treated in the postrefractive corneal ectasia population, there was a 21 year old enrolled who was treated at age 22 – differences between pediatric and adult corneas may still be manifest in ectasia given what we know from keratoconus with regard to the differences in disease progression depending on age. Therefore, this finding may underscore the need to consider pediatric data separately and the inability to extrapolate from adult data.

At times, during the course of this review, use of clinical literature has been deemed inappropriate in this review to some extent as alluded to in the introduction of my review (based on whether the file is a 505b1 vs. 505b2 submission, for example). CDER has not yet clarified the actual regulatory status of clinical literature.

| Table 44: Mean Change from Baseline $K_{\text{max}}$ in the Randomized Study Eye by Age (UVX-001 [Keratoconus] ITT Population) |
|---|---|---|---|---|
| Visit | Statistic | Change from Baseline | Change from Baseline |
| | | CXL Group (N=17) | Control Group (N=12) | CXL Group (N=17) | Control Group (N=12) |
| | | | | |
| Baseline | n | 17 | 12 | 12 | 17 |
| | Mean | 60.4 | 63.4 | 61.0 | 60.8 |
| | SD | 6.51 | 8.66 | 8.68 | 8.16 |
| | Observed | 60.2 | 64.2 | 60.5 | 60.4 |
| | Mean | 8.86 | 9.93 | 7.62 | 8.93 |
| | SD | 3.38 | 2.39 | 1.27 | 2.70 |
| | Month 6 | n | 17 | 12 | 12 | 17 |
| | Mean | 60.3 | 64.0 | 58.9 | 61.2 |
| | SD | 8.59 | 9.50 | 7.65 | 9.65 |
| | Observed | 59.6 | 62.8 | 58.9 | 62.4 |
| | Mean | 8.30 | 10.51 | 7.65 | 10.60 |
| | SD | 2.80 | 2.80 | 1.90 | 3.69 |
| | Month 12 | n | 17 | 12 | 12 | 17 |
| | LOCF | Mean | 59.9 | 64.0 | 58.3 | 61.2 |
| | SD | 8.39 | 9.50 | 7.16 | 9.65 |
| | Observed | 58.9 | -- | 58.1 | -- |
| | Mean | 5.75 | -- | 7.86 | -- |
| | SD | 1.07 | -- | 2.75 | -- |

Reference ID: 3720940
Table 45: Mean Change from Baseline Kmax in the Randomized Study Eye by Age (UVX-002 ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>Change from Baseline</th>
<th>Change from Baseline</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Age ≤ 35 years</td>
<td>CXL Group (N=55)</td>
<td>Control Group (N=44)</td>
</tr>
<tr>
<td>Baseline</td>
<td>n</td>
<td>55</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>62.3</td>
<td>62.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>10.50</td>
<td>10.29</td>
</tr>
<tr>
<td>Month 3</td>
<td>n</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>62.0</td>
<td>62.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>9.50</td>
<td>10.58</td>
</tr>
<tr>
<td>Month 6</td>
<td>n</td>
<td>55</td>
<td>44</td>
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<tr>
<td>LOCF</td>
<td>Mean</td>
<td>61.1</td>
<td>63.2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8.76</td>
<td>10.99</td>
</tr>
<tr>
<td>Month 6</td>
<td>n</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>Observed</td>
<td>Mean</td>
<td>61.6</td>
<td>66.9</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8.94</td>
<td>13.06</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
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<td>44</td>
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<td>LOCF</td>
<td>Mean</td>
<td>60.4</td>
<td>63.3</td>
</tr>
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<td></td>
<td>SD</td>
<td>9.00</td>
<td>10.98</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td>52</td>
<td>1</td>
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<tr>
<td>Observed</td>
<td>Mean</td>
<td>60.7</td>
<td>61.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>9.17</td>
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</tr>
</tbody>
</table>
### Table 46: Mean Change from Baseline Kmax in the Randomized Study Eye by Gender (UVX-001 [Keratoconus] ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
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<th>Change from Baseline</th>
<th>Male</th>
<th>Change from Baseline</th>
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<tr>
<td></td>
<td></td>
<td>CXL Group (N=8)</td>
<td>Control Group (N=11)</td>
<td>CXL Group (N=8)</td>
<td>Control Group (N=11)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>8</td>
<td>11</td>
<td>21</td>
<td>18</td>
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<td></td>
<td>Mean</td>
<td>57.2</td>
<td>62.8</td>
<td>61.9</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.62</td>
<td>10.18</td>
<td>7.84</td>
<td>7.23</td>
</tr>
<tr>
<td>Month 3</td>
<td>n</td>
<td>8</td>
<td>11</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>56.5</td>
<td>63.1</td>
<td>61.8</td>
<td>61.3</td>
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<td></td>
<td>SD</td>
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<td>12.20</td>
<td>8.86</td>
<td>7.49</td>
</tr>
<tr>
<td>Month 6</td>
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<td>63.6</td>
<td>61.3</td>
<td>61.6</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.73</td>
<td>12.04</td>
<td>8.65</td>
<td>7.91</td>
</tr>
<tr>
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<td>6</td>
<td>20</td>
<td>12</td>
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<td>66.5</td>
<td>60.8</td>
<td>60.6</td>
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<td>4.73</td>
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<td>8.50</td>
<td>8.11</td>
</tr>
<tr>
<td>Month 12</td>
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<td>21</td>
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</tr>
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<td>63.6</td>
<td>60.9</td>
<td>61.6</td>
</tr>
<tr>
<td></td>
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<td>4.94</td>
<td>12.04</td>
<td>8.17</td>
<td>7.91</td>
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<tr>
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<td>0</td>
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<tr>
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<td>Mean</td>
<td>54.9</td>
<td>--</td>
<td>60.0</td>
<td>--</td>
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<tr>
<td></td>
<td>SD</td>
<td>5.71</td>
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<td>Visit</td>
<td>Statistic</td>
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<td></td>
<td></td>
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<tr>
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<td>-----------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CXL Group (N=19)</td>
<td>Control Group (N=24)</td>
<td>CXL Group (N=19)</td>
</tr>
<tr>
<td>Baseline</td>
<td>n</td>
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<td>19</td>
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<td></td>
<td>Mean</td>
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<td>57.0</td>
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<td></td>
<td>SD</td>
<td></td>
<td>13.02</td>
<td>7.97</td>
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</tr>
<tr>
<td>Month 3</td>
<td>n</td>
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<td>18</td>
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<td>Mean</td>
<td></td>
<td>60.3</td>
<td>59.6</td>
<td>21.2</td>
</tr>
<tr>
<td>Month 6</td>
<td>n</td>
<td></td>
<td>19</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>59.2</td>
<td>59.0</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
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<td>12.18</td>
<td>13.75</td>
<td>1.76</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
<td></td>
<td>19</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>58.7</td>
<td>59.1</td>
<td>-1.9</td>
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<tr>
<td></td>
<td>SD</td>
<td></td>
<td>11.47</td>
<td>13.76</td>
<td>4.00</td>
</tr>
<tr>
<td>Month 12</td>
<td>n</td>
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<td>18</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
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<td>Mean</td>
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<tr>
<td></td>
<td>SD</td>
<td></td>
<td>11.71</td>
<td>--</td>
<td>4.09</td>
</tr>
</tbody>
</table>
Avedro Response to CDRH Request #2b:
Avedro agrees to conduct a post-approval study (PAS) to monitor long-term safety and effectiveness of CXL. Table 48 provides a synopsis of the proposed PAS.

Table 48: Summary of Proposed Post-Approval Study

| Title | A Phase IV, Prospective, Observational Study of the Long-term Safety and Efficacy of the KXL System with Photrex (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes with Progressive Keratoconus or Corneal Ectasia |

Reviewer Comment: A postapproval study would be recommended if the product were approved. CDRH requested DEPI to review the proposal and provide comment for the advisory committee briefing materials. A preliminary review was done by DEPI for the purposes of preparing for the advisory committee meeting, however, advisory committee recommendations for the postapproval study will need to be taken into consideration before proceeding. At a bare minimum, I would
Comment that rigorous methodology and analyses be prespecified, that the device to be marketed be used to obtain the data, that vulnerable subpopulations receive adequate enrollment to allow interpretation of results, and that long term data (minimum 3-5 years) be obtained.

The CDRH statistical reviewer astutely recommended that Kmax values for the untreated eyes be measured at all study visits (at least at baseline and months 1, 3, 6, and 12) so that changes in mean Kmax value be better understood by the end of the study. I would add that data from untreated fellow eyes should not be limited to Kmax, but rather, comprehensive data collection should be conducted in these eyes to help serve as a potential source of control-like data – given the problems encountered in the current study with retaining and untreated control arm this is an important consideration.

Furthermore, CDRH has recommended either a panel homework assignment or Network of Experts call or some form of communication with experts in the field of cornea in order to determine critical study design issues for any future crosslinking trials (IND, postapproval, etc.)
5. **BIORESEARCH MONITORING PROGRAM INSPECTION (BIMO)**

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 Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.18 (SN 0027, Module 1.6.2) where we provided validated audit trail reports for UVX-002 and UVX-003 to address the gaps in study data monitoring for the period from June to September 2010. In the agency’s 01 August 2014 preliminary comments, the OSI acknowledged that their inspectional findings of the four top enrolling sites for UVX-002 and UVX-003 did not raise concerns about data integrity or human subject safety and agreed that the gaps in documentation of study monitoring have been adequately addressed.

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 can be found in the complete and final audit report. The audit findings were similar to that of FDA’s in there was no evidence of research misconduct, data falsification or fabrication at the site.

Efficacy data were generally accurately reported and had an error rate of <0.5%. Most of the discrepancies and audit findings were related to non-numeric data that involved text or drawings.

Avedro notes that the types and rates of adverse events reported in this study were consistent with those reported in the UVX-002 and UVX-003 studies.

**Reviewer Comment:** This audit was performed with interaction with the CDER clinical team and I have limited knowledge of what transpired. I have been advised by CDER management to proceed with my review, however, it is unclear what data (if any) will require re-review post-audit since the Applicant refers to an error rate in some of the data collection, albeit small.
6. ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

6.1. Complete Response Item #15

The orphan designation for this combination product is for “keratoconus,” but the studies provided enrolled subjects with “progressive keratoconus.” Please discuss the similarities/differences between these two diagnoses, as they may have impact labeling and the orphan indication.

Avedro Response:

Avedro’s orphan drug designation 11-3449 is for riboflavin ophthalmic solution and UV-A light for the treatment of keratoconus. Avedro contacted the Office of Orphan Products Development (OOPD) to inquire as to what the implications would be if NDA 203-324 were to be approved for “progressive keratoconus,” a subset of the population that was granted orphan designation. A copy of their 14 May 2014 response is provided.

According to the OOPD, as long as the marketing approval is covered by that orphan drug designation (including a subset of the designated disease or condition), the sponsor is eligible for the incentive afforded by the orphan drug designation. Designation 11-3449 was granted based on the entire keratoconus population in the United States. Therefore, a marketing application for riboflavin ophthalmic solution and UV-A light for the treatment of progressive keratoconus, which is a subset of the population, is covered under orphan drug designation 11-3449.

Reviewer Comment: This topic has been reviewed above. The Applicant has stated in a response reviewed above that the indication will be for progressive keratoconus since that was the population (intended to be) studied.
Reviewer Comment: Literature is discussed below in a separate section. During a focused literature review, additional articles published with Dr. Hersh on study data/results were identified.
6.3. Complete Response Item #17

You market similar products containing riboflavin ophthalmic solution, e.g. VibeX, in Europe which are used with a device for CXL. Please submit any postmarketing data on the VibeX product(s) which could be relevant for the safety profile of your proposed riboflavin ophthalmic solution products and to the device.

Avedro Response:

The following Avedro’s riboflavin ophthalmic solutions were CE certified in November 2012:

- 0.12 % riboflavin, 0% dextran
- 0.12 % riboflavin, 0.8% dextran
- 0.12 % riboflavin, 20% dextran

Evaluation of Avedro’s riboflavin ophthalmic solutions for corneal cross-linking between the time periods of December 1, 2012 and 31 March 2014 was performed and the results are provided below:

- There were only 5 complaints registered during this time period, none of which were associated with the use of riboflavin ophthalmic solution.
- There were no complaints registered against the 104 units that were distributed.
- No field safety actions or recalls associated with Avedro’s riboflavin ophthalmic solutions.

The KXL System was CE certified in December 2010. The frequency of incidents and malfunctions associated with the use of the KXL System for corneal cross-linking until 31 December 2013 is provided below:

- No deaths occurred.
- There were no field safety actions or recalls.
- No complaints registered that were directly attributable to the device.

Based upon Avedro’s review of available post marketing data, the use of Avedro’s riboflavin ophthalmic solutions and KXL system for cross-linking presents very low risk.

Reviewer Comment: The Applicant has not provided any data obtained with the KXL system nor alluded to how many patients have been treated with the KXL System since 2010. Since the treatment parameters of the KXL system as used in Europe are believed to be very different than the product proposed for marketing (accelerated crosslinking vs. standard “Dresden” protocol) based on the Applicant’s statements at the advisory committee meeting and public information online, any data collected in Europe would have limited utility in evaluating the device proposed for market in the US.
Interactive Requests and Additional Review:

A challenge in this review was the fact that the prespecified endpoints and analyses (in the 3 study protocols) were revised in the final statistical analysis plan submitted after the last subject completed the last study visit and after a number of publications had been published on a selection of study results (at least 5 based on the findings of the CDRH literature review discussed below. The following is a slide created by CDER statisticians for the advisory committee meeting (note that only a single publication is alluded to below, however, the Applicant agreed at the panel that there were additional publications):

![Primary Efficacy Evaluation: Dates of Key Events](image)

The three study protocols defined the same endpoints and analyses as below (cut and paste from the UVX-001 Protocol in excerpts due to length of this section):
9.0 Data Analysis and Statistical Considerations

A detailed statistical analysis plan (SAP) will be developed for analysis of all data for this study. Required analyses and target endpoints that will be included in this SAP are summarized below. The methods by which each of these analyses is performed will be included in the SAP. The required analyses and target endpoints include, but are not limited to those listed below.

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software. All subjects who are enrolled in this study will be included in the safety analysis. All two sided testing and confidence intervals will use a significance level of 5%. The superiority hypotheses will be tested at a significance level of 2.5%.

Data for eyes treated for corneal ectasia and for eyes treated for progressive keratoconus will be analyzed separately.

9.5 Primary Efficacy Criteria

9.5.1 Keratometry

The change in maximum keratometry (Kmax) from baseline will be evaluated at 3 months for all eyes treated and those in the control group. Data will be summarized using descriptive statistics and the differences in mean changes between the CXL group and the control group at 3 months will be evaluated using a two sample t-test to test the following hypothesis:

\[ H_0: \mu_{\text{CXL}} - \mu_C = 0 \text{ versus } H_A: \mu_{\text{CXL}} - \mu_C > 0 \]

where \( \mu_C \) is the mean difference between the 3 month Kmax reading and the baseline Kmax for control group and \( \mu_{\text{CXL}} \) is the mean difference between the 3 month Kmax reading and the baseline Kmax for the CXL group.

If it assumed the data from both treatment groups are normally distributed, then the test statistic from the ANOVA for testing the above hypothesis is a t-test.

As a secondary analysis of this primary endpoint, the change in maximum keratometry (Kmax) from baseline will be evaluated at 1, 3, 6, and 12 months for all eyes treated and those in the control group and a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time.
9.6 Secondary Efficacy Criteria

9.6.1 Manifest Refraction
The change in manifest refraction spherical equivalent from baseline will be evaluated at 3 months. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test at each time point.

As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.

9.6.2 Visual Acuity
Change in BSCVA and UCVA compared to the baseline examination will be evaluated at 3 months postoperatively. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test.

As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.

9.6.3 Central Pachymetry
The change in central pachymetry (as measured by Pentacam) from baseline will be evaluated at 3 months postoperatively. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test.

As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.

9.7 Clinical Safety Endpoint Criteria

9.7.1 Adverse Events and Complications
All subject questionnaire data, complications, and adverse events will be tabulated and summarized.

9.7.2 Key Safety Parameters
For each time point, the following key safety parameters will be estimated for the entire cohort.

1) Percentage of eyes that had a loss of 2 or more lines in BSCVA
2) Percentage of eyes that had a BSCVA worse than 20/40
3) Percentage of eyes that had a greater than 2D increase in Kmax

9.8 Study Success
Study success is defined as a difference of at least 1 diopter in the primary efficacy criteria (mean change in Kmax from baseline to 3 months) between the CXL treatment group and control group.

As a secondary analysis of study success, the difference in the mean change in Kmax from baseline across time at 1, 3, 6, and 12 months will be evaluated for the treatment group and compared to the mean change in Kmax in the control group at 3 months.

9.9 Refractive Status Vision Profile
The RSVP will be administered pre-treatment at screening to establish the subject’s baseline and at 1, 3, 6 and 12 months after CXL. The change in RSVP from baseline will also be evaluated at 1, 3, 6 and 12 months postoperatively. Data will be summarized using descriptive statistics. A lower RSVP score indicates less dysfunction.

The secondary safety endpoint will be the difference in the composite score for the RSVP administered at 3 months after CXL and the pre-treatment or baseline composite score. Therefore, it is desired to determine if the composite score for the RSVP has decreased significantly from the preoperative assessment by the 3 month time point. Published literature indicates that a difference of 6 points or more on the composite scores is a clinically significant change.\(^1\)

In contrast, the study report describes the following endpoints and analyses (UVX-001 study report body – again, in excerpts due to length):
9.7.1.3.2. Efficacy Endpoints

The primary efficacy parameter was corneal curvature, as measured by maximum keratometry ($K_{\text{max}}$). $K_{\text{max}}$ was evaluated at baseline and at Months 1, 3, 6, and 12. Study success was defined as a difference of $\geq 1$ D in the mean change in $K_{\text{max}}$ from baseline to Month 12 between the CXL group and the control group. The primary efficacy endpoint compared baseline and Month 12 data for the study eye only, for each subject. The difference between the baseline and Month 12 $K_{\text{max}}$ values was calculated as Month12 $K_{\text{max}}$ minus baseline $K_{\text{max}}$. The baseline score was defined as the closest measurement prior to treatment for the eye in question; i.e., in some analyses, a subject could be represented more than once if the study eye randomized to the sham treatment had been crossed over to CXL treatment and/or the fellow eye had received CXL treatment.

Other efficacy parameters included evaluations of $K_{\text{max}}$ over time for all CXL treated eyes (eyes randomized to CXL treatment, eyes randomized to sham and subsequently treated with CXL, and fellow eyes subsequently treated with CXL) and non-study CXL-treated eyes. The categorical distribution of $K_{\text{max}}$ values was evaluated, including the proportion of subjects who experienced a $\geq 1$ D decrease from baseline $K_{\text{max}}$. Mean change from baseline $K_{\text{max}}$ was evaluated for subjects who only received riboflavin with dextran and subjects who did not achieve a corneal thickness < 400 microns after treatment with riboflavin with dextran and subsequently received riboflavin without dextran. Mean changes from baseline in best spectacle-corrected visual acuity (BSCVA) and uncorrected visual acuity and categorical changes from baseline in BSCVA were evaluated by treatment group.

9.7.1.5. Safety Evaluation

Safety endpoints included the following:

- **AEs**
- **Subject symptoms**
- **VA (BSCVA and UCVA)** using logMar units. LogMar was calculated as the log of the reciprocal of the Snellen fraction.
- **Loss of VA**
  - Loss of 3 or more lines in BSCVA (+0.3 logMAR change)
  - BSCVA worse than 20/40 (> 0.3 logMAR)
- **Manifest refraction**, calculated as MRSE, which is equal to the spherical component $+0.5 \times$ the cylindrical component
- **Pachymetry** (pupil center [\mu m], apex [\mu m], thinnest location [\mu m])
- Changes in endothelial cell density
- **Slit-lamp examination of the cornea and lens**
- **Changes in keratometry measurements on Pentacam images**
  - Corneal Front (CF K1 [D], CF K2 [D], CF Km [D], Axis [flat/steepl])
  - Indices in 8 mm zone (ISV, IVA, KI, CKI, IHA, IHD, RMin, TKC)
Reviewer Comment: Note that significant changes were made to prespecified endpoints and analyses including the decision not to evaluate results from the RSVP despite the fact that it had been prespecified as a secondary safety endpoint and the fact that the protocol committed to evaluation of the prespecified endpoints and analyses in any future SAP. I believe this was due to concerns that the RSVP was not validated for the population proposed for indication in this NDA. However, I have not seen any official by FDA PRO experts regarding this matter.

Note also that other changes were made such as the decision to specify evaluation of Kmax from pentacam measurements rather than manual keratometry, the decision to modify BSCVA from loss of 2 lines to loss of 3 lines or more (additional analyses were requested by the committee which should be requested in such a way to generate information regarding subjects who lost 2 lines of vision or more), the decision to remove the specific safety evaluation for increase of 2 D in Kmax (which in the literature has been considered a treatment failure -sometimes even when only 1 D increase in Kmax was noted) and the decision to switch prespecified secondary effectiveness endpoints to safety endpoints (such as manifest refraction and visual acuity). It appears the final SAP was submitted to CDER in 2011 and therefore CDER was resistant to my assertion that the specific differences between the prespecified endpoints and Final SAP (or study report) endpoints and analyses required inclusion and discussion in the advisory committee briefing materials and in the FDA presentation to the committee. I decided to truncate my presentation at the advisory committee to avoid engaging in the
clinical presentation, which I felt lacked critical detail and clarity. CDER, OCP and office level management were aware there were outstanding concerns as we approached the advisory committee.

For the purposes of my review, however, CDER agreed to request analyses based on the prespecified endpoints in the protocol (except for the RSVP) although CDER made agreements with the Applicant to receive many of these analyses after the advisory committee meeting (or at a point in which I would be unable to incorporate such information into my presentation).

Of note, regarding the RSVP, the CDRH statistical reviewer was able to provide abbreviated information from the RSVP data submitted in the database for my review. His preliminary examination of the data revealed that while the treatment arm performed slightly better than the control arm (on at least some questions), both were dissatisfied, for example, with the question relating to reading. Such information does not allow for definitive interpretation for the purposes of my review, however, I felt an understanding of the type of information the data submitted would reveal was important. In the absence of official review of the data by PRO experts (which CDER objected to), I felt some effort was required to understand the data that was chosen to be ignored in the final SAP. Since there were not one, but TWO questionnaires prespecified in the protocol as safety endpoints, I believe that consideration of patient reported outcomes is critical to making a determination on the file. The questionnaires have likely not been validated for the indicated population in these trials, but ignoring the data seems inappropriate without official review from PRO experts.

Regarding the additional interactive analyses discussed below – note that these analyses were received in February and March and with very little time or opportunity to review the material prior to the advisory committee or even deadline of the clinical review.

Furthermore, much of the review of this information is, by necessity and time of receipt, occurring after the advisory committee at which the need for a new cohort and stratification of data was strongly recommended by the committee. Therefore, review of these analyses using the unmodified cohort had become somewhat obsolete. However, since the analyses were requested, a limited review is being performed with those limitations and caveats in mind. The need for additional analyses beyond these was made clear at the advisory committee and subsequent internal meetings.
Agency Request

1. Pre-specified analyses as delineated in the protocol, please provide analysis and discussion of the following:
   a. Safety
      i. BCVA

      Per the protocol: “For each time point, the following key safety parameters will be estimated for the entire cohort.

      1) Percentage of eyes that had a BSCVA worse than 20/40
      2) Percentage of eyes that had a greater than 2D increase in “Kmax”

Avedro Response to Question 1.a.i.1:

For each study, the proportions of subjects who had BSCVA worse than 20/40 are presented, using the ITT population. No inferential statistics or analyses were performed.

The proportions of subjects who had BSCVA worse than 20/40 were generally similar or smaller in the CXL group as compared to the control group, except at Week 1 and Month 1. As expected due to debridement of the corneal epithelium in the CXL group, a greater proportion of subjects in the CXL group had BSCVA worse than 20/40 at Week 1 and Month 1.

Results for individual studies are presented in Table 1 through Table 4 and described below.

UVX-001: Keratoconus

Table 1 summarizes the proportion of subjects who had a BSCVA worse than 20/40 (yes/no) using observed values and LOCF. As no subjects in the control group had a BSCVA observation at Month 12, results at Month 12 are displayed for both observed values and using LOCF. The text below describes the observed values, unless otherwise indicated.

At baseline, the proportion of subjects with BSCVA worse than 20/40 was 58.6% and 64.3% in the CXL and control groups, respectively. The proportion of subjects with BSCVA worse than 20/40 was higher in the CXL group than in the control group at Week 1 (85.2% vs. 44.4%) and, to a lesser extent, at Month 1 (69.0% vs. 50.0%). At Month 3, the proportion of subjects with BSCVA worse than 20/40 was comparable between treatment groups; at Month 6, the proportion of subjects with BSCVA worse than 20/40 was 42.9% in the CXL group and 52.9% in the control group. At Month 12, 6 (30.0%) subjects in the CXL group had BSCVA worse than 20/40. In the LOCF
analysis, 11 (37.9%) subjects in the CXL group and 16 (55.2%) subjects in the control group had BSCVA worse than 20/40 at Month 12.

**UVX-001: Corneal Ectasia**

Table 2 summarizes the proportion of subjects who had a BSCVA worse than 20/40 (yes/no) using observed values and LOCF. As no subjects in the control group had an observation at Month 12, results at Month 12 are displayed for both observed values and using LOCF. The text below describes the observed values, unless otherwise indicated.

At baseline, the proportion of subjects with BSCVA worse than 20/40 was 43.5% and 50.0% in the CXL and control groups, respectively. The proportion of subjects with BSCVA worse than 20/40 was higher in the CXL group than in the control group at Week 1 (60.9% vs. 50.0%) and Month 1 (58.3% vs. 48.0%). Conversely, the proportion of subjects with BSCVA worse than 20/40 was lower in the CXL group than in the control group at Month 3 (21.7% vs. 54.2%) and Month 6 (14.3% vs. 66.7%). At Month 12, 5 (26.3%) subjects in the CXL group had BSCVA worse than 20/40. In the LOCF analysis, 7 (29.2%) subjects in the CXL group and 14 (56.0%) subjects in the control group had BSCVA worse than 20/40 at Month 12.

**UVX-002: Progressive Keratoconus**

Table 3 summarizes the results of subjects in the Safety population who had a BSCVA worse than 20/40 (yes/no) using observed values and LOCF. As only 1 subject in the control group had an observation at Month 12, results at Month 12 are displayed for both observed values and using LOCF. The text below describes the observed values, unless otherwise indicated.

At baseline, the proportion of subjects with BSCVA worse than 20/40 was 52.2% and 52.1% in the CXL and control groups, respectively. The proportion of subjects with BSCVA worse than 20/40 was higher in the CXL group than in the control group at Week 1 (75.8% vs. 52.8%). At subsequent visits through Month 6, the proportion of subjects in the CXL group with BSCVA worse than 20/40 was generally comparable to or lower than the proportions in the control group (Month 1, 59.2% vs. 52.9%; Month 3, 48.5% vs. 57.4%; Month 6, 41.2% vs. 58.8%). At Month 12, 31 (47.0%) subjects in the CXL group had BSCVA worse than 20/40. In the LOCF analysis, 33 (45.2%) subjects in the CXL group and 40 (54.8%) subjects in the control group had BSCVA worse than 20/40 at Month 12.

**UVX-003: Corneal Ectasia**

Table 4 summarizes the results of subjects in the Safety population who had a BSCVA worse than 20/40 (yes/no) using observed values and LOCF. As only 2 subjects in the control group had an observation at Month 12, results at Month 12 are displayed for both observed values and using LOCF. The text below describes the observed values, unless otherwise indicated.

At baseline, the proportion of subjects with BSCVA worse than 20/40 was 44.6% and 38.7% in the CXL and control groups, respectively. The proportion of subjects with BSCVA worse than 20/40 was higher in the CXL group than in the control group at Week 1 (74.2% vs. 44.1%), Month 1 (50.8% vs. 33.3%), and Month 6 (36.7% vs. 41.2%).
22.2%). At Month 3, the proportion of subjects with BSCVA worse than 20/40 was comparable between treatment groups. At Month 12, 18 (33.3%) subjects in the CXL group had BSCVA worse than 20/40. In the LOCF analysis, 21 (31.3%) subjects in the CXL group and 24 (38.1%) subjects in the control group had BSCVA worse than 20/40 at Month 12.

**Reviewer Comment:** BSCVA will require additional review once additional analyses are requested (as developed based on advisory committee recommendations. In particular, BSCVA analyses will need to consider loss of 2 or more lines of BSCVA as prespecified. This is significant since the proposed indicated population suffers from disease corneas and therefore evaluation of BSCVA in the absence of consideration of baseline value may misrepresent the loss related to the procedure (compared to the baseline disease process). Loss of the control arm to crossover greatly complicates this review as variability of BSCVA due to natural course of disease is lost if values are carried forward.

Kmax increase ≥ 2 D (received by this reviewer from CDER 2/16/2015, sent by Applicant 2/13/2015)
Avedro Response to Question 1.a.i.2:

The proportions of study eyes that had an increase from baseline in $K_{\text{max}}$ of $\geq 2$ D are presented, using the ITT population. No inferential statistics or analyses were performed. Across studies, the proportion of study eyes that had a $\geq 2$ D increase in $K_{\text{max}}$ at Month 1 was greater in the CXL group as compared to the control group; this is consistent with the changes seen in the CXL group post epithelial debridement. At all other time points, the proportion of eyes with $\geq 2$ D increase in $K_{\text{max}}$ was smaller, and progressively decreased over time, in the CXL group compared to the control group.

The observed data for randomized study eyes that had a $\geq 2$ D increase in $K_{\text{max}}$ are summarized in Table 5 for progressive keratoconus subjects and in Table 6 for corneal ectasia subjects.

### Table 5: Percentage of eyes with $\geq 2$ D Increase in $K_{\text{max}}$ in Progressive Keratoconus Subjects (Observed, ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>UVX-001</th>
<th>UVX-002</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL Group (N=29)</td>
<td>Control Group (N=29)</td>
</tr>
<tr>
<td>Visit</td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>Month 1</td>
<td>8/29</td>
<td>27.6</td>
</tr>
<tr>
<td>Month 6</td>
<td>3/28</td>
<td>10.7</td>
</tr>
<tr>
<td>Month 12</td>
<td>0/20</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 6: Percentage of eyes with $\geq 2$ D Increase in $K_{\text{max}}$ in Corneal Ectasia Subjects (Observed, ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>UVX-001</th>
<th>UVX-003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL Group (N=24)</td>
<td>Control Group (N=25)</td>
</tr>
<tr>
<td>Visit</td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>Month 1</td>
<td>5/24</td>
<td>20.8</td>
</tr>
<tr>
<td>Month 3</td>
<td>2/23</td>
<td>8.7</td>
</tr>
<tr>
<td>Month 6</td>
<td>0/22</td>
<td>0</td>
</tr>
<tr>
<td>Month 12</td>
<td>0/20</td>
<td>0</td>
</tr>
</tbody>
</table>

Reviewer Comment: $K_{\text{max}}$ increase $\geq 2$ D as reported above was a prespecified safety endpoint supported by the literature as such changes may represent “treatment failures” and at the very least
represent potentially significant disease progression. I believe this information deserves to be conveyed in the labeling. The data presented here raises some question about efficacy (for example, see the difference in percentage of corneal ectasia subjects with observed Kmax increase ≥ 2 D between study arms in UVX-003: 5.6% at month 12 in the CXL arm vs. 5.3% at month 6 in the control arm with no data at month 12).

Disposition (received by this reviewer from CDER 2/20/2015, sent by Applicant 2/20/2015)

CDER requested the following in an effort to improve accountability data since poor accountability in control arm at 12 months was greatly attributed to “crossover” to the treatment arm which was built into the study design:

We understand that the study duration for the sham subjects could be longer than 12 months, depending on the timing of the crossover from sham to CXL. The higher discontinuation rate for sham subjects in the disposition tables could be attributed to the longer study duration for these subjects. Please provide disposition tables that cover the study duration from Day 0 to Month 12 (First 12 months). It is expected that the information for CXL subjects to remain the same. Sham subjects that remained in the study 12 months from Day 0 will be considered as completing 12 months of the study.

Avedro’s Response:

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.

Reviewer Comment: The Applicant makes the statement that in these analyses they are defining study completers as subjects who “remained in the study for at least the start of the Month 12 visit.
window”. This does not appear consistent with CDER’s request nor does this appear to be an accurate way to assess accountability – a subject would actually need to have been at the Month 12 visit to complete the study – being in the study at the start of the Month 12 visit is meaningless unless data was actually collected towards that final study visit. It is very concerning that greater clarity has not been provided regarding what is meant by this language – especially since this revision to subject disposition impacted not just the sham arm but also the CXL arm. This analysis falsely inflates the numbers and conceals that very real problem with lack of data in the randomized arm assigned at the month 12 timepoint. Accountability is not a significant problem if the month 3 visit is used for efficacy analysis – as intended by the study design. By switching the timing of the endpoint and manipulating accountability to cover up the limitations, I am very concerned that we are obscuring a key limitation with using month 12 data (albeit by study design). I disagree with using this accountability method for sole presentation of accountability/disposition data and do not believe this should be used in any labeling or material distributed to the public as it is misleading and potentially flawed. Furthermore, it conceals information of critical importance to convey regarding a study limitation.

In addition, I will add that it is unclear whether this disposition data is pertinent to safety analyses (which would also consider fellow eye data but should still include separate information regarding subjects remaining in randomized arm and crossed over as relevant to safety analyses) or efficacy data (which would only be pertinent to subjects who remain in the study in the randomized arm assigned at every study visit). Alternatively, the efficacy data are being re-defined by FDA (yet another post hoc redefinition) to include treatment effect post-crosslinking in both arms (i.e., including sham eyes which received crosslinking treatment). While such data/consideration is interesting and may be appropriate for supplemental consideration, I don’t believe presentation of accountability/disposition should be driven by these post hoc analyses.

Treatment Parameters (received by this reviewer from CDER 2/20/2015, sent by Applicant 2/20/2015)

2. Evaluation of data collected
d. Treatment Parameters
   i. To evaluate the differences between the device studied (UV-X) and the device to be marketed (KXL System), the following are needed:
      1. Data regarding patient positioning during the procedures and a discussion addressing the effect that variability in patient position may have had on study results.
      2. Justification for why the differences in focusing will not affect device performance
**Reviewer Comment:** This information has been previously reviewed in the Complete Response section above. This additional information does not change my impression regarding the potentially serious concerns with the differences in devices.

**Pediatric Subjects (received by this reviewer from CDER 2/20/2015, sent by Applicant 2/20/2015)**

### 3. Pediatric Subjects

Reorganize the pediatric information (separate tables) for the primary efficacy variable and for endothelial cell counts to describe subject’s ≤ 16 years of age and ≤ 21 years of age.
A total of 33 pediatric subjects (< 21 years of age) 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. The analysis of the pediatric population by years of age (< 16 years of age and 16-21 years of age) is included in Table 1.

Table 1: Pediatric Population

<table>
<thead>
<tr>
<th>Age</th>
<th>UVX-001 (Keratoconus)</th>
<th>UVX-002</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL Group</td>
<td>Control Group</td>
<td>CXL Group</td>
</tr>
<tr>
<td>Age &lt; 16</td>
<td>--</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Age 16-21</td>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

The number of subjects in the pediatric population is too small to conduct meaningful statistical analyses; therefore, a discussion of outcomes is appropriate in this instance.

The primary efficacy endpoint was the difference in mean change from baseline $K_{\text{max}}$ (LOCF) between the randomized study eye and the control eye in the ITT Population. Study success was defined as a difference of $\geq 1$ D in the mean change in $K_{\text{max}}$ from baseline to Month 12 between the CXL group and the control group. Efficacy results are summarized using both LOCF and observed values.

UVX-001

In UVX-001, one pediatric subject < 16 years of age was randomized into the control group. The $K_{\text{max}}$ data, LOCF and observed, for that subject are provided in Table 2. Five pediatric subjects 16 – 21 years of age were enrolled: two in the CXL group and three in the control group. The $K_{\text{max}}$ data for this subpopulation, both LOCF and observed, are provided in Table 3. Based on both LOCF and observed values, the difference between treatment groups did not meet the primary efficacy endpoint.

UVX-002

In UVX-002, six (6) pediatric subjects <16 years of age were randomized into the study: four (4) in the CXL group and two (2) in the control group. The $K_{\text{max}}$ data, LOCF and observed, for these subjects are provided in Table 4. Using LOCF, the difference between treatment groups meet or exceed 1.0 D at Month 6 and Month 12. For observed values, the difference between treatment groups also meet or exceed 1.0 D at Month 3, Month 6 and Month 12.
Twenty-one (21) pediatric subjects 16 – 21 years of age were randomized into study UVX-002: thirteen (13) in the CXL group and eight (8) in the control group. The \( \kappa_{\text{max}} \) data, LOCF and observed, for these subjects are provided in Table 5. Using LOCF, the difference between treatment groups exceeded 1.0 D at Month 6 and Month 12. For observed values, the difference between treatment groups also exceeded 1.0 D at Month 3, Month 6 and Month 12.

Overall, efficacy results from the UVX-002 pediatric subjects aged <16 years and 16-21 years are consistent with the overall population studied in that the results met the primary efficacy endpoint.
Avedro Response to Question 3 (Endothelial Cell Counts)

A total of 33 pediatric subjects (< 21 years of age) 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.

As per the protocol, endothelial cell counts (ECC) were collected via specular microscopy at Screening, Month 3 and Month 12.

UVX-001

In UVX-001, one (1) progressive keratoconus pediatric subject < 16 years of age was randomized into the control group. The endothelial cell count data, observed, for that subject are provided in Table 6. The subject experienced a decrease in ECC at Month 3 of -166 cells/mm². As most subjects in the control group crossed-over to receive CXL treatment, no measurement was obtained at Month 12.

Five (5) progressive keratoconus pediatric subjects 16 – 21 years of age were enrolled: two (2) in the CXL group and three in the Control group. The endothelial cell count data (observed), for those subjects are provided in Table 7. The mean change in baseline for the CXL group at Month 3 and Month 12 was -85 cells/mm² and 3 cells/mm², respectively. At Month 3, the mean change in baseline for the Control group was 153 cells/mm². As most subjects in the control group crossed-over to receive CXL treatment, no measurement was obtained at Month 12.

UVX-002

Six (6) progressive keratoconus pediatric subjects < 16 years of age were enrolled: four (4) in the CXL group and two (2) in the Control group. The endothelial cell count data (observed), for those subjects are provided in Table 8. The mean change in baseline for the CXL group at Month 3 and Month 12 was 192 cells/mm² and -65 cells/mm², respectively. At Month 3, the mean change in baseline for the Control group was -60 cells/mm². As most subjects in the control group crossed-over to receive CXL treatment, no measurement was obtained at Month 12.

Twenty-one (21) progressive keratoconus pediatric subjects 16 – 21 years of age were enrolled: thirteen (13) in the CXL group and eight (8) in the Control group. The endothelial cell count data (observed), for those subjects are provided in Table 9. The mean change in baseline for the CXL group at Month 3 and Month 12 was -279 cells/mm² and -191 cells/mm², respectively. At Month 3, the mean change in baseline for the Control group was -148 cells/mm². As most subjects in the control group crossed-over to receive CXL treatment, no measurement was obtained at Month 12.

Overall, the differences between treatments for the mean change from baseline were not clinically significant. Furthermore, reductions are seen in both the cross-linked group and the control group and are consistent with the known variability of ECC measurements in these patient populations.
Reviewer Comments: Pediatric Safety and Effectiveness outcomes were reviewed above as part of the complete response. I believe this new stratification by age was requested by CDER (and is relevant to CDER pediatric age ranges). Due to the need for additional pediatric analyses (and a new safety and effectiveness cohort) as identified in the deficiencies below (related to advisory committee recommendations) I am deferring further review until such analyses are available. Outstanding concerns regarding pediatric safety and effectiveness have been mentioned in prior review comments and the information here does not alter my prior recommendations.

Endothelial Cell Counts (received by this reviewer from CDER 2/20/2015, sent by Applicant 2/20/2015)

4. Endothelial Cell Counts

Provide a description of the specific instruments and methods used to evaluate endothelial cell counts in the individual clinical studies. Include a discussion of the variability around these measurements and a discussion of your cell count results.
4. Endothelial Cell Counts

Provide a description of the specific instruments and methods used to evaluate endothelial cell counts in the individual clinical studies. Include a discussion of the variability around these measurements and a discussion of your cell count results.

For all three studies (UVX-001, UVX-002, and UVX-003), endothelial cell counts were required per protocol to be obtained for all randomized eyes at Screening (baseline) and at Months 3 and 12. Endothelial cell counts were obtained using specular microscopy. No specific instructions were provided to the sites regarding methodology for acquisition or analysis of the endothelial cell counts. Endothelial cell densities were determined by technicians at individual sites.

Specular microscopy was used to assess endothelial cell counts in the UVX studies since it is a readily available tool used in clinical practice to visualize and analyze the corneal endothelium. It is a non-invasive, photographic method of obtaining endothelial cell counts and utilizes specular reflection of light from the corneal endothelium. The limitation of this technique is that the image quality and accuracy of cell counts depends on the clarity, and refractive and reflective properties, of the cornea.

In a normal, healthy population, estimates of endothelial cell counts have a variability of ± 10% (McCary, 2008), with coefficient of variation (CV) value ranging from 0.2 to 0.3 (Yee 1985, Hashemian 2006). CV is a measure of polymegathism or variation in endothelial cell size. As the CV increases, the variability in estimating endothelial cell counts also increases. There appears to be an increase in pleomorphism and polymegathism in eyes with keratoconus as compared to normal eyes with CV values in keratoconic eyes of approximately 0.35 (Mohamed-Sameh 2014).

In the UVX studies, the mean changes from baseline were less than 5% across studies. This magnitude of change is within the established variance in measurement error, especially for the keratoconus and ectasia populations. There were individual subjects with changes in ECC that were greater than 10% in magnitude, however these changes were equally distributed in both directions, that is, increases and decreases in ECC from baseline. Additionally, decreases in ECC did not correlate with changes in pachymetry and were not associated with any physiologic effects.

As agreed at the 03 Feb 2015 teleconference, the data from a consistent cohort of subjects is summarized and presented in Table 10 through Table 13. In the CXL group, all subjects who had an ECC measurement at each of the three protocol-required time points (Screening, Month 3, and Month 12) are included. For the Control group, data are presented through Month 3 and all subjects who had an ECC measurement at Screening and Month 3 are included. Reductions are seen in both the cross-linked group and the control group and are consistent with the known variability of ECC measurements in these patient populations.
Reviewer Comments: Note that no specific instructions were provided to study sites regarding the acquisition nor analysis of endothelial cell counts. Endothelial cell densities were determined by technicians at individual sites. The methodology, or lack thereof, described is poor and likely contributed to the nonphysiologic increases observed in the “noisy” endothelial data. It is very difficult to draw meaningful conclusions for data derived in such a way. Therefore, it is difficult to draw definitive conclusions regarding safety as related to the potential for endothelial cell damage in the current data set.

Visual Acuity (received by this reviewer from CDER 3/4/2015, sent by Applicant 3/3/2015)

1. Pre-specified analyses as delineated in the protocol, please provide analysis and discussion of the following:

   b. Secondary Efficacy Criteria
      
      ii. Visual Acuity

      Per the protocol: “Change in BSCVA and UCVA compared to the baseline examination will be evaluated at 3 months postoperatively. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test. As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.”
Reviewer Comment: The Applicant confirms that analyses previously reported in the study report were consistent with this prespecified endpoint and merely recategorized from effectiveness to safety endpoints. The decision to recategorize these analyses is interesting as there may be some support for effectiveness in this data given the “trends” towards greater improvement in the CXL group compared to the control. Note, ranges in the data should be noted since “mean” values mask much of the variation captured. Note also there are a number of limitations and concerns with this data, for example, the loss of the control arm to “crossover” and the use of LOCF data are serious limitations not to mention concerns with methodology in this unmasked trial which can strongly impact a measurement that is subjective, such as visual acuity testing (which has subjective elements in subject effort and tester effort/pushing).
Pachymetry (received by this reviewer from CDER 3/4/2015, sent by Applicant 3/3/2015)

1. Pre-specified analyses as delineated in the protocol, please provide analysis and discussion of the following:
   b. Secondary Efficacy Criteria
      iii. Central Pachymetry

Per the protocol: “The change in central pachymetry (as measured by Pentacam) from baseline will be evaluated at 3 months postoperatively. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test. As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.”

Avedro Response to Question 1 b.iii:.

Changes from baseline in central pachymetry (as measured by Pentacam) were evaluated at Months 1, 3, 6, and 12 in the ITT population on both observed cases and with LOCF. Changes from baseline in corneal thickness at the apex and the thinnest location were summarized using descriptive statistics; differences between treatment groups for mean changes from baseline were analyzed using a 2-sample t-test. This information was provided in the Clinical Study Reports for UVX-001 (keratoconus, Section 12.5.1.5; corneal ectasia, Section 12.5.2.5), UVX-002 (Section 12.5.5) and UVX-003 (Section 12.5.5).

In the statistical analysis plan, this parameter was classified as a safety endpoint and therefore, the secondary analysis of this endpoint using a repeated measure analysis of variance (ANOVA), was not performed. We have now run the ANOVA and the results for Studies UVX-001 (keratoconus), UVX-002, UVX-001 (ectasia), and UVX-003 for the change in central pachymetry, as measured by corneal thickness at apex and corneal thickness at thinnest location, are provided in Table 9 through Table 12 and Table 13 through Table 16, respectively.

The results of these analyses show that the differences between groups in least squares means change from baseline were statistically significant at Months 1 and 3 due to reductions in the corneal thickness in the CXL group. This reduction in corneal thickness is an expected consequence of the corneal debridement in the CXL group and continued epithelial remodeling after re-epithelialization.

Differences between groups in change from baseline in corneal thickness diminished at the later time points with corneal thickness in the CXL group trending back towards baseline at Month 12.

Reviewer Comment: The Applicant confirms that data previously reported in the clinical study report was consistent with this prespecified endpoint, however, categorization of this endpoint was changed from effectiveness to safety. The Applicant’s discussion does not clarify how this data could be used to
support effectiveness. The trend in the CXL arm back towards baseline at Month 12 is of interest as some published literature has cited concern regarding the corneal thinning which occurs during crosslinking. This may be a longterm outcome of interest in a future postapproval study.

IOP (received by this reviewer from CDER 3/4/2015, sent by Applicant 3/3/2015)

2. Evaluation of Data Collected
   b. IOP
      i. While IOP data was collected in the study, no general analysis or organized presentation of data across the population has been provided. An analysis is requested regarding the number (and percent: n/N & %) of subjects demonstrating percent reduction (or increase) in mean IOP at each visit from baseline in increments of 10% (e.g., increase in IOP < 10% but >0%; 0% change; decrease in IOP < 10% but >0%; > = 10%, but less than 20%, and so on in both directions) should be presented. The overall outcomes could be further stratified by baseline mean diurnal IOP (10-14 mmHg, 15-20 mmHg, 21-25, mmHg, 26-30 mmHg, > 31 mmHg, etc.).

Avedro’s Response to 2.b.i:

Provided in the corresponding tables (Table 14.3.14) are the categorical change from baseline of IOP in the randomized eye for UVX-001 (Progressive Keratoconus), UVX-002, UVX-001 (Corneal Ectasia) and UVX-003. The categorical distributions of change from baseline in IOP do not suggest any trends. Across all studies, changes in IOP were distributed within a wide spread in both CXL and Control groups and may be representative of the normal diurnal variation in IOP.

Reviewer Comment: Alteration of the cornea has the potential to affect the accuracy of IOP measurement and therefore, since the Applicant reported on IOP (i.e., the very limited/rare occurrence of IOP elevations>30 mm Hg captured in the population studied) we requested these analyses to determine if any of the data collected raised concern that IOP measurements may have been distinctly different before and after treatment (within a subject) which could indicate that post-CXL IOP measurement may be inaccurate or require adjustment to compare to pre-CXL measurement. The Applicant is correct that diurnal variation in IOP is a known phenomenon and ideally, study methodology would have taken this into consideration and timed the measurement of IOP carefully. However, as this was not a study designed to address IOP specifically, such considerations were not included in the protocol.

I discussed these data with glaucoma expert Dr. Julie Kim. The lack of clear and prespecified detail regarding methodology raises concern that IOP measurements in the study (while intended to be performed by goldman applanation tonometry unless contraindicated) may or may not have been performed with consideration that horizontal and vertical measurement may be needed for subjects
with high astigmatism (which is common in keratoconus and ectasia subjects). We note in the current dataset that pachymetry decreased initially ~20-30 um from baseline then decreased to ~1-10 um from baseline by 12 months. Correspondingly one would expect gross initial underestimation with less underestimation around month 12 which is consistent with UVX-001 and UVX-002 patterns of initial IOP decrease then lesser decrease later on. This does not take into account corneal hysteresis. One would expect higher IOP readings based on increased stiffness alone in crosslinking because more force would be needed to flatten the K. Underestimation is a clinical concern because we would not want to miss increased IOP.

In a PAS, if IOP is being assessed, we recommend more rigorous IOP methodology for subjects with high astigmatism and to take concurrent pachymetry measurements for more interpretable results. One question we would like to answer in a postapproval study would be: “Does UV Xlinking cause under-estimation of IOP measurements?”

Manifest Refraction (received by this reviewer from CDER 3/6/2015, sent by Applicant 3/6/2015)

1. Pre-specified analyses as delineated in the protocol, please provide analysis and discussion of the following:
   
   b. Secondary Efficacy Criteria
   
   i. Manifest Refraction

   Per the protocol: “The change in manifest refraction spherical equivalent from baseline will be evaluated at 3 months. Data will be summarized using descriptive statistics. Differences in the mean changes from baseline between the two treatment groups will be tested using a two sample t-test at each time point. As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatments across time at 1, 3, 6, and 12 months.”

   Due to the data entry errors in the reported manifest refractions, i.e., “+” instead of “-” for several data entries. Examples include but are not limited to patients 230: Month 1, 4312: Month 1, 1301: Week 1. Please submit revised descriptive statistics including tables such as Table 40 in Study 1, Table 24 in Study 2, Tables 14.3.2 for each study.

Avedro Response to Question 1.b.i.

Avedro has performed a comprehensive review of the manifest refraction spherical equivalent (MRSE) data listings which resulted in data corrections outlined in Table 1.

Reviewer Comment: A list of approximately 23 subjects in whom dataline listings required correction was provided.
These entries were corrected and the resulting revised descriptive statistics and summary tables are provided below. Correcting the errors reduced variance in the data but did not affect the overall results.

**UVX-001 - Progressive Keratoconus**

Table 14.3.2 (UVX-001 Progressive Keratoconus) presents MRSE in the randomized eye for the safety population using observed values and LOCF.

Table 2 summarizes MRSE by treatment and visit for corneal ectasia subjects using observed values. Subjects were moderately myopic on entry. Mean MRSE at baseline was $-4.7 \pm 4.00$ D and $-5.8 \pm 5.90$ D in the CXL and control groups, respectively. In the CXL group, mean changes from baseline in MRSE (observed values) ranged from 0.0 D to 1.2 D. In the control group, mean change from baseline in MRSE ranged from $-0.3$ D to 0.0 D. The difference between treatments was not statistically or clinically significant at any time point.

**UVX-002**

Table 14.3.2 (UVX-002) presents MRSE in the randomized eye for the safety population using observed values and LOCF.

Table 3 summarizes MRSE by treatment and visit for observed values. Subjects were moderately myopic on entry. Mean MRSE at baseline was $-3.7 \pm 4.35$ D and $-4.6 \pm 4.89$ D in the CXL and control groups, respectively. In the CXL group, mean changes from baseline in MRSE ranged from $-0.2$ D to 0.1 D. In the control group, mean change from baseline in MRSE ranged from 0.2 D to 0.6 D (N=1). The difference between treatments was not statistically or clinically significant at any time point.

**UVX-001 – Corneal Ectasia**

Table 14.3.2 (UVX-001 Corneal Ectasia) presents MRSE in the randomized eye for the safety population using observed values and LOCF.

Table 4 summarizes MRSE by treatment and visit for corneal ectasia subjects using observed values. Subjects were moderately myopic on entry. Mean MRSE at baseline was $-3.4 \pm 4.40$ D and $-5.5 \pm 5.55$ D in the CXL and control groups, respectively. In the CXL group, mean changes from baseline in MRSE ranged from $-0.2$ D to 0.1 D. In the control group, mean change from baseline in MRSE ranged from $-0.2$ D to 0.0 D. The difference between treatments was not statistically or clinically significant at any time point.

**UVX-003**

Table 14.3.2 (UVX-003) presents MRSE in the randomized eye for the safety population using observed values and LOCF.
Reviewer Comments: The analyses were reviewed and ANOVA analyses noted. The differences described between groups were also noted and lack of clinical and/or statistical significance in most cases. As with most analyses in this file, the ranges reported are of concern, while the means mask much of the information. The Applicant’s discussion does indicate that this data provides any additional support for effectiveness (despite the fact that this was prespecified as an effectiveness endpoint rather than safety – perhaps this is why the endpoint was reclassified). As additional analyses will be requested (including identification of a new cohort for safety and effectiveness), further review will be deferred until such updated analyses are available.

ITT (received by this reviewer from CDER 3/6/2015, sent by Applicant 3/6/2015)

CDER requested the following: Please conduct an analysis of the mean change in $K_{\text{max}}$ from baseline to Month 12 according to the intent-to-treat principle. For subjects in the sham group, their last $K_{\text{max}}$ data recorded at or prior to 12 months (relative to Day 0/Baseline) are used in the analysis regardless of whether their study eyes received CXL treatment prior to Month 12. This analysis compares the efficacy in subjects who had been treated with CXL for 12 months to the efficacy in subjects whose CXL treatment was delayed by three months or six months depending on the visit.
Reviewer Comment: While these results are interesting, they underscore the fact that the control arm was not simply “lost” at 12 months, but rather there was conversion of the control arm to a delayed treatment arm. This does present an interesting analysis of treatment effect in light of the delay in treatment between the control arm compared to the control, but it does not negate the fact that observed control data in the absence of treatment is not available in this study at month 12 (at least, not in a sufficient number of subjects). This was not a well-controlled 12 month study. Rather, this study included a “controlled phase” of 3 months – and even this control was quite poorly chosen since the sham procedure included administration of riboflavin (albeit without epithelial removal or UV illumination). It is unclear why administration of the drug component was felt to be necessary in the “sham” arm. While riboflavin absorption is expected to be poorer in the absence of epithelial debridement, no measure nor observations were recorded to convey whether riboflavin fluorescence was visible in such corneas/eyes. Furthermore, diseased corneas may have any number of abnormal features, epithelial defects or epithelial erosions. A “treatment effect” or improvement in Kmax was actually seen in the progressive keratoconus control arm at 1 month post-treatment – raising any number of questions about why this might have been observed. Seeing a treatment effect in the
control arm after cross-linking is somewhat weakened by the fact that the same type of improvement of Kmax was noted in this control population prior to cross-linking. This population may have been significantly different from the experimental arm due to baseline disease (less progression? Note the number of enrollment criteria protocol deviations in the control arm vs. experimental arm).

Manual Keratometry (received by this reviewer from CDER 3/10/2015, sent by Applicant 3/9/2015)

Since the prespecified endpoints/analyses did not specify whether pentacam or manual keratometry measurements would be used in evaluation of the primary efficacy endpoint, analyses were requested using manual keratometry for comparison to the pentacam results (since the prespecified primary efficacy endpoint was failed for the progressive keratoconus population using pentacam measurements).
Review comments: Additional tables are included in the response. The response is complete. These data deserved exploration in an effort to increase support of product efficacy. Based on the results reported and the Applicant’s discussion, these data do not significantly alter the review of this product (i.e., I am no more or less convinced of product efficacy). They do potentially support the results of the pentacam – meaning that subtle signs of effectiveness may have been consistently captured.

Refractive Stability (received by this reviewer from CDER 3/11/2015, sent by sponsor 3/10/2015):
The Applicant changed the time of the analysis of the primary efficacy endpoint from 3 months post-crosslinking to 12 months post-crosslinking. Literature was cited to support this change, due to the belief that the stability of the corneal response to treatment would occur by 6 or 12 months post-procedure, but not by 3 months. Due to concerns regarding the use of literature in this review, it appeared that the stability of the corneal response should be evaluated using the dataset collected, rather than relying on a selection of literature chosen by the Applicant.

Therefore, the Applicant was asked to provide the following analyses to evaluate refractive stability:

2.c. REFRACTIVE STABILITY

You cite literature to support the appropriate timing of the efficacy endpoint based on stability of the cornea. The following additional analyses are requested:

i. For each study and each arm: the mean within-subject change in Kmax between each consecutive visit (with a standard deviation and range), and

ii. For each study and each arm: the 95% confidence interval that with subject change in Kmax between each consecutive visit was less than or equal to 1D

iii. Analyses to show what percentage of subjects have a change in manifest refractive spherical equivalent (MRSE) ≤ 0.50, ≤0.75 and ≤ 1.00 D between each consecutive visit beginning at baseline. We also request these analyses be performed with the baseline “reset” at month 3 and at month 6.

iv. Analyses to show the mean rate of change in MRSE as determined by paired analysis (and whether the following has been achieved: less than or equal to 0.50 D per year (or 0.04 D/month) between 2 refractions performed at least 3 months apart).

Avedro’s Response to 2.c.i-ii.:

Analysis of refractive stability based on Kmax was not a pre-specified analysis in the protocol or the statistical analysis plan. Per the Agency’s request, Avedro has completed the analyses of the mean within-subject changes in Kmax between consecutive visits (baseline to Month 3, Month 3 to Month 6, and Month 6 to Month 12). These analyses have been conducted for each study using a consistent cohort of subjects in the CXL group who had Kmax readings at each of the visits. Similar analyses have not been conducted for subjects in the Control group since subjects in the Control group did not have Kmax data for all visits through 12 months.

Table 1 through Table 4 summarize the mean within-subject changes in Kmax between consecutive visits as well as provide the proportions of subjects that demonstrated a change in Kmax between each consecutive visit of ≤ 1 diopter (D).
### Table 1: Change in $K_{\text{max}}$ between Consecutive Visits in the CXL Group
(Please see the notes for the CXL Group, UVX-001, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in $K_{\text{max}} \leq 1.0$ D</td>
<td>n/N 17/20</td>
<td>15/20</td>
<td>17/20</td>
</tr>
<tr>
<td>%</td>
<td>85.00 %</td>
<td>75.00 %</td>
<td>85.00 %</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.6211, 0.9679)</td>
<td>(0.5090, 0.9134)</td>
<td>(0.6211, 0.9679)</td>
</tr>
<tr>
<td>Mean Change in $K_{\text{max}}$ (D)</td>
<td>Mean -0.88</td>
<td>0.05</td>
<td>-0.73</td>
</tr>
<tr>
<td>SD</td>
<td>1.79</td>
<td>2.46</td>
<td>1.78</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-5.4, 2.5</td>
<td>-5.0, 7.7</td>
<td>-4.2, 2.5</td>
</tr>
</tbody>
</table>

### Table 2: Change in $K_{\text{max}}$ between Consecutive Visits in the CXL Group
(UVX-002, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in $K_{\text{max}} \leq 1.0$ D</td>
<td>n/N 46/64</td>
<td>56/64</td>
<td>53/64</td>
</tr>
<tr>
<td>%</td>
<td>71.88 %</td>
<td>87.50 %</td>
<td>82.81 %</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.5924, 0.8240)</td>
<td>(0.7685, 0.9445)</td>
<td>(0.7132, 0.9110)</td>
</tr>
<tr>
<td>Mean Change in $K_{\text{max}}$ (D)</td>
<td>Mean -0.77</td>
<td>-0.56</td>
<td>-0.62</td>
</tr>
<tr>
<td>SD</td>
<td>4.69</td>
<td>2.50</td>
<td>3.77</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-32.7, 5.5</td>
<td>-8.8, 7.0</td>
<td>-17.3, 7.4</td>
</tr>
</tbody>
</table>
### Table 3: Change in \(K_{\text{max}}\) between Consecutive Visits in the CXL Group
(Corneal Ectasia Subjects, UVX-001, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in (K_{\text{max}} \leq 1.0) D</td>
<td>15/19</td>
<td>19/19</td>
<td>17/19</td>
</tr>
<tr>
<td>%</td>
<td>78.95 %</td>
<td>100.00 %</td>
<td>89.47 %</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.5443, 0.9395)</td>
<td>(0.8235, 1.0000)</td>
<td>(0.6686, 0.9870)</td>
</tr>
<tr>
<td>Mean Change in (K_{\text{max}}) (D)</td>
<td>Mean</td>
<td>-0.06</td>
<td>-0.82</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.15</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>-2.5, 2.2</td>
<td>-4.5, 0.5</td>
</tr>
</tbody>
</table>

### Table 4: Change in \(K_{\text{max}}\) between Consecutive Visits in the CXL Group
(UVX-003, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in (K_{\text{max}} \leq 1.0) D</td>
<td>41/51</td>
<td>46/51</td>
<td>43/51</td>
</tr>
<tr>
<td>%</td>
<td>80.39 %</td>
<td>90.20 %</td>
<td>84.31 %</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.6688, 0.9018)</td>
<td>(0.7859, 0.9674)</td>
<td>(0.7141, 0.9298)</td>
</tr>
<tr>
<td>Mean Change in (K_{\text{max}}) (D)</td>
<td>Mean</td>
<td>-0.06</td>
<td>-0.41</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>2.36</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>-8.6, 6.8</td>
<td>-11.2, 3.9</td>
</tr>
</tbody>
</table>

**Avedro’s Response to 2.e.iii-iv:**

Analysis of refractive stability based on MRSE was not pre-specified in the study protocol or the statistical analysis plan. Per the Agency’s request, refractive stability was assessed using the mean change (paired differences) in MRSE between consecutive manifest refractions. Refractive stability for a consistent cohort of study eyes in the CXL group that completed each of the consecutive manifest refractions is presented in Table 5 through Table 8 for UVX-001 (Progressive Keratoconus), UVX-002, UVX-001 (Corneal Ectasia), and UVX-003. Mean annual change in MRSE was below 0.5 D/year between 6 and 12 months in UVX-001 (Progressive Keratoconus), UVX-002, and UVX-001 (Corneal Ectasia), and was within 1 D during the same interval in UVX-003.
### Table 5: Change in MRSE between Consecutive Visits in the CXL Group (Progressive Keratoconus Subjects, UVX-001, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in MRSE &lt;= 1.0 D</td>
<td>n/N</td>
<td>9/20</td>
<td>19/20</td>
</tr>
<tr>
<td>%</td>
<td>45.00 %</td>
<td>95.00 %</td>
<td>95.00 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.2306, 0.6847)</td>
<td>(0.7513, 0.9987)</td>
<td>(0.7513, 0.9987)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.75 D</td>
<td>n/N</td>
<td>9/20</td>
<td>16/20</td>
</tr>
<tr>
<td>%</td>
<td>45.00 %</td>
<td>80.00 %</td>
<td>85.00 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.2306, 0.6847)</td>
<td>(0.5634, 0.9427)</td>
<td>(0.6211, 0.9679)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.5 D</td>
<td>n/N</td>
<td>9/20</td>
<td>16/20</td>
</tr>
<tr>
<td>%</td>
<td>45.00 %</td>
<td>80.00 %</td>
<td>85.00 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.2306, 0.6847)</td>
<td>(0.5634, 0.9427)</td>
<td>(0.6211, 0.9679)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D)</td>
<td>Mean</td>
<td>1.53</td>
<td>-0.52</td>
</tr>
<tr>
<td>CI</td>
<td>(0.43, 2.64)</td>
<td>(-1.21, 0.17)</td>
<td>(-0.25, 0.53)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D) per Year</td>
<td>Mean</td>
<td>6.12</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

### Table 6: Change in MRSE between Consecutive Visits in the CXL Group (UVX-002, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in MRSE &lt;= 1.0 D</td>
<td>n/N</td>
<td>48/65</td>
<td>58/65</td>
</tr>
<tr>
<td>%</td>
<td>73.85 %</td>
<td>89.23 %</td>
<td>78.46 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.6146, 0.8397)</td>
<td>(0.7906, 0.9556)</td>
<td>(0.6651, 0.8769)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.75 D</td>
<td>n/N</td>
<td>44/65</td>
<td>57/65</td>
</tr>
<tr>
<td>%</td>
<td>67.69 %</td>
<td>87.69 %</td>
<td>70.77 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.5495, 0.7877)</td>
<td>(0.7718, 0.9453)</td>
<td>(0.5817, 0.8140)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.5 D</td>
<td>n/N</td>
<td>36/65</td>
<td>51/65</td>
</tr>
<tr>
<td>%</td>
<td>55.38 %</td>
<td>78.46 %</td>
<td>63.08 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.4253, 0.6773)</td>
<td>(0.6651, 0.8769)</td>
<td>(0.5020, 0.7472)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D)</td>
<td>Mean</td>
<td>0.03</td>
<td>-0.07</td>
</tr>
<tr>
<td>CI</td>
<td>(-0.60, 0.67)</td>
<td>(-0.37, 0.24)</td>
<td>(-0.47, 0.52)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D) per Year</td>
<td>Mean</td>
<td>0.12</td>
<td>-0.28</td>
</tr>
</tbody>
</table>
### Table 7: Change in MRSE between Consecutive Visits in the CXL Group (Corneal Ectasia Subjects, UVX-001, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in MRSE &lt;= 1.0 D</td>
<td>n/N</td>
<td>15/19</td>
<td>18/19</td>
</tr>
<tr>
<td>%</td>
<td>78.95 %</td>
<td>94.74 %</td>
<td>89.47 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.5443, 0.9395)</td>
<td>(0.7397, 0.9987)</td>
<td>(0.6686, 0.9870)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.75 D</td>
<td>n/N</td>
<td>14/19</td>
<td>17/19</td>
</tr>
<tr>
<td>%</td>
<td>73.68 %</td>
<td>89.47 %</td>
<td>73.68 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.4880, 0.9085)</td>
<td>(0.6686, 0.9870)</td>
<td>(0.4880, 0.9085)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.5 D</td>
<td>n/N</td>
<td>11/19</td>
<td>17/19</td>
</tr>
<tr>
<td>%</td>
<td>57.89 %</td>
<td>89.47 %</td>
<td>68.42 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.3350, 0.7975)</td>
<td>(0.6686, 0.9870)</td>
<td>(0.4345, 0.8742)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D)</td>
<td>Mean</td>
<td>-0.13</td>
<td>-0.01</td>
</tr>
<tr>
<td>CI</td>
<td>(-1.35, 1.10)</td>
<td>(-0.72, 0.70)</td>
<td>(-0.58, 0.71)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D) per Year</td>
<td>Mean</td>
<td>-0.52</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

### Table 8: Change in MRSE between Consecutive Visits in the CXL Group (UVX-003, Consistent Cohort)

<table>
<thead>
<tr>
<th>Stability Criterion</th>
<th>Baseline to Month 3</th>
<th>Month 3 to Month 6</th>
<th>Month 6 to Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in MRSE &lt;= 1.0 D</td>
<td>n/N</td>
<td>39/52</td>
<td>46/52</td>
</tr>
<tr>
<td>%</td>
<td>75.00 %</td>
<td>88.46 %</td>
<td>78.85 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.6105, 0.8597)</td>
<td>(0.7656, 0.9565)</td>
<td>(0.6530, 0.8894)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.75 D</td>
<td>n/N</td>
<td>38/52</td>
<td>45/52</td>
</tr>
<tr>
<td>%</td>
<td>73.08 %</td>
<td>86.54 %</td>
<td>75.00 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.5898, 0.8443)</td>
<td>(0.7421, 0.9441)</td>
<td>(0.6105, 0.8597)</td>
</tr>
<tr>
<td>Change in MRSE &lt;= 0.5 D</td>
<td>n/N</td>
<td>36/52</td>
<td>42/52</td>
</tr>
<tr>
<td>%</td>
<td>69.23 %</td>
<td>80.77 %</td>
<td>65.38 %</td>
</tr>
<tr>
<td>(CI)</td>
<td>(0.5490, 0.8128)</td>
<td>(0.6747, 0.9037)</td>
<td>(0.5091, 0.7803)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D)</td>
<td>Mean</td>
<td>0.55</td>
<td>-0.10</td>
</tr>
<tr>
<td>CI</td>
<td>(-0.21, 1.31)</td>
<td>(-0.44, 0.24)</td>
<td>(-0.22, 1.01)</td>
</tr>
<tr>
<td>Mean Change in MRSE (D) per Year</td>
<td>Mean</td>
<td>2.20</td>
<td>-0.40</td>
</tr>
</tbody>
</table>
Reviewer Comment: Note in Table 2 that the minimum values include -32.5 and -17.3. These bizarre (i.e. nonphysiologic?) values suggest that there were significant errors in measurement potentially due to poor methodology and/or the disease process.

As discussed by the advisory committee, it does not appear that stability has been achieved by the 12 month visit post-crosslinking. A change in Kmax of 1D was considered by the sponsor to be clinically meaningful in the determination of their prespecified endpoints and analyses. While the majority of the population met this very low bar, it is concerning that the percentage was not higher. In addition, the ranges reported indicate a tremendous amount of variability. This (and the MRSE data) may reflect the inherent variability in these measurements in diseased corneas or the difficulty in acquiring measurements in these diseases. Or perhaps, it is a reflection of the fact that diseased corneas may not achieve refractive stability at a rate of 90-99% of the population, despite treatment.

Any statement or claim that the cornea, disease, or refraction has been “stabilized” would appear to be unsupported. Without control data it is hard to say whether the refractive changes are occurring at a rate comparable to the underlying disease process or slower/faster. Regardless, this data provides a non-literature derived source to understand the refractive changes occurring in these corneas across time. One potential concern with the data as presented is that it is unclear whether the “changes” were considered as absolute values or whether improvement (i.e., decrease in Kmax) could have been masked by the binning. However, additional information to address this point is not needed at this time since the advisory committee has already determined that they do not believe stability of the corneal response was achieved by the 12 month study visit but did not request additional data on this subject.

Literature Review

There was enormous confusion regarding the use of literature in this review and the regulatory status of the file (505b1 vs 505 b2).

On CDRH’s original round of review of this NDA in fall 2013-early spring 2014, we noted our serious concerns with the study and the data set. At a mid-cycle meeting, CDER management acknowledged the obvious weakness of the study but said that the question to answer is whether the product is safe and efficacious and alluded to the global literature and experience with crosslinking to answer this question. Thus, early in this review, the expectation was that literature was to be relied upon heavily, since the pivotal trials were significantly flawed. However, a year later (and after the complete response had been received by the agency), in December of 2014 CDER management stated that a literature review could not be used in the FDA “backgrounder” to be prepared for the advisory committee since literature could not be used to make a determination on this file. CDER management stated at that time that the file
was actually a 505 (b) (1) submission. This led to months of confusion and re-consideration of the file as we attempted to prepare for the panel in light of this significant new regulatory information. The situation was further complicated by CDER’s repeated use of literature in the backgrounder and our realization that the Applicant has repeatedly submitted forms to this file indicated they believe this to be a 505(b)(2) submission in which literature is intended to support approval. The Applicant even made this statement directly in their briefing materials provided to the advisory committee. However, despite numerous requests for clarification from CDRH at internal meetings, neither Office of Combination Products (OCP) nor CDER provided clear feedback regarding the regulatory status of the file (505b1 vs. 2) until a meeting on March 11, 2015 where it became clear that CDER was once again proposing to use literature to support clinical safety and effectiveness if necessary for approval.

At the end of January 2015, at a point in time when it would be impossible to complete a comprehensive and thorough literature review in time for the February 24, 2015 advisory committee date, CDRH was advised by the team that they could conduct a literature review if they felt one was necessary. Thus, due to the limited time available a very limited/focused review was requested (by DOED) and performed (by CDER’s DEPI group) by using extremely strict criteria – the emphasis was on maintaining an unbiased view of the literature so that if literature was mentioned in the review or at the advisory committee, it would have been derived through an unbiased literature review process. We note that none of the literature reports on the exact drug/device combination currently proposed for market (as confirmed by the Applicant at the advisory committee) and therefore this literature was gathered as background information to describe very general safety and effectiveness considerations reported in the literature for corneal collagen crosslinking in progressive keratoconus and postrefractive corneal ectasia.

CDRH DEPI colleagues conducted the review and extracted data with some interaction with this clinical reviewer. Their review has been completed and initially resulted in 44 articles which were ultimately limited to four articles identified as being randomized, controlled studies (based on a selection criteria offered in Pubmed that may not be a thoroughly applied tool, but rather subject to self-identification by the author at the time of publication) in humans that were reported in English and did not pertain to a significantly different crosslinking technique (accelerated, epi-on, or combined with intracorneal ring segments, as examples). Articles reporting on any data included in the pivotal studies were also excluded. Results and limitations of the review are reported in the DEPI review and have been considered by this reviewer – again we note this was NOT a through or comprehensive review of the literature and our DEPI colleagues had recommended a much more thorough and comprehensive review to address
questions raised in the review but we were unable request a more thorough review due to
CDER’s desire to move forward with the advisory committee without delay.

During the literature review, the following 9 articles were discovered which are reporting on
subjects enrolled under UVX-002 and UVX-003 (based on the clinicaltrials.gov numbers cited in
the articles).

<table>
<thead>
<tr>
<th>First Author</th>
<th>Date of Publication</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenstein SA</td>
<td>6/14/2012</td>
<td>Effect of topographic cone location on outcomes of corneal collagen cross-linking for keratoconus and corneal ectasia.</td>
</tr>
<tr>
<td>Brooks NO</td>
<td>2/22/2012</td>
<td>Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia.</td>
</tr>
<tr>
<td>Greenstein SA</td>
<td>2/11/2012</td>
<td>Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia.</td>
</tr>
<tr>
<td>Greenstein SA</td>
<td>10/14/2011</td>
<td>In vivo biomechanical changes after corneal collagen cross-linking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial.</td>
</tr>
<tr>
<td>Hersh PS</td>
<td>12/25/2010</td>
<td>Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results.</td>
</tr>
<tr>
<td>Greenstein SA</td>
<td>11/30/2010</td>
<td>Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis.</td>
</tr>
</tbody>
</table>

**Reviewer Comment:** Note that a number of topics for this subset of study subjects including: subject characteristics influencing outcomes, Effect of topographic cone location on outcomes, Patient subjective visual function, Higher-order aberrations after corneal collagen crosslinking, In vivo biomechanical changes after corneal collagen cross-linking, Corneal topography indices after corneal collagen crosslinking, Corneal thickness changes, and Natural history of corneal haze after collagen crosslinking to name several.

**Advisory Committee (2/24/2015) Recommendations:**

**Reviewer Comment:** CDER and CDRH were unable to create a joint “backgrounder” (or briefing material document) to communicate significant information to the advisory committee. Some comments from my clinical review were incorporated into early versions of that document by CDER and/or OCP, however, the final product did not include information I believed to be critical. I consistently made clear that my contributions and involvement on the backgrounder were always provided with the caveat that my division management would need to review and edit the document prior to finalizing the document. As the document progressed without this occurring (and as internal meetings with CDER and OCP became increasingly uncomfortable), my later suggested
contributions/comments on the document were sent to my branch and division management (for inclusion with other contributions from CDRH). DOED management expressed significant concerns with the resultant backgrounder and asked CDER to postpone the panel until the significant issues could be addressed. CDER elected to proceed with the panel date and the mail-out of the backgrounder. As DOED did not feel the backgrounder presented the key study information accurately and transparently, DOED management requested removal of its name from the briefing materials. Subsequently, CDER conducted the mail out of the same document with the removal of the CDRH review division’s name. Due to such issues, ODE Office level was briefed numerous times over the course of this review and their input was sought and utilized by CDER and OCP (Office of Combination Products) when they deemed appropriate.

While some advisory committee members attempted to use literature or the unmet medical need to overcome the inarguable limitations of the study presented when answering the voting questions, there was a clear concern expressed in the preceding committee discussion that additional analyses needed to be performed on the current dataset.

Reviewer Comments: Panel transcript can be reviewed for specific details regarding the discussion and votes. I allude to specific concerns in the deficiencies at the end of this review as pertain to the need for ongoing review on this file.

The transcript will need to be reviewed in order to create a comprehensive list of information/data/analyses that were recommended by the advisory committee but are currently outstanding. A preliminary list of issues raised at the advisory committee meeting based on notes taken by various DOED personnel were developed into draft deficiencies and were provided to CDER at an internal post-committee meeting.

LABELING

As identified above, the following recommendations have been made in addition to comments made in my separate preliminary labeling review (from 3/9/2015):

1) Labeling should identify additional specific treatment parameter recommendations, as were studied (for example, induction time, zone of epithelial debridement, etc.)

2) Additional risk mitigation including labeling recommendation related to maintaining a beam centered on the cornea may be necessary (if not already included). This is in addition to the Applicant’s assertion that “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.”

3) Kmax increase ≥ 2 D as reported in the review above was a prespecified safety endpoint supported by the literature as such changes may represent “treatment failures” and at the very
least represent potentially significant disease progression. I believe this information merits inclusion in the labeling.

**Reviewer Comments:** Due to the fact that a determination regarding approvability cannot be made at this time and significant additional data/analyses are needed, I am deferring further labeling review until the next round of review. I have noted previously that use of a PRO relevant to adverse event reporting (glare, haloes, etc.) in the labeling is of concern in the absence of a formal review by FDA PRO experts.

**RISK/BENEFIT Discussion**

**Reviewer Comment:** Based on discussions with management, it is premature to engage in a complete discussion of risks and benefits at this time, in the absence of a complete review of the data submitted and outstanding analyses requested by the Advisory Committee. Outstanding preclinical concerns have been mentioned in this review contributing to uncertainties in device performance. Safety and effectiveness concerns specific to each of the proposed indicated populations have been described in this review in addition to specific concerns in the pediatric population. At this time, a request for additional information is being recommended.

**Recommendation:** Additional Information Needed Prior to Making a Determination (NDA terminology: Complete Response)

**SIGNIFICANT 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 followup 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.

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.

   c. There is concern that all subject enrolled in the studies may not have had progressive disease, as intended. Therefore, please remove also remove (b) (4)
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).
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.
Attachments:

1. CDER Regulatory Briefing Meeting Presentation (presented by CDRH)
3. CDRH Statistical Review (Xin Fang)
4. CDRH literature Review (Youlin Qi)
5. CDRH postapproval study section prepared for backgrounder for advisory committee meeting (Youlin Qi)

Maryam Mokhtarzadeh -S
2015.03.24 22:18:32 -04'00'
NDA 203324: KXL System

Maryam Mokhtarzadeh, M.D.
Medical Officer
Division of Ophthalmic and Ear, Nose and Throat Devices
FDA/CDRH/ODE
THE DEVICE PROPOSED FOR MARKETING: KXL SYSTEM
Crosslinking (CXL) Procedure

Irreversible alteration of the cornea

http://lasereyeconsultant.co.uk/collagen-cross-linking
Consequences of Devices that Alter the Cornea

- **Refractive effects**
  - Quality of vision (visual disturbances, etc.)

- **Potential effect on Intraocular Pressure (IOP) measurement**
  - Ability to monitor/detect glaucoma

- **Potential effect on future surgery**
  - Ex. cataract surgery, corneal transplant
Ultraviolet Light Safety Considerations

Include:

• Limbal stem cell damage
• Endothelial damage
• Cataract
• Retinal damage
UV Exposure vs. Damage Threshold after 30 minute Riboflavin Application

KXL System

Components include:

- UV-A light source
- Radio Frequency Identification (RFID) Card
- Onboard computer system
Devices

- All three clinical pivotal studies on UV-X
- Applicant proposes KXL System to be marketed
- Numerous differences between the devices

http://avedro.com/medical-professionals/products/iroc-innocross/uv-x-1000/
http://avedro.com/medical-professionals/products/kxl/
### Significant Differences*

<table>
<thead>
<tr>
<th></th>
<th>UV-X</th>
<th>KXL System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Dimensions</td>
<td>32x5x5 cm</td>
<td>60x60x150 cm, maximum extended position</td>
</tr>
<tr>
<td>Patient Position</td>
<td>Sitting or supine capability</td>
<td>Supine</td>
</tr>
<tr>
<td>Illumination Diameter</td>
<td>Variable (7.5 mm, 9.5 mm, 11.5 mm)</td>
<td>Fixed (9.0 mm)</td>
</tr>
<tr>
<td>Focusing</td>
<td>Subjective</td>
<td>Objective</td>
</tr>
</tbody>
</table>

* New information received in the last week raises new concerns regarding the differences between the devices.
Number of Study Subjects by Illumination Diameter (CXL Group)*

<table>
<thead>
<tr>
<th>Illumination Diameter</th>
<th>UVX-001 Ectasia</th>
<th>UVX-001 Keratoconus</th>
<th>UVX-002 Keratoconus</th>
<th>UVX-003 Ectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium (9.5 mm)</td>
<td>24</td>
<td>29</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>Large (11.0 mm)</td>
<td>--</td>
<td>--</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

*ITT Population
Proposed Device for Marketing

• Different from IND device
  » Equivalence of safety and effectiveness outcomes cannot be established based on preclinical data alone

• Advisory committee:
  » Expressed significant concerns about differences and lack of data with device to be marketed
  » Recommended identification of new cohort for assessment of safety and effectiveness
    – Removal of eyes treated with large diameter

• Applicant stated no literature (and no data) exists on KXL system to be marketed (2/24/15)
UVX-001, UVX-002, UVX-003

THE CLINICAL STUDIES
Data Collected

Each subject:

• 1 Study eye
  » Treated
    – CXL at time 0
  » Sham (control)
    – Sham surgery at time 0
    – Eligible for CXL at 3 months or later

• 1 Fellow eye
  » Eligible for CXL at 3 months or later
  » No data collected prior to 3 months
Concerns Regarding Follow-up

- 12 months follow-up after crosslinking
  - Not based on refractive stability within population studied
    - Refractive device evaluation usually performed at time point of refractive stability

- “Controlled phase” 3 months long
  - Very few sham (control) eyes remain at 12 months for evaluation without CXL
Key Enrollment Criteria:
Proposed IFU for the treatment of corneal ectasia following refractive surgery

Having a diagnosis of:
Corneal ectasia after corneal refractive surgery (e.g., LASIK, photorefractive keratectomy [PRK], or epi-LASIK)
Key Enrollment Criteria: Proposed IFU for the treatment of progressive keratoconus

Having a diagnosis of:

Progressive keratoconus defined as one or more of the following changes over a period of 24 months or less before randomization:

i. An increase of ≥1.00 D in the steepest keratometry value (or simK)

ii. An increase of ≥1.00 D in regular astigmatism evaluated by subjective manifest refraction

iii. A myopic shift (decrease in the spherical equivalent) of ≥ 0.50D on subjective manifest refraction

iv. A decrease ≥0.1 mm in the BOZR (Back Optical Zone Radius) in rigid contact lens wearers where other information is not available

[NOTE: Patients with a clear history of progression but without prior documentation may be followed and re-examined at a later visit to confirm progression.]
Progressive Keratoconus Study Population Concerns

1/4 Progression criteria raised significant concern at advisory committee meeting

» Recommended new safety and effectiveness cohort analysis based on 3/4 criteria
Post-Refractive Corneal Ectasia Study Population Concerns

- No definition of progression
- No exclusion for corneal implants
- No exclusion for previous cross-linking
- No stratification by each prior refractive intervention/device exposure nor time since exposure
  - Stratification based on prior PRK vs. LASIK demonstrates absence of efficacy in population s/p PRK or s/p PRK & LASIK
  - Advisory committee recommended additional analyses to evaluate safety and effectiveness of subpopulations within this cohort

Reference ID: 3720940
Additional Study Population Concern

- Drug selection based on corneal thickness
  - Intent to swell cornea to minimum thickness necessary to proceed with UV exposure

- Advisory committee
  - Expressed concern that safety and effectiveness could differ if cornea swollen
  - Recommended stratification of NDA cohort based on corneal thickness (and need for swelling) prior to UV exposure
Pediatric Corneas

Advisory Committee:

• “No question” they are different from adult corneas

Crosslinking textbook:

• “unknowns are magnified when considering the pediatric population”
• “...one can expect different outcomes of CXL in the pediatric KC eye, as younger cornea tissue has lesser natural collagen cross-linking combined with this longer duration of progression and severity of the disease.”


Reference ID: 3720940
Concerns with Primary Effectiveness Endpoint (Kmax)

- **Kmax Data**
  - Wide variability within subjects
    - Included nonphysiologic results
    - Sham arm showed improvement at 1 month
  - Failure to meet prespecified study success criteria for progressive keratoconus
  - LOCF utilized for 12 months assessment
    - Raises significant concerns
Concerns with Primary Effectiveness Endpoint (Kmax)

• Advisory committee expressed concerns about utilizing Kmax as a sole indicator of effectiveness
  » Recommended additional effectiveness analyses
Other Effectiveness Endpoints

• CDRH requested analysis of other prespecified effectiveness endpoints
  » Received subsequent to advisory committee preparation
  » Review ongoing
Concerns with Safety Endpoints

- **Protocol**
  - Identified specific safety endpoints and analyses
  - Data collected per protocol
- **Final SAP (after last subject visit and after publication of some study results)**
  - Significant changes made to prespecified endpoints
  - Analyses removed/significantly altered
Concerns with Safety Endpoints

• NDA submission
  » Prior to advisory committee meeting lacked analysis of several key safety endpoints identified in protocol
  » Prior to advisory committee, numerous additional analyses requested by CDRH review team
    – Received subsequent to advisory committee preparation, review ongoing
  » Advisory committee recommended further additional analyses
Safety Concerns: Patient Report Outcomes (PROs)

- 2 PRO’s prespecified as safety endpoints
- All data collected
- No analysis performed by Applicant on data from 1 PRO
  » Final SAP removed 1 PRO endpoint
- No review by FDA’s PRO experts performed on either questionnaire
Importance of PRO’s

- FDA guidance published
- Patients and refractive device community vocal regarding importance
  - PROWL (LASIK) questionnaire developed (FDA/NIH/ DOD)
- CDRH reviews all PROs used in ophthalmic device trials
PROs: Advisory Committee Meeting

• Concerns with failure to present PRO results were echoed by the open public hearing speakers and the advisory committee

• Recommended complete analysis of all PRO data collected and evaluation of the validity of the questionnaires used
Role of Literature in NDA Review

- Initially discussed as critical to review (Fall 2013)
- DOED notified literature cannot be used for safety and effectiveness assessment (December 2014)
- Briefing materials for advisory committee meeting contained biased literature references provided by Applicant (January 2015)
- CDRH (DEPI) conducted extremely limited literature review in preparation for advisory committee meeting due to CDER’s decision to proceed with February committee meeting (February 2015)
Role of Literature in NDA Review

• Literature review was not presented at the advisory committee meeting
  » However, some members of advisory committee voted for approval based on their own interpretation of literature support for crosslinking as a general procedure

• Surgical methodology/technique differs widely in literature and inadequately described

• No literature exists on the combination product proposed for marketing
  » Applicant acknowledged lack of literature on this combination product (2/24/2015)
Question

Given the following:

- Equivalence of safety and effectiveness outcomes between UV-X and KXL System cannot be established based on preclinical data alone
- Lack of clinical data on KXL System to be marketed
- Current study cohort incorporates many subgroups which should be removed from cohort utilized for determination of safety and effectiveness (N potentially insufficient)
- Need for additional safety analyses
- Need for additional effectiveness analyses
- Lack of comprehensive and unbiased literature review

Can any decision about approvability on this combination product be made at this time?
Preliminary Clinical Labeling Review
(CDRH)
3/9/2015
From: Maryam Mokhtarzadeh, MD
ICIB/DOED/ODE

To: Bradley Cunningham, DSDB Branch Chief
Dexiu Shi, Physicist and Laser Reviewer
Tieuvi Nguyen, ICIB Branch Chief
Malvina Eydelman, DOED Division Director

Re: NDA 203324 (Response to Complete Letter – Preliminary Labeling Review only)
Photrex, Photrex Visous, KXL Device, Avedro, Inc.
riboflavin ophthalmic solution (20% dextran),
riboflavin ophthalmic solution (0% dextran),
UV-A Irradiation
(Previously: Riboflavin ophthalmic solution 0.12% (KXL system)

Proposed Indications for Use:
- For the treatment of progressive keratoconus
- For the treatment of corneal ectasia following refractive surgery

Date: March 6, 2015 (Preliminary Review; Review should be ongoing as the need for additional analyses has been identified by the advisory committee and it is unclear how CDER plans to incorporate the additional analyses needed prior to making a determination on this file.)

Recommendation: Complete Response – Additional Information Needed
Note: It is premature to decide on the precise indications for use that may be approved in the absence of complete analyses performed on the data submitted. There are outstanding issues identified by the advisory committee that need to be requested from the sponsor and will require review.
The file used to generate this labeling review was the “User Manual” file available on the Sharepoint website (dated 1/9/2015). An email sent by the Project Manager (Jacquelyn Smith) on 3/4/2015 directed me to this file for my labeling review (http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas/NDA%20203324%20Riboflavin%20Ophthalmic%20Solution/Forms/AllItems.aspx). In addition, the drug labeling files available through this link were also read and will be referenced in this review, as needed.

Reviewer Comment to the Team: Regarding Combination Product Labeling – it is unclear how it has been decided how information will be divided between the drug and device labeling (for example, clinical data). This will likely require discussion with the team as well as representatives from the Office of Combination Products to resolve. In addition, it is unclear how each labeling (drug and device) will reference each other since the products are intended to be used together. I would propose that each clearly state that users are expected to familiarize themselves with both drug and device labeling and that neither is complete alone. Contraindications, warnings and precautions do not currently appear to be complete. These will require discussion to determine whether the drug and device labeling should each be complete with regard to these items or whether concerns should be split (for example, according to which product introduces risk). Finally, both drug and device labeling should clearly identify that the device studied was not the KXL system. The specific language will need to be discussed. Furthermore, the specific device usage (treatment parameters, instructions, etc.) in the clinical study will need to be provided as well as clinical data.

Reviewer Comment to the Team: Regarding: “Highlights of Prescribing Information” and “Full Prescribing Information” (i.e., drug labeling):

1) Clarification is needed on the exact area of epithelial debridement used in the study since it appears that additional instruction may have been provided outside of the protocol.

2) The contraindications do not include all relevant exclusion criteria used in the study and identified in other sources as contraindications to corneal collagen crosslinking, for example, severe corneal scarring or opacification. It is unclear how the contraindications currently in the labeling were determined since they do not appear to be comprehensive. (Same applies to warnings and precautions).

3) The clinical data is not presented correctly. The advisory committee provided valuable insight regarding the poolability of data and additional analyses and information are needed from the Applicant in order to generate correct labeling.

4) In the “Clinical Studies” section it is inappropriate to state
5) Clarification is needed regarding the statement. This statement does not appear to be accurate.

6) 

7) It is unclear.

8) It is unclear how the endpoints included in this labeling were chosen – these are neither the prespecified not the complete listing of post-specified endpoints. While improvement in $K_{\text{max}}$ are reported, increases in $K_{\text{max}}$ have not been reported. This selection of results is incomplete and misleading.


Deficiency: On Page 1-1 the following statement appears: This statement is inappropriate. Please correct any errors that appear in this manual and remove this statement in order to provide correct instructions for use.

Reviewer Comment: Contraindications, Warnings and Precautions are currently incomplete and require discussion as mentioned above.

Reviewer Comment: Please note that I have specific concern with regard to use in pediatric subjects as well as subjects with postrefractive corneal ectasia. These concerns are outlined in my review of the material submitted in the complete response. These specific concerns are in addition to general concerns with the study.

Indications for Use:

per device labeling:

Deficiency: Your User Manual states:
Please update/revise all language in the User manual to reflect the final name of the drug product (Photextra Viscous) and the exact indication language (addition of the word “progressive” before keratoconus).

Deficiency: Page 1-3 states “WARNING: Never look directly into the UV light beam direct the beam towards a person except for therapeutic purposes.” If accurate, please revise this statement to “WARNING: Never look directly into the UV light beam nor direct the beam towards a person except for therapeutic purposes.” If this statement is inaccurate, or not the warning intended, please revise to clarify.

Reviewer Comment to Engineer: Page 1-4 of the User Manual describes potential interference with radio communications. Due to the fact that this laser treatment occurs over a duration of thirty minutes, it seems plausible that some form of entertainment may be used by the patient – iPod? Radio? Please advise whether additional specific labeling may be provide regarding such interactions in light of the potential for use of entertainment devices.

Deficiency: Page 3-3 lists the system’s parameters. An asterisk appears by “UV Energy” but it is unclear to what this refers. Please clarify the significance of this asterisk.

Deficiency: Page 3-4 mentions the induction period 30 minutes). However, there is no information regarding what induction period was studied nor by what criteria the user is intended to select an induction period. Please clarify in order to provide adequate instructions for use.

Deficiency: Page 3-15 describes treatment and indicates that the patient should perform certain actions. However, no script is provided to direct the operator to communicate to the patient specific instructions. Please revise your User Manual to include such script to ensure that patients are accurately instructed regarding the importance of their involvement and cooperation throughout the procedure and are directed to appropriate behavior to ensure safe use of the device.

Deficiency: You have not provided patient labeling. Please provide such labeling to ensure that patients are adequately informed regarding the combination product with which they are being treated.
Deficiency: Page 3-17 states Therefore, please remove and provide specific instruction regarding postoperative care after crosslinking has been performed. (CDER will need to review any mention of drug products in the postoperative regimen and will need to ensure consistency with the drug labeling).

Deficiency: Page 3-18 discusses Pausing or Canaling a Treatment. It is unclear what data has been collected regarding treatments which are paused and resumed or cancelled prior to completion. Please provide such data, if it exists. If not, please state in the labeling if the results of such treatment interruptions have not been studied.

Deficiency: Your labeling has not clarified the frequency nor the duration of the device use. Based on the clinical data provided to support this NDA, it appears that the treatment is intended as a one-time treatment only and that specific induction and treatment times were studied. If there is additional data available to support other frequencies or durations of use, please provide it. Otherwise, please revise your labeling to clearly state the frequency and duration of use.

Reviewer Comment to Engineer: I have not identified specific instructions with regard to calibration or routine maintenance, in fact the manual seems to indicate no maintenance is required on page 4-1. Please comment on whether or not this is appropriate and/or provide deficiencies if needed.

Reviewer Comment to DOED: I believe consistency with other laser labeling will be necessary and therefore recommend a cross-disciplinary review of such labeling to ensure inclusion of critical elements. For example, I believe labeling from refractive laser procedures may be helpful to consider. The Applicant’s current labeling is very general and since DOED was not involved in the generation of the study protocol at the IND stage, many significant considerations for the labeling have never been communicated with the sponsor (for example, concern regarding use in subjects with nystagmus, etc.)

ADDENDUM 3/6/2015 3 pm

Reviewer Comment: In addition to the comments above, potential long term concerns, such as lack of data regarding long term sequelae, has not been communicated at present in the labeling. I believe such information is critical to convey to users. Due to the alteration of the cornea, there may be future concerns such as the accuracy of IOP measurements, any complications/considerations that may occur at the time of future surgery (cataract surgery? Corneal transplant surgery?), etc. These have not been studied but our knowledge of corneal surgery/alteration indicates that this could be a future problem.
Reviewer Comment: In my clinical review, I note the following language from the sponsor's Complete response which should appear in the device labeling:

4.2. Complete Response Item #13b

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.

Avedro Response:

Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.14 (SN 0027, Module 1.6.2) and to response Item #13C (Section 4.3) for additional safety and efficacy information by subpopulations.

From section 3.14:

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 III 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.

Reviewer Comments: Response is adequate, however, additional risk mitigation including labeling recommendation related to maintaining a beam centered on the cornea may be necessary (if not already included). From a device perspective, this is an important treatment parameter.
----- Attachment 3 -----

CDRH Statistical Review
(Xin Fang)
MEMORANDUM

Date: 01/12/2015

From: Xin Fang, Ph.D., Mathematical Statistician, HFZ-550
CODB, Division of Biostatistics, OSB

Due date: 01/06/2015 for mid-cycle meeting, final review due date is not set.

To: Maritze Ortega, ODE/DOED

Through: Branch Chief (Yun-Ling Xu), Cardiovascular and Ophthalmic Devices Branch, DBS, OSB

1. BACKGROUND

In response to the Agency’s March 14, 2014 Complete Response (CR) letter and a face-to-face type-A meeting held on August 6, 2014, the sponsor resubmits its NDA under NDA 203324/SN0028 to address the deficiency items conveyed in the CR letter. Items 13-14 in the CR letter are statistical/clinical deficiencies consisting of comments from both CDER statistical reviewer and CDRH clinical reviewer because the test product is a drug-device combination product. No CDRH statistical reviewer was consulted prior to the finalized CR letter. This review provides statistical comments to the review team and the sponsor based on the sponsor’s responses to the Agency’s deficiency Items 13-14.

The combination product comprises riboflavin ophthalmic solution administered as a photosensitizer in conjunction with a UVA 365 nm wavelength light source (the KXL system). The KXL system creates a UVA irradiation to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking, which stiffens the cornea.

A brief related regulatory history and summary of previous reviews are listed below:
- On March 08, 2012, the sponsor submits its original NDA 203324
- On May 04, 2012, the Agency issued a refuse to file letter due to non-statistical issues
On September 16, 2013, the sponsor resubmits its NDA under NDA 203324/SN0007.

On February 28, 2014, the CDER statistical reviewer concluded:
- “The use of different time-points and methods for the primary efficacy analysis led to varying conclusions. The efficacy of CXL treatment observed in corneal ectasia subjects was statistically significant and clinically meaningful at Month 3 according to the analysis specified in the protocol, but this was not the case for keratoconus subjects. A duration of three months might have been too short for a demonstration of a clinically meaningful treatment effect. Although statistically significant and clinically meaningful improvement in Kmax was demonstrated in the Applicant’s analysis, their analysis relied heavily on imputed data based on the LOCF approach. The Applicant’s results were not all confirmed by alternative analyses. Although CXL does appear to have activity in keratoconus subjects, the study design makes a conclusive recommendation based on the statistical evaluation difficult.”

On March 14, 2014, the Agency issued CR letter with 17 deficiency items including two deficiency items from both CDER statistical reviewer and CDRH review team. DBS statistical reviewer was not consulted at this time.

On August 6, 2014, a meeting was held between the Agency two-center review team and the sponsor to discuss a path forward for another NDA resubmission. A DBS reviewer attended this meeting because the CDER statistical reviewer will not support the CDRH review team in the subsequent NDA resubmission.

On September 29, 2014, the sponsor resubmits its NDA under NDA 203324/SN0028 to address the deficiency items in the CR letter.

A summary of the three supporting phase-3 clinical studies submitted under NDA 203324 is depicted in the Table 1 below. There are two major statistical issues:
- The pre-specified primary effectiveness time point in these three studies is 3 months post treatment, at which no statistical significance is achieved for Keratoconus subjects in Studies UVX-001 and -002 but statistical significance is achieved for Ectasia subjects in Study UVX-001 and -003. Later, the sponsor performed post hoc analyses of the primary endpoint at 12 months post treatment, and statistical significance is achieved for both Keratoconus and Ectasia subjects. However, the study design allowed the eyes randomized to the sham control treatment to be crossed over to receive the CXL treatment at 3 months post treatment, and almost all sham subjects have the CXL treatment at 12 months. Therefore, the post-hoc analysis at 12 months used the observations from 3 - 6 months in Sham subjects (LOCF).
- Non-physiological values of Kmax, such as negative numbers or zeroes, are observed in Study UVX-001. It is not clear whether these erroneous outputs are the results of malfunction of the utilized measurement devices.
### Table 1. Summary of the Pivotal Supporting Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase and Design</th>
<th>Treatment</th>
<th>Number of Subjects</th>
<th>Primary Endpoint</th>
<th>Study Result (ITT + LOCF)</th>
<th>Major Statistical Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVX-001</td>
<td>Phase-3, randomized, open-label, sham controlled, parallel arm, single US center</td>
<td>1: CXL (using riboflavin/UV irradiation) 2: Sham control</td>
<td>Keratoconus: CXL: n=29 Sham: n=29  Ectasia: CXL: n=24 Sham: n=25</td>
<td>Change from baseline in maximum corneal curvature, as measured by maximum keratometry (Kmax) at 3 months</td>
<td>Keratoconus: Difference at 3M = -0.5 p-value at 3M &gt;0.20  Difference at 12M = -1.9 p-value at 12M = &lt;0.022*  Ectasia: Difference at 3M = -0.9 p-value at 3M &lt; 0.039*  Difference at 12M = -2.0 p-value at 12M ≤ 0.001*</td>
<td>1. As the original time point in all three studies was intended to be Month 3, the study design allowed the eyes randomized to the sham control treatment to be crossed over to receive the CXL treatment at that time point. Therefore, the post-hoc analysis at 12 months used the observations from 3 - 6 months in Sham group (LOCF). 2. Non-physiological values of Kmax, such as negative numbers or zeroes, are observed in Study UVX-001. It is not clear whether these erroneous outputs are the results of malfunction of the utilized measurement devices.</td>
</tr>
<tr>
<td>UVX-002</td>
<td>Phase-3, randomized, open-label, sham controlled, parallel arm, 10 US centers</td>
<td></td>
<td>Keratoconus: CXL: n=73 Sham: n=74</td>
<td></td>
<td>Keratoconus: Difference at 3M = -1.3 p-value at 3M &gt; 0.11  Difference at 12M = -2.3 p-value at 12M &lt;0.002*  Ectasia (3 months): Difference at 3M = -0.8 p-value at 3M &lt; 0.042*  Difference at 12M = -1.1 p-value at 12M &lt; 0.009*</td>
<td>2. Non-physiological values of Kmax, such as negative numbers or zeroes, are observed in Study UVX-001. It is not clear whether these erroneous outputs are the results of malfunction of the utilized measurement devices.</td>
</tr>
<tr>
<td>UVX-003</td>
<td>Phase-3, randomized, open-label, sham controlled, parallel arm, 9 US centers</td>
<td>Ectasia: CXL: n=67 Sham: n=63</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: sponsor’s Tables 15 and 20 in UVX-001 study report, Tables 14.2.1.1.3 in UVX-002 and UVX-003 study report, and CDER statistical review

Tables 6-12

Note: p-values are summarized from the direct t-test, Wilcoxon test and ANCOVA model reported from the sponsor reports and CDER statistical review.

The sponsor’s responses to the Agency’s CR letter Item 13-14 are described below followed by the reviewer’s comments:

- **CDRH Comment #13a.1a**: The response to item 13a (i.e. aperture/illumination diameter) clarified the total number of subjects treated under the large diameter setting. However, in light of the number of subjects affected, we request the following additional data in order to evaluate the distribution of this event across study eyes and subpopulations:

  Please list the total number of eyes treated with the medium vs. large aperture settings by study (i.e. UVX-001, UVX-002, UVX-003). Please subdivide this group into the number of eyes in subjects with keratoconus and the number of eyes in subjects with postrefractive corneal ectasia treated with each aperture setting. Please subdivide this last group (post refractive corneal ectasia) based on the specific refractive treatment after which ectasia developed (i.e. subjects s/p LASIK, s/p PRK, s/p epi-LASIK, etc). Finally, please separately list the number of eyes treated with the large aperture setting in pediatric subjects, which CDRH identifies as individuals from birth to 21 years of age (see “premarket Assessment...
of Pediatric Medical Devices: Guidance for Industry and Food and Drug Administration Staff” issued on March 24, 2014, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationsandGuidance/GuidanceDocuments/ucm089742.pdf). Please subdivide the pediatric data to separately list subjects between 14-18 years of age (up to their 18th birthday) and subjects between 18-21 years of age for each study.

**Sponsor’s response:**

The total number of eyes treated with the medium versus large aperture settings by study and by indication was provided in NDA 203-324 Sequence 0021 (dated 21 February 2014) and is provided in Table 2 for ease of reference. No subjects received treatment using the small aperture setting and subjects in UVX-001 received treatment using the medium aperture setting only.

As requested in the agency’s 01 August 2014 preliminary comments, provided in Table 3 is a breakdown of the specific refractive treatment (LASIK only, LASIK and PRK, and PRK only) after which ectasia developed for subjects enrolled in UVX-001 and UVX-003. Regardless of aperture setting, the majority of subjects enrolled developed ectasia following LASIK only (96% in UVX-001; 89% in UVX-003).

The number of eyes treated with the large aperture setting subdivided by the pediatric subgroups is provided in Table 4. Only subjects in UVX-002 and UVX-003 received the large aperture setting and of those, no pediatric subjects enrolled in UVX-003. Of the ten (10) subjects who were treated with the large aperture setting in UVX-002, only two were within the pediatrics subgroup range of 14 – 18 (up to their 18th birthday) years of age (subject 10218) and 18 – 21 years of age (subject 10217).

**Reviewer’s comment:** The sponsor’s response is acceptable. The sponsor provides descriptive statistics in Tables 2-4 for the Agency’s request.

- **CDRH Request #13a.1b:** Please review the demographic and baseline data from the eyes which were treated under the large aperture setting in order to determine if there were any common features which may be relevant to the investigator’s choice to use the largest aperture setting as opposed to the medium or small settings. If common features are identified, please provide additional information to support whether adequate data exists in the subjects treated with the medium aperture setting to ensure that absence of the large aperture setting in the device you intend to market does not compromise the safety and effectiveness of your device for any identifiable subpopulation that was studied.

**Sponsor’s response:**
In order to identify any additional common features that may have been relevant to the investigator’s choice of aperture, available baseline and demographic data including gender, age, baseline Kmax and corneal thickness at the thinnest point were reviewed. These data are presented in Table 5 and Table 6, respectively for the pooled keratoconus and pooled ectasia populations. There do not appear to be any differences between the groups treated with the medium aperture and those treated with the large aperture in any of the demographic or baseline variables. Given the small number of patients treated with the large aperture in each of the two indications, no formal analyses were conducted.

**Reviewer’s comment:** The sponsor’s response is acceptable. The sponsor provides descriptive statistics in Tables 4-5 for the Agency’s request. The listed mean baseline values (gender, age, Kmax, thickness) are comparable between medium and large aperture groups.

- **CDRH Request #13a.2:** You previously stated (in your February 2014 submission regarding this issue) that “As part of site start-up and training, 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.” In order to better characterize variations in study procedures which occurred based on investigator discretion and variations which were identified as protocol deviations please provide the following:
  a. An organized listing of the number of protocol deviations in each study by category (for example, deviations pertaining to enrollment criteria, out of window visits, device settings, etc.) with subcategories where relevant.
  b. A discussion regarding any additional events pertaining to device settings or use that were varied based on “investigator discretion”.
  c. A discussion regarding if (and how) variations in study procedures based on investigator discretion were distinguished from protocol deviations.

**Reviewer’s comment:** The review of the sponsor’s response to Item 13a.2 is clinically relevant and is deferred to the clinical review.

- **CDRH Request #13b:** 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.

**Reviewer’s comment:** The review of the sponsor’s response to Item 13b is clinically relevant and deferred to the clinical review.
• **CDRH Request #13c.1:** 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.

The sponsor provides its response in the type-A meeting. However, the Agency asks further clarification: “You provide additional safety analyses in the current submission. However, it is unclear whether how many subjects required ocular surgery over the course of the trial (e.g., laser interventions, cataract surgery, corneal transplant, etc.). Please provide a discussion regarding the incidence and etiology of surgical interventions and the distribution between the treatment arms and subpopulations (pediatric subjects, patient s/p LASIK, etc.)”

**Reviewer’s comment:** The review of the sponsor’s response to Item 13c.1 is clinically relevant and is deferred to the clinical review.

• **CDRH Request #13c.2a:** In order to better characterize the data available and the risk/benefit profile of this combination product in potentially vulnerable subpopulations we request the following information:
  a) Please provide an accountability table for the following subpopulations, including details regarding availability at each study visit in addition to randomized arm and whether or not the subject had “crossed over” or had the fellow eye treated:
    i) Subjects between 14-18 years of age (up to their 18th birthday)
    ii) Subjects between 18-21 years of age
    iii) Subjects treated for postrefractive corneal ectasia subdivided by the specific refractive treatment after which ectasia developed (i.e. s/p LASIK, s/p PRK, s/p epi-LASIK, etc.)

**Reviewer’s comment:** Item 13c.2a requests subject dispositions in subgroup, which are provided by the sponsor. The review of the sponsor’s response to Item 13c.1 is deferred to the clinical review.

• **CDRH Request #13c.2b:** Your enrollment criteria regarding subjects with “postrefractive corneal ectasia” are broad. Please provide a discussion characterizing the population actually studied with regard to ocular history and disease severity, progression, duration, etc.

**Reviewer’s comment:** Item 13c.2b is clinically relevant. The review of the sponsor’s response to Item 13c.2b is deferred to the clinical review.
• **CDRH Request #13c.2c:** To support the correlation of the general study results to the performance seen in these subpopulations, please provide a discussion of overall safety and effectiveness results by study for the following subpopulations (please consider results both with LOCF and observed values and include sample size at each visit; please also consider both 3 month and 12 month efficacy results):
  
i) Subjects between 14-18 years of age (up to their 18th birthday)
  ii) Subjects between 18-21 years of age
  iii) Subjects treated for postrefractive corneal ectasia subdivided by specific refractive surgery (i.e. s/p LASIK, s/p PRK, s/p epi-LASIK, etc.)

In this discussion, please comment on any differences identified in safety or effectiveness for potentially vulnerable subpopulations and discuss any risk mitigation measures proposed.

**Sponsor’s response:** … …

**Efficacy by Subpopulations – Pediatrics**

There were a combined total of 33 pediatric subjects enrolled in UVX-001 and UVX-002. No pediatric subjects were enrolled in UVX-003.

In UVX-001, one pediatric subject 14 – 18 years of age was randomized into the control group. The $K_{max}$ data, LOCF and observed, for that subject are provided in Table 20. Five pediatric subjects 18 – 21 years of age were enrolled, two in the CXL group and three in the control group. The $K_{max}$ data for this subpopulation, both LOCF and observed, are provided in Table 21. Based on both LOCF and observed values, the difference between treatment groups did not meet the primary efficacy endpoint.

In UVX-002, ten (10) pediatric subjects 14 – 18 years of age were randomized into the study; seven in the CXL group and three in the control group. The $K_{max}$ data, LOCF and observed, for these subjects are provided in Table 22. Using LOCF, the difference between treatment groups greatly exceeded 1.0 D at Month 6 (−6.1 D CXL vs. 1.0 D control) and Month 12 (−5.9 D CXL vs. 1.0 D control). For observed values, the difference between treatment groups also greatly exceeded 1.0 D at Month 3 (−7.1 D CXL vs. −1.6 D control) and Month 6 (−6.1 D CXL vs. 0.9 D control); at Month 12 the observed change from baseline in the CXL group alone was −6.6 D (n=6).

Seventeen (17) pediatric subjects 18 – 21 years of age were randomized into the study: ten in the CXL group and seven in the control group. The $K_{max}$ data, LOCF and observed, for these subjects are provided in Table 23. Using LOCF, the difference between treatment groups exceeded 1.0 D at Month 6 (−0.8 D CXL vs. 2.8 D control) and Month 12 (−3.2 D CXL vs. 2.8 D control). For observed values, the difference between treatment groups also exceeded 1.0 D at Month 3 (−1.2 D CXL vs. 0.5 D control) and Month 6 (−1.2 D CXL vs. 5.7 D control); at Month 12, the observed change from baseline in the CXL group was −3.2 D.
Efficacy by Subpopulations – Refractive Surgery

The majority of subjects enrolled in UVX-001 developed ectasia following LASIK only. Only one subject developed ectasia following LASIK and PRK and no subjects enrolled developed ectasia following PRK only.

For subjects who developed ectasia following LASIK only, the $K_{\text{max}}$ data for this subpopulation, both LOCF and observed, are provided in Table 24. Using LOCF, the difference between treatment groups exceeded 1.0 D at Month 6 (-0.8 D CXL vs. 1.0 D control) and Month 12 (-1.2 D CXL vs. 1.0 D control). For observed values, the difference between treatment groups met or exceeded 1.0 D at Month 3 (-0.1 D CXL vs. 0.9 D control) and Month 6 (-0.8 D CXL vs. 1.6 D control); at Month 12, the observed change from baseline for the CXL group was -1.4 D.

One subject in the CXL group developed ectasia following LASIK and PRK. The $K_{\text{max}}$ data for this subject, both LOCF and observed, are provided in Table 25. Only observed data up to Month 3 are available.

The majority of subjects enrolled in UVX-003 developed ectasia following LASIK only. Seven subjects developed ectasia following LASIK and PRK and five subjects developed ectasia following PRK only.

The $K_{\text{max}}$ data (LOCF and observed) for the subjects who developed ectasia following LASIK are provided in Table 26. The difference between treatment groups exceeded 1.0 D at Month 6 (-0.6 D CXL vs. 0.7 D control) and Month 12 (-0.5 D CXL vs. 0.7 D control) based on LOCF. Using observed data, the difference between treatment groups did not meet the primary efficacy endpoint at Month 3 (-0.1 D CXL vs. 0.6 D control) but did at Month 6 (-0.5 D CXL vs. 0.6 D control) and Month 12 (-0.6 D CXL vs. 0.4 D control).

The $K_{\text{max}}$ data (LOCF and observed) for subjects who developed ectasia following LASIK and PRK are provided in Table 27. Using LOCF, the difference between treatment groups did not meet the efficacy endpoint at Month 6 (0.0 D CXL vs. -1.7 D control) or at Month 12 (-0.5 D CXL vs. -1.7 D control). For observed values, the difference between treatment groups exceeded 1.0 D at Month 3 (0.0 D CXL vs. 1.1 D control) but not at Month 6 (-0.3 D CXL vs. -4.1 D control); at Month 12, the change from baseline in the CXL group was -0.8 D).

The $K_{\text{max}}$ data (LOCF and observed) for the subjects who developed ectasia following PRK only are provided in Table 28. Using LOCF, the difference between treatment groups did not exceed 1.0 D at Month 6 (-0.4 D CXL vs. 0.0 D control) or at Month 12 (-0.4 D CXL vs. 0.0 control). For observed values, the difference between treatment groups did not exceed 1.0 D at Month 3 (-0.6 D CXL vs. 0.0 control) or Month 6 (-0.4 D CXL vs. 0 control); at Month 12, the change from baseline in the CXL group was -0.4 D.

As the majority of subjects in both UVX-001 and UVX-003 studies enrolled developed ectasia following LASIK only, the efficacy results from this group are consistent with the overall study results in that the results met the primary efficacy endpoint.

Data from the seven subjects who developed ectasia following LASIK and PRK and the five subjects who developed ectasia following PRK in Study UVX-003 are not consistent with the overall population in that the results did not meet the primary efficacy endpoint in these small numbers of subjects.
## Table 20: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: Age 14-18 (UVX-001, ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>CXL Group (N=95)</th>
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<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaver</td>
<td>Mean</td>
<td>65.8</td>
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<td></td>
<td>SD</td>
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<tr>
<td>Month 3</td>
<td>Mean</td>
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<td>5.1</td>
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<td></td>
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<tr>
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<tr>
<td>Month 12</td>
<td>Mean</td>
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## Table 21: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: Age 18-21 (UVX-001, ITT Population)

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## Table 23: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: Age 18-11 (UVX-001, ITT Population)

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## Table 24: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: LASIK Only (UVX-001, ITT Population)

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<tr>
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## Table 25: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: LASIK and PRK (UVX-001, ITT Population)

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## Table 26: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: LASIK Only (UVX-003, ITT Population)

<table>
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<tr>
<td>Month 6</td>
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## Table 27: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: LASIK and PRK (UVX-003, ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
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## Table 28: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye: PRK Only (UVX-003, ITT Population)

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<td>44.6</td>
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<td>SD</td>
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</tr>
</tbody>
</table>
Reviewer’s comment: The sponsor’s response is acceptable. It provides the descriptive statistics for the subgroups requested by the Agency. Due to the limited sample size in these subgroup, other unbalanced factors, multiplicity and post-hoc issue, statistical references should be exercised in caution for these subgroups. From a statistical perspective, it is difficult to draw a statistical inference from this kind of analyses.

• **CDRH Request #13c.2d:** Your enrollment criteria selected subjects with progressive keratoconus while your proposed indication for use is simply for keratoconus. The risk/benefit considerations could be different between these populations since some keratoconus patients remain stable for years and some progress. Please provide a discussion regarding whether any data was obtained on subjects who did not meet the enrollment criteria and what data is available to support approval for a general keratoconus population rather than a progressive keratoconus population in light of the differences in the risk/benefit profile.

  **Sponsor’s response:** To be consistent with the population studied in the clinical trials, the proposed indication will be revised to those subjects with progressive keratoconus.

  **Reviewer’s comment:** The sponsor’s response is acceptable. The sponsor limits the proposed indication to the population studied in the clinical trials.

• **CDRH Request #13d:** 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.

  **Sponsor’s response:**
  Please refer to Avedro’s response provided in the Type A Meeting Briefing Package, Section 3.16 (SN 0027, Module 1.6.2) and response to Item #13C for additional safety and efficacy information by subpopulations.

  In Section 3.16 of the type-A meeting package, the sponsor’s response are “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 $\geq 15$ letters decreases for the CXL group consistent with the healing process post debridement. By Month 12, only 1 (1.6%) CXL subject lost $\geq 15$ letters in BSCVA in Study UVX-002 and 2 (3.8%) in UVX-003.”

Reviewer’s comment: Item 13.d is clinically relevant and the review of the sponsor’s response is deferred to the clinical review.

- CDRH Request #14.1: With regard to the “output printing error” on the Pentacam which occurred in study UVX-001, we are concerned that this may indicate a larger problem with reliability of data generated from this device. Therefore, we recommend the following additional information be submitted:

  a. Please review study output from this Pentacam to determine whether any other data generated from this instrument was non physiologic (e.g. do not limit “nonphysiologic” Kmax to mean negative or zero values. Please also evaluate pachymetry and any other measurements collected, to the extent possible.) This is requested in order to determine whether the “error” was an isolated event or a more extensive problem.

  b. Please provide a discussion regarding whether this “output printing error” could represent a device malfunction that could have impacted accuracy of data in other subjects at this site.

  c. Please provide revised analyses after eliminating any erroneous or nonphysiologic study data identified since even a relatively small number of such errors could potentially affect the results.

Sponsor’s response:

a. Avedro has conducted a thorough review of the Kmax data for Study UVX-001 and has not identified any nonphysiologic Kmax values, other than the Kmax value of -0.3 diopters (D) at Month 1 for Subject 00230 which was previously identified and determined to be an “output printing error”. For the purpose of this review, nonphysiologic Kmax values in this keratoconus and ectasia population were defined as those that were less than 30 D or greater than 100 D. All Kmax values in this study were generated from the same Pentacam and ranged from 42 to 89 D. A review of the pachymetry data generated by this Pentacam was also conducted and did not yield any non-physiologic values; pachymetry values ranged from 123 to 611 $\mu$m.
b. The “output printing error” that generated the negative Kmax value (-0.3 D) for Subject 00230 appears to be an isolated event and does not represent a device malfunction. Avedro obtained the source Pentacam file for this event and sent it to for full investigation. Per their investigation, the issue was a software error. The file was generated using software version 1.16r61 which had a bug such that whenever a negative curvature value appeared anywhere on the corneal surface, it was displayed as Kmax. The bug was fixed with the next released Pentacam software. Per the error was a rare event and could be clearly identified (by the negative sign) when it did occur. Upon reprinting the Pentacam data for this exam using new software, the new output for Kmax was 64.4 D which is consistent with the K values on the topographic map for this scan. Additionally, Avedro reviewed all available Pentacam printouts from this site and compared the Kmax values to the K readings on the topographic map to ensure that the Kmax values and location were consistent with the maps; no discrepancies were found.

c. Since the only Kmax errors that occurred were at the 1 month timepoint, there is no impact on the primary efficacy analyses.

**Reviewer’s comment:** The sponsor’s responses to Item 14.1 are acceptable. According to the sponsor, the nonphysiological Kmax value was produced by a bug in the operating software of Pentacam. The updated Kmax is 64.4 D instead of -0.3 D at Month 1 for Subject

- **CDRH Request #14.2a:** You submitted additional literature in response to Complete Response Item #14. One article entitled, “A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus” (Wittig-Silva 2014) contains a discussion regarding demographic factors that have been suggested to be associated with disease progression after crosslinking or progression of crosslinking effect years after treatment.

  a. Please provide an analysis/discussion of any criteria that could be used to identify patients at risk for these outcomes based on data from your study.

  b. We believe long-term data are necessary to support device safety and effectiveness. Your submission does not include discussion of post-approval plans or a Post-Approval Study (PAS) protocol to address long-term safety and effectiveness concerns raised in the literature. Please provide such a proposal or justify not doing so.

**Sponsor’s response to Item 14.2a:**
Wittig et al (Ophthalmology 2014) observed continuing flattening in $K_{\text{max}}$ even after 2 years post CXL treatment; however, no information regarding baseline or demographic characteristics of these eyes is provided in the publication.

In the UVX studies, we saw a continued flattening in $K_{\text{max}}$ from 3 to 12 months in the CXL groups; however, since study eyes were only followed until 12 months, it is difficult to assess whether the study eyes had stabilized or would continue to flatten over time. In their discussion, Wittig et al. reference the findings of another group (Asri et al, J Cataract Refract Surg 2011) suggesting that age of more than 35 years and female gender were risk factors for progression of disease after CXL. Avedro reviewed the keratoconus data from Studies UVX-001 and UVX-002 to look for any trends based on age or gender. Efficacy ($K_{\text{max}}$) data based on age of $\leq 35$ years or $>35$ years for Studies UVX-001 and UVX-002. These data are presented in Table 44 and Table 45, respectively. The outcomes after CXL for the groups with age at treatment $>35$ years appear to be as good as or better than the outcomes in the groups with age $\leq 35$ years with no evidence of disease progression after CXL. Additionally, no evidence of an increased risk of disease progression was seen in subjects of female gender in the UVX-001 and UVX-002 studies. Efficacy ($K_{\text{max}}$) data based on gender for Studies UVX-001 and UVX-002 are presented in Table 46 and Table 47, respectively. In both studies, female subjects showed a greater degree of flattening after CXL compared with male subjects over the 12 month period.
Reviewer's comment: The sponsor’s response is acceptable. This reviewer also performs poolability analyses for Keratoconus age subgroup (>35 or otherwise) and Keratoconus gender subgroup using treatment-by-subgroup interaction effect in an ANOVA model with fixed effects of treatment, subgroup, and treatment-by-subgroup interaction. No statistical significance is found for the interaction effect at two-sided 0.15 alpha level at Month 12.

Using the similar analyses, this reviewer finds that the treatment-by-subgroup interaction effect are statistically significant for Ectasia age subgroup (studies UVX-001, 003) and Ectasia gender subgroup (UVX-003) at a two-sided 0.15 alpha level at Month 12, but the interaction effect appears to be quantitative rather than qualitative, so it may not be a major concern from statistical perspective. It appears that the younger subgroup and female subgroup obtain more reduction of Kmax from baseline to Month 12 as shown in the following figure.

Sponsors response to Item 14.2b:
Avedro agrees to conduct a post-approval study (PAS) to monitor long-term safety and effectiveness of CXL. Table 48 provides a synopsis of the proposed PAS.
<table>
<thead>
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<th>Title</th>
<th>Summary of Proposed Post-Approval Study</th>
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<td>A Phase IV, Prospective, Observational Study of the Long-term Safety</td>
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<tr>
<td>and Efficacy of the KXL System with Photrexa (Riboflavin Ophthalmic</td>
<td></td>
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<tr>
<td>Solution) for Corneal Collagen Cross-Linking in Eyes with Progressive</td>
<td></td>
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<tr>
<td>Keratoconus or Corneal Ectasia</td>
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**Reviewer’s comment:** In the post-approval study, the Kmax values for the untreated eyes are recommended to be measured at Months 1, 3, 6, and 12 so that the changes of mean Kmax value in untreated eyes across various time points can be well understood at the end of the study.
2. Questions for sponsor and ODE/OIVD

Comments to ODE

- The sponsor provides the requested descriptive statistics for deficiency Items 13-14 in the CR letter. Since they are clinically oriented, this reviewer would like to defer to the review team regarding whether the responses are acceptable.
- Regarding the post-approval study, the Kmax values for the untreated eyes are recommended to be measured at Months 1, 3, 6, and 12 so that the changes of mean Kmax value in untreated eyes across various time points can be well understood at the end of the study. However, this reviewer would like to defer to the review team regarding whether this suggestion is appropriate for a post-approval study.

Deficiencies for the Sponsor

- none

Xin Fang, Ph.D.

cc: Maryam Mokhtarzadeh, MD.
Bradley Cunningham, MS
Xu Yan, Ph.D.
Yun-Ling Xu, Ph.D.
DBS Reviews
**Systematic Literature Review on Corneal Collagen Crosslinking (CXL) Procedures**  
**For the Treatment of Keratoconus and Secondary Ectasia**

The objective of this systematic literature review is to summarize the relative safety and efficacy of corneal collagen crosslinking (CXL) procedures for the treatment of keratoconus and secondary ectasia.

CXL procedures aim to induce chemical reactions in the corneal stroma and ultimately result in the formation of covalent bonds between the collagen molecules, fibers and microfibrils. The standard CXL procedure included in this literature review is used for the treatment of progressive keratoconus and/or post-refractive corneal ectasia. The procedure includes the application of 0.1-0.12% photosensitizer riboflavin (vitamin B2) drops to the cornea every 3-5 minutes for 15-30 minutes, with or without 20% dextran, after a central area (7.00-9.00 mm) of the corneal epithelium is removed, and subsequently, the corneal surface is irradiated with ultraviolet light (~365 nm UVA) for 30 minutes (equivalent to 3 mW/cm²). This procedure with the inclusion of dextran is commonly known as the Dresden Protocol.[1]

A search of the PubMed database was conducted on February 6, 2015 with the following search terms used to retrieve English-language peer-reviewed articles published since January 1, 2003 on randomized clinical trials (RCT) of CXL procedures: “keratoconus” OR “ectasia” AND “crosslinking” OR “cross-linking” OR “cross-linkage.”

The initial search resulted in 44 unique articles. Articles were selected for inclusion in the literature review if they reported on clinical studies with RCT study designs conducted in humans that evaluated the safety and efficacy of standard CXL procedures for the treatment of keratoconus and secondary ectasia. Based on the review of the abstracts, five articles were excluded because non-standard method (accelerated or transepithelial CXL) was used. These non-standard methods are not proposed for the device under review. A full article review was then conducted on the remaining 39 articles, and 33 articles were excluded because of non-RCT study design. One excluded article reported interim results of a study in which full results were later published. This latter article was included in this review. Overall, four articles on CXL procedures were included in this systematic literature review.

**Overview of the studies included in the systematic review of the literature**

The four articles selected for inclusion in the systematic review were published between 2010 and 2014. None of the studies was conducted in US. The studies were conducted in Brazil[2],...
Britain, Peru and Australia. All of the studies were designed primarily for efficacy outcomes with some safety outcomes included.

Renesto et al. studied impression cytologic (IC) involving 32 patients of keratoconus assigned randomly to receive CXL (19 eyes) or riboflavin 0.1% eyedrops (21 eyes) observed for 3 months.

O’Brart et al. recruited 24 patients with early/moderate bilateral keratoconus with recent progression. One eye of each patient received CXL treatment while the other eye received no treatment (control). Twenty-two patients completed follow-up (18 months).

Henriquez et al. evaluated the efficacy and safety of the CXL procedure in a study of 10 eyes of 10 patients with progressive keratoconus that received CXL treatment (cases), and 10 eyes (number of subjects not specified) with progressive keratoconus as the control group. The control group received no treatment except glasses. The length of follow-up was 12 months.

Wittig-Silva et al. conducted a study enrolling 100 eyes diagnosed with progressive keratoconus, with 48 control eyes and 46 treated eyes completing 36 months of follow-up. A modified version of the Dresden protocol was utilized. The controls received no treatment; although, patients were offered compassionate CXL treatment if continuing and significant disease progression was noted during the course of the study. 12 eyes from the control group were offered compassionate treatments at least 6 months after entering the study. Data collection for the purpose of this study was terminated for compassionately treated eyes at the time of the procedure.

The mean age from these studies varied from 22.7 to 29.6 years old, and ranged from 11 to 50 years old. The enrolled patients from these studies were 113 (57.7%) males and 83 (42.3%) females.

All the patients recruited for these studies had keratoconus, and only one study did not mention whether the keratoconus was progressive or not. The other three studies’ patients had progressive keratoconus. None of the studies reported on the safety or efficacy of the CXL procedure for patients with secondary ectasia.

Across the studies, the treatment groups underwent CXL procedures while the controls were chosen from either the other eyes of the same patients or additional patients with the same diagnosis. The controls received no treatment except in one study where riboflavin 0.1%
eye drops were applied.

**Summary of Efficacy**

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

**Keratometry**

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

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

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

**Visual Acuity**

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

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

Henriquez et al.\[4\] reported an UCVA of 0.46 logarithm of the minimum angle of resolution at 12 months postoperatively as compared to 1.18 logarithm preoperatively (P<0.001) for patients that underwent the CXL procedure.

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

Henriquez et al.\cite{4} reported a 2.25 D reduction in the mean spherical equivalent (P = 0.01) in the treatment group.

Wittig-Silva et al.\cite{5} reported a manifest cylinder increased only significant in the control group by 1.17±0.49 D (P = 0.020) at 36 months.

**Assessment of Efficacy and Critique**

These articles support the efficacy of the CXL procedure for keratoconus based on flattening the corneal curvature measured by keratometry data, improvement in visual functioning measured by UCVA or BSCVA. The information is less consistent in the refractive status change in that one article by O’Brart et al.\cite{3} reported improvement in BSCVA in both treated and non-treated eyes, and in another larger study (Wittig-Silva et al), obscure data obtained about the refractive change, perhaps contributed to baseline mean corneal curvature (Kmax) appearing steeper by 1.65 D in the treatment group compared with the control group (P=0.052). Further bias in the findings may have been induced through the 12 patients that crossed-over after six months when disease progressed more than expected and data collection had to be terminated at that point in Wittig-Silva et al. Information on the efficacy of the CXL procedure for the treatment of secondary ectasia was not available.

**Summary of Safety**

**Corneal Edema/Subepithelial Infiltrates/Inflammation**

Wittig-Silva et al.\cite{5} reported one case of mild, diffuse corneal edema with small paracentral infiltrate 1 week after treatment. This was attributed to the premature (day 3) resumption of rigid contact lens wear and was treated with a prolonged course of fluorometholone acetate 0.1%. The BSCVA was not adversely affected. By 12 months, there was only a faint corneal scar.

In a second case, subepithelial infiltrates and anterior chamber inflammation were observed 2 days after treatment in a patient with a history of severe atopy. This was treated as possible microbial keratitis with removal of the bandage soft contact lens and the frequent application of ofloxacin eye drops. There were no organisms identified on either Gram stain or culture from corneal scrapings. The clinical signs had resolved by 3 months after CXL. The BSCVA
improved from 0.6 logMAR at baseline to 0.3 logMAR at 6 months in this eye.

A third case was noted to have peripheral corneal vascularization 3 years after CXL treatment. However, there was evidence of acne rosacea and vascularization in both the treated eye and the untreated fellow eye. This change was thought to be unrelated to the CXL treatment. There were no other treatment-related adverse events.

Henriquez et al.\textsuperscript{[4]} reported one eye presented 1 day postoperatively with Descemet folds and corneal edema, which resolved after 10 days of topical corticosteroid treatment.

\textbf{Striae}
Wittig-Silva et al.\textsuperscript{[5]} reported some highly reflective striae in the mid to posterior stroma by confocal microscopy 6 weeks postoperatively. These changes were not observed prior to the treatment or in any of the control eyes. The striae were most prominent 1 to 3 months after CXL and became progressively less marked with subsequent follow-up.

\textbf{Endothelial Cell Density}
Wittig-Silva et al.\textsuperscript{[5]} compared with the baseline specular microscopy, and found no significant reduction in endothelial cell density was observed at any of the time points up to 36 months following treatment.

Henriquez et al.\textsuperscript{[4]} also found no statistically significant differences between preoperative and postoperative (up to 12 months) endothelial cell counts and macular thicknesses.

\textbf{Intraocular Pressure}
Wittig-Silva et al.\textsuperscript{[5]} reported that no significant difference was detected for the mean change in intraocular pressure from baseline to 36 months in either group (measured by Tono-Pen).

\textbf{Central Corneal Thickness}
Wittig-Silva et al.\textsuperscript{[5]} reported a significant reduction in corneal thickness measured using computerized videokeratography in both groups at 36 months (control group: -17.01±3.63 mm, \(P<0.001\); treatment group: -19.52±5.06 mm, \(P<0.001\)) but not observed in the treatment group using the manual pachymeter (treatment group: +5.86 ±4.30 mm, \(P = 0.181\)).

Henriquez et al.\textsuperscript{[4]} found that in the treatment group itself the thinnest point of the cornea was statistically thinner at the 12 month follow-up than preoperatively by a mean of 13.4 mm (\(P = 0.03\)). No statistically significant differences were found between preoperative and postoperative values at the apex of the keratoconus or pupil center.

\textbf{Corneal Transplant}
Only Wittig-Silva et al.\[5\] reported 5 eyes from the control group underwent corneal transplantation during the follow-up period, and 9 patients (5 treated and 4 control eyes) withdrew from the trial for personal reasons. No eyes from the treatment group underwent corneal transplantation surgery from the four studies.

**Ocular Surface Changes**
Renesto et al.\[2\] studied ocular surface morphological changes with observation of goblet cells that are related to the occurrence of dry eye. The patients in the treatment group showed a decrease in goblet cell density on the superior conjunctiva after CXL (P = 0.008) but no difference on the temporal conjunctiva (P>0.05) or in the cornea. Patients in control group demonstrated improvement in cell-to-cell contact of epithelial cells and reduced keratinization on the temporal conjunctiva after treatment (P = 0.003 and P = 0.034, respectively) but no changes on the superior conjunctiva (P>0.05) or in the cornea. Comparison of IC total scores after treatment revealed no difference between the two groups.

**Assessment of Safety and Critique**
These studies did not reveal any new major safety concerns for the CXL procedure. However, these studies were primarily designed as efficacy studies, with relatively small sample sizes which may not be able to detect statistical significance for clinically relevant differences. The incidences for adverse events such as corneal infiltrate and corneal edema caused by endothelial cell loss were rare. In addition, due to the small studies, treatment failure demonstrated by keratometry value increase, endothelial cell apoptosis, limbal stem cell damage, secondary surgical intervention with corneal transplant, impact to the natural crystalline lens and the retina were not seen among these articles. Pediatric effect such as any particular outcomes that could be different from adult patients was not analyzed, although some studies do include patients as young as 11 years old.

**Overall Conclusions**
This literature review focused on the safety and efficacy of the CXL procedure for the treatment of keratoconus and secondary ectasia as reported since 2003 through RCT studies. Four studies were found with the procedure performed in keratoconus patients, using either the other eyes from the same patients or additional patients with the same diagnosis as control group. The controls received no treatment except in one study\[2\] that applied only riboflavin (0.1%) eye drops.

A few well-known adverse events for corneal surgeries such as the corneal Edema/Subepithelial Infiltrates/Inflammation and Striae were observed. Corneal transplant...
was not documented in treated eyes among these studies. Central corneal thickness has no conclusive result because inconsistent data obtained between manual pachmetry and computerized videokeratography. Ocular Surface Changes observed regional variations between the treatment and control group but overall no statistical significant difference was found. Certain adverse events which are expected to occur during corneal surgeries were not detected or reported on, such as treatment failure demonstrated by keratometry value increase, endothelial cell apoptosis, limbal stem cell damage, secondary surgical intervention with corneal transplant, impact to the natural crystalline lens and the retina. Since only one study has a sample size larger than 50 eyes, it is difficult to detect rarer adverse events from these small studies. More investigations with larger sample studies are warranted to further evaluate the safety of the procedures.

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

References

5. Wittig-Silva, C., et al., A Randomized, controlled trial of corneal collagen cross linking in

Document History:
Drafted: Youlin Qi, February 12, 2015
Reviewed with comments and edits: Christopher Ronk, February 12, 2015
Revised: Youlin Qi, February 13, 2015
Reviewed with comments and edits: Christopher Ronk, February 13, 2015
Revised: Youlin Qi, February 13, 2015
Reviewed/Cleared with comments and edits: Christopher Ronk, February 13, 2015
Revised: Youlin Qi, February 13, 2015
Reviewed/Cleared with comments and edits: Christopher Ronk, February 13, 2015
Revised: Christopher Ronk, February 17, 2015
Reviewed with comments: Caños, February 17, 2015
Revised: Youlin Qi, February 17, 2015
Reviewed with comments/edits: Caños, February 17, 2015
Revised: Youlin Qi, February 17, 2015
Reviewed with comments/edits: Caños, February 17, 2015
Revised: Youlin Qi, February 17, 2015
Review/Cleared with edits: Caños, February 17, 2015
Reviewed/Cleared: Marinac-DabicFebruary 17, 2015
Reviewed with Comments: Aron Yustein, February 18, 2015
Revised: Christopher Ronk, February 18, 2015
Revised: Youlin Qi, 2:30pm February 18, 2015
Reviewed with comments: Christopher Ronk, February 18, 2015
Revised: Youlin Qi, 3:25pm February 18, 2015
Reviewed/Cleared: Christopher Ronk, February 18, 2015
Revised: Caños, February 18, 2015
Reviewed/Cleared: Aron Yustein, February 19, 2015
Finalized: Caños, February 19, 2015
----- Attachment 5 -----

CDRH Postapproval study section prepared for backgrounder for advisory committee meeting
(Youlin Qi)
Post-Approval Study (PAS)

Note: The inclusion of a Post-Approval Study (PAS) section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this NDA, PMA combination product. The issues noted below are FDA’s comments regarding potential post-approval studies (if FDA finds the combination product approvable), for the Panel to include in the deliberations.

The FDA review team has identified the following potential post-market issues:

- Adverse events, including corneal opacity, corneal infiltrate, corneal edema, recurrent epithelial defect, BSCVA loss of 2 lines or more and secondary surgical intervention (such as corneal transplant)
- Long-term stability of keratometry, refraction, pachymetry
- Long-term impact on IOP and its measurement
- Long-term health of the corneal endothelium, corneal stroma, limbal stem cells, natural crystalline lens and retina
- Long-term safety and efficacy in the pediatric population
- Potential differences in safety and efficacy outcomes across different racial/ethnic groups, by various refractive procedures undergone and by variations in working distance, focusing target and illumination aperture

FDA is seeking input from the Panel on potential post-market concerns and the corresponding need for evaluation in a PAS.

The applicant proposed a PAS to evaluate long-term safety and efficacy of corneal collagen cross-linking performed with Photrex (riboflavin ophthalmic solution) and the KXL System in eyes with progressive keratoconus or corneal ectasia.
FDA Assessment of Proposed Study

The PAS proposed by the applicant will not address all of the identified post-market concerns. In addition, there are issues related to the proposed methodology of the PAS, i.e.,

Panel Questions

Please discuss if there are unanswered questions on the long-term safety, efficacy, and the benefit-risk profile, or if there are any additional safety or efficacy concerns that should be assessed in the postmarket setting, and discuss recommendations for a post-approval study to evaluate these concerns, such as:

a. the endpoints that should be assessed
b. the inclusion of specific patient populations
c. the duration of follow-up
d. and the study design
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/s/

JACQUELYN E SMITH
03/25/2015
Date: March 24, 2015

From: Senior Electronics Engineer (Jeffrey L. Silberberg), CDRH/OSEL/DBP

Subject: EMC consult for NDA203324 Avedro KXL UV irradiation system

To: Jacqueline Smith, CDER/OND/OAP/DTOP
To: Brad Cunningham, CDRH/ODE/DOED/DSDB
To: Dexiu Shi, CDRH/ODE/DOED/DSDB
cc: Maritze Ortega, CDRH/ODE/DOED/DSDB

Scope

This is in response to your request for a review of the EMC issues in the sponsor’s submissions dated March 10, 2015 in response to our e-mail dated March 9, 2015.

Recommendations

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, required that EMC testing be repeated.

You said that the change involved You said that this 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 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 “UT” 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, “0% $U_T$ for 0.5 cycles”, to “40% $U_T$ for 5 cycles”, to “70% $U_T$ for 25/30 cycles”, and to “0% $U_T$ for 250/300 cycles”. This information is needed so that we can assess conformity of the 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.

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, required that EMC testing be repeated.

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

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 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 Itallic, 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, to “0% $U_T$ for 0.5 cycles”, to “40% $U_T$ for 5 cycles”, and to “70% $U_T$ for 25/30 cycles”, and to “0% $U_T$ for 250/300 cycles”. This information is needed so that we can assess conformity of the 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.

Jeffrey L. Silberberg
Senior Electronics Engineer
Division of Biomedical Physics
OSEL/CDRH/FDA

2015.03.24
17:20:33 -04'00'

Reference ID: 3721012
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
03/25/2015
Memorandum

Date: February 10, 2014
Bradley S. Cunningham -S
2014.02.10 15:40:04 -05'00'

From: Brad Cunningham, MS
Lieutenant Commander, USPHS
Chief,
Diagnostic and Surgical Devices Branch

To: Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

Re: NDA 203324
Photrex, Photrex<sup>[1]</sup> KXL Device
riboflavin ophthalmic solution (20% dextran),
riboflavin ophthalmic solution (0% dextran),
UV-A Irradiation
(Previously: Riboflavin ophthalmic solution 0.12% <sup>[2]</sup> KXL system)
Avedro, Inc.

Indications for Use

The applicant proposes the following indications for their product:

Background

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

The KXL® System is a UVA irradiation system whereby an electronic medical device with a light emitting diode (LED) is used to deliver a dose of UVA light (365 nm wavelength) in a circular pattern to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Irradiating the Photrex or Photrex<sup>[3]</sup> (riboflavin ophthalmic solution) creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system.
The KXL System is used in conjunction with a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console. The UV total energy is the product of the intensity of the irradiance (UV power) and the UV irradiation time. The following are the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA. For the KXL System to be marketed in the United States, the maximum allowable treatment parameters will be limited to 3 mW/cm² for 30 minutes and a maximum energy density of 5.4 J/cm².

Avedro’s riboflavin ophthalmic solutions, Photrexa and Photrexa are sterile, phosphate buffered saline solutions containing 0.12% riboflavin (Vitamin B2) in either 20% dextran or 0% dextran, respectively. The drug products are supplied as pre-filled 3-mL glass syringe packaged in a sealed secondary light-block pouch. Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photosensitizer.

**Summary**

CDRH was requested to review the NDA 203324 by the Division of Transplant and Ophthalmology Products (DTOP). Within the CDRH, consult requests were made for various review areas including clinical, optical radiation hazard, electromagnetic compatibility and software. Below is a brief summary of each area:

1. **Clinical**

   There are some major concerns regarding this “first of a kind” medical product. The device used in the clinical trials is not identical to the device proposed for approval. One major concern relates to differences observed between the two device proposed for marketing and the device used in the clinical trial. Differences include a fixed illumination diameter in the device proposed for marketing approval (9mm) and a variable illumination diameter in the device used in the trial (7, 9, 11 mm). With regard to the indication for keratoconus, the orphan designation is for keratoconus. However, the clinical studies enrolled subjects with progressive keratoconus. We believe there may be differences in the risk/benefit considerations between these two populations since some keratoconus patients remain stable for years and some progress.

   Regarding the mechanics of the clinical trial, due to the potential for subject crossover from the control arm to the treatment arm at 3 months, a variety of concerns arise including reduced accountability beyond the 3 month visit for the control arm and concern regarding the use of last observation carried forward
(LOCF) analyses to supplement the month 12 data. However, we note that using the 3 month visit data without LOCF analyses (as initially intended based on the study design), the applicant does not meet pre-specified effectiveness endpoint targets for all indications. Regardless, we strongly believe that long-term data would be valuable for this technology. Also, three separate clinical studies are reported and the poolability across studies has not been established. Therefore, there are concerns regarding the limited sample size for each treatment group. [The planned sample size was 160 subjects (80 eyes per treatment group) for UVX-002 and UVX-003. For UVX-001, the planned sample size was 320 subjects (160 per indication, with 80 eyes per treatment group).

The applicant also included pediatric patients in their study. However, we do not believe sufficient data is available from this study to support labeled use for pediatric patients (there were 16 patients between 14-18 years of age).

We believe that the approval of this combination product would represent a major milestone in ophthalmic patient care. Thus, we strongly believe that the clinical concerns raised by the CDRH warrant, at minimum, an advisory committee meeting.

2. Electromagnetic Compatibility

Because this device will be used in close proximity to other electronic devices, it is important to evaluate the electromagnetic compatibility (EMC) of this device, as well as the immunity of this device to electromagnetic interference.

The applicant claims conformity to EN 60601-1-2 as well as to IEC 60601-1-2. However, the EMC test reports do not cite IEC 60601-1-2 and this standard represents FDA’s most current thinking and “best practices” for electromagnetic compatibility considerations.

While there are concerns regarding test reports and labeling, there are also larger concerns that result in the collection of additional testing information.

3. Software

This software contained in this medical product represents a major level of concern (LOC) as any malfunction could result in major injury to a patient. Therefore, the we reviewed the software documentation submitted by the applicant in-depth in areas including the device hazard analysis, software requirements specifications, software design specifications, software development environment and verification and validation activities.
In general, the software documentation was satisfactorily completed. However, there are concerns regarding cyber security and run-time error detection, which are important to device functionality and patient information. Thus, there is additional information needed to complete our review.

4. **Optical Radiation Hazard analysis**

The power settings for the UV-light delivery may be hazardous to the eye. The total energy output for the device was not reviewed during the IND; neither were the irradiance levels. There have not been limitations set for the output levels by neither software nor hardware controls. The only mitigation proposed by the company was to make treatment cards available for purchase that limit the output; the cards available for purchase in the US would limit the device to settings used in the study. While this proposal would “limit” the device output, it does not sufficiently limit the possibility of raising the power beyond the levels in the investigational studies. At minimum, we would expect a software lockout, as we require in refractive laser devices (i.e., LASIK). However, please note that the lockouts used for refractive lasers are only treatment-range lockouts, not lockouts for power settings. Therefore, it does not completely eliminate the possibility of emission of excessive power levels. Thus, the most appropriate mitigation is a hardware modification that limits power output to ensure safer levels of energy.

The applicant appears to contend their device is a “Class 1 laser device.” However, it is not clear whether they mean a group 1 laser per ISO 15004-2 or whether they believe they are a class 1 laser per 21 CFR 1040. In either event, based on their assessment, they believe they are a low-risk laser device, which is not correct based on our initial evaluation of the laser output specifications.

**Recommendation**

We have identified several areas of deficiency within the application. While the reviews for clinical and optical radiation hazard remain ongoing, we do have deficiencies to immediately convey interactively to the applicant for response. In addition to the deficiencies identified below, we believe that because this device/drug combination product is a first-of-a-kind, many of these issues should be presented to an ophthalmic advisory committee of experts. This advisory committee consultation would serve to help define the regulatory path moving forward with regards to clinical study design, device issues and post-approval study considerations.
**Deficiencies**

*Clinical*

1. You provide a listing of 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) in Table 8, Section 3.2R. This table indicates that the potential illumination diameters used in the trial include “Variable steps 7.0, 9.0 and 11.0 mm” while the device proposed to be marketed has an illumination diameter “Fixed at 9.0 mm”. Please address the following so we may evaluate the impact that variability may have had on study safety and effectiveness results and their applicability to expected post-market device performance:

   a. Please explain how investigators were instructed to choose the appropriate illumination diameter for use.

   b. Please clarify how many subjects in each study were treated with each illumination diameter.

   c. Please provide analyses of safety and effectiveness results stratified by illumination diameter used.

   d. Please discuss how the labeling will instruct users regarding appropriate device use in light of a fixed diameter for the proposed device for marketing approval (for example, selection of patient population).

   e. Please 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, please provide this information.

This information is requested so that we may assess whether these differences could impact the safety or effectiveness of the device.
Optical Radiation Hazard

2. The sponsor states a Radio Frequency Identification (RFID) activation card will be used to determine the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage. The proposed treatment parameters that will be allowed by the RFID activation card in KXL Systems for the United States are:

   Induction Period: 30 minutes
   Irradiance: 3 mW/cm²
   Total Energy: 5.4 J/cm²
   Exposure Time: 30 minutes

However, a RFID card may not be sufficient to lockout elevated power output that was not adequately studied in the clinical trials provided to support this marketing approval application. We believe that the most effective means to limit the power output of this device is to implement a hardware modification to limit the maximum power. Therefore, please provide justification for how a RFID can appropriately limit the power output to safer levels (those used in the study to support this marketing approval application). Alternatively, we strongly recommend that you implement a hardware modification to limit the power output.

3. On Page 4-5, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), you specify that:

   6.2.6.4. Output power shall be controlled to %.
   6.2.6.8. Power uniformity over the illuminated area shall be % RMS.

Please address the following concerns:

a. A tolerance range (%) is given for UV-A output. Please provide your rationale for why this tolerance range is selected and/or the justification that the % illumination fluctuation will be safe for proposed treatment.

b. Please provide the test result to demonstrate power uniformity over the illuminated area is % RMS for KXL system.

4. You state that “UVA radiation is generated by UV LED (365nm).” Please address the following concerns:

a. You only provided the Homogeneity Measurement Master Validation plan (VAL-00005). However, you did not provide any test results. Please provide this
information and ensure you explain the homogeneity criteria and provide the test results to demonstrate the UV-A treatment beam is homogeneous over entire treatment area.

b. Please be advised that the \( \text{(b)(4)} \) may be hazardous to the device operator. Therefore, please provide information regarding any mitigation method(s) used to address eye safety concerns for operators.

5. You state that the KXL system used two targeting lasers for illumination, and both targeting lasers are considered as a Class I laser based on IEC 60825-1:2007. However, you do not provide the basic technical characteristics of the two lasers. Please provide this information. In addition, it is unclear how you determined the classification of the lasers and LEDs. Please provide detailed information for how this determination was made so we may fully evaluate the laser and optical radiation safety analyses.

EMC

6. On page 60 and 61 of the device-information document, there is a table of “recognized standards” with which the KXL System is claimed to comply. However, for many of the standards listed, there is 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 important. Also, FDA does not recognize EN standards, and there are several on the list. Conformity with IEC 60601-1-2 is claimed; however, the EMC test report cites EN 60601-1-2. While the two standards are essentially identical, please be consistent in your claims of conformity. Finally, please submit an FDA Form 3654 for each standard to which conformity is claimed.

7. Even though you state conformance to IEC 60601-1-2, the immunity pass/fail criteria specified in the EMC test report do not appear to 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 have not specified the performance that you 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, please specify the Essential Performance explicitly. Any future EMC testing to IEC 60601-1-2 that you submit 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.

8. Regarding immunity tests, IEC 60601-1-2:2007 indicates that for ME EQUIPMENT and ME SYSTEMS that have multiple voltage settings or autoranging voltage capability (for voltage input), 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 shows that the testing was performed only at VAC/Hz. We note 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 provide the results of this testing for review.

9. The EMC test reports you provide identify the modifications (listed below) that were made to the KXL System in order to pass the tests. Please note that the EMC testing should be done on the final version of your 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, please confirm that all of these modifications (listed below) will be included in all units to be marketed:

- [b] (4)

If these features will not be included in the marketed version of your device, please provide an explanation for why the testing you completed is appropriate to support an EMC evaluation of your device or please re-test your device without the additional modification that would not be included in a marketed device.

10. 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. Please 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. Please 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

11. The KXL System incorporates wireless remote control and radio frequency identification (RFID) capabilities. However, we were not able to find information on the effective radiated power of either wireless device or the communication service or protocol used by the wireless remote control. Please provide this information and also address all the issues raised in the 2013 FDA guidance Radio Frequency Wireless Technology in Medical
Devices (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidance documents/ucm077210.htm), including performing wireless coexistence testing or submitting a justification as to why wireless coexistence testing is not needed.

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”.

Reference ID: 3720918
Software

13. You did not provide information on Cybersecurity for your RFID activation card. Please discuss, in detail, information on your design considerations, including mitigations pertaining to intentional and unintentional cybersecurity risks including:

   a. A specific list of all cybersecurity risks that were considered in your design.

   b. A specific list and justification for all cybersecurity controls that you established, and the justification as to why such controls are adequate. Please provide the evidence that the controls perform as intended.

   Please incorporate, as appropriate, the information identified here in your Hazard Analysis.

14. Regarding Run-Time Error Detection, please identify what tools, (such as static analysis tools), if any, you used to detect run-time errors. For any such tool used, please identify what error types the tool detects, your method and process of applying the tool(s), and a summary report and/or conclusion about the results.

   Note: some common run-time errors are:

   1. Un-initialized variables
   2. Type mismatches
   3. Memory leaks
   4. Buffer over/under flow
   5. Dead and unreachable code
OFFICE OF DEVICE EVALUATION
CLINICAL REVIEW

From: Maryam Mokhtarzadeh, MD
ICIB/DOED/ODE

To: Bradley Cunningham, DSDB Branch Chief
Dexiu Shi, Physicist and Laser Reviewer
Tina Kiang, ICIB Branch Chief
Malvina Eydelman, DOED Division Director

Re: NDA 203324
Photrexa, Phototrexa KXL Device
riboflavin ophthalmic solution (20% dextran),
riboflavin ophthalmic solution (0% dextran),
UV-A Irradiation
(Previously: Riboflavin ophthalmic solution 0.12% (KXL system)
Avedro, Inc.

Proposed Indications for Use:
(per form 356h):
(per drug labeling):
(per device labeling in the “device-info-appendices” PDF file, Appendix 5.1. 1-1)

Reviewer Comment: Although the NDA was initially submitted for a drug product with the proprietary name in the most recent submission the sponsor appears to be requesting the following proprietary names for their Riboflavin product: Photrex and Phototrexa. This request is being made since “At a teleconference held on 22 May 2012 between Avedro and the Division of Medication Error Prevention and Analysis (DMEPA), Avedro was notified of DMEPA’s preliminary findings that the proposed proprietary name was unacceptable."

Date: February 7, 2014 (Preliminary Review; Review Ongoing)

Recommendation: Significant Concerns Identified; Major Deficiency

Background Information:
Keratoconus is a degenerative ocular disorder characterized by progressive thinning and steepening of the central cornea, leading to increasing myopia, irregular astigmatism,
protrusion and eventual loss of best spectacle-corrected visual acuity. Onset generally occurs in puberty or early adulthood and, if untreated, patients experience progressive vision impairment.

Corneal ectasia is a complication of refractive surgeries including LASIK and, more rarely, PRK. The cornea is weakened so that it protrudes under the force of intraocular pressure and bows outward. This results in loss of uncorrected visual acuity and loss of best spectacle corrected visual acuity.

Current standard of care includes prescription eye glasses or contact lenses, surgical insertion of physical supports to alter the abnormal corneal curvature, and eventually, replacement of the damaged tissue by corneal transplant, if necessary.

Corneal collagen cross-linking has been demonstrated to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma and stabilizing corneal curvature, thus slowing or stopping the progression of keratoconus and corneal ectasia following refractive surgery. Potential additional clinical benefits are corneal flattening and improvement in both uncorrected and best spectacle corrected visual acuity.

Cross-linking has been incorporated into clinical practice internationally and reports over the past decade (or longer) have generally been positive although it is widely acknowledged that drug dosage, laser settings, and technique vary substantially throughout the literature. In academic meetings it is generally acknowledged that crosslinking has been widely adopted (internationally) and techniques and applications continue to advance despite the lack of large, good quality studies, particularly those with long-term data, to support the safety and effectiveness of a single, consistent indication and technique.

As per this submission, “Riboflavin is a naturally occurring compound (as Vitamin B2), is non-toxic and is an ideal photosensitizer to promote cross-linking in the cornea. In the cornea, UVA light administered alone has been shown to induce weak corneal collagen cross-linking, while riboflavin alone has no cross-linking effects. When administered in combination, UVA light with riboflavin photosensitizer increases the number of corneal collagen cross-links resulting in a shortening and thickening of the collagen fibrils and stiffening of the cornea.” (emphasis added)

*Reviewer Comment: The statement above emphasizes the role of the device (i.e., UVA light source) in achieving the intended therapeutic effect.*
The table below indicates that depending on drug dosage and laser settings, the depth of treatment within the cornea may vary:

Table 2: Depth of Polymerization as a function of Energy Dosage and Concentration of Photosensitizer

**Device Description**

The Applicant’s riboflavin ophthalmic solution/UVA irradiation is a combination product consisting of a UVA 365 nm wavelength light source (the KXL system) and riboflavin administered as a photosensitizer in conjunction with UVA.

Information pertaining to the KXL® System is located in Module 3.2.R.3 (device information).

The KXL® System is a UVA irradiation system whereby an electronic medical device with a light emitting diode (LED) is used to deliver a dose of UVA light (365 nm wavelength) in a circular pattern to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Irradiating the Photrex or Photrexa (riboflavin ophthalmic solution) creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system.

The KXL System is used in conjunction with a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console. The UV total energy is the product of the intensity of the irradiance (UV power) and the UV irradiation time. The following are the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA. For the KXL System to be marketed in the United States, the maximum allowable treatment parameters will be limited to 3 mW/cm² for 30 minutes and a maximum energy density of 5.4 J/cm².

*Reviewer Comments:* It is unclear whether the RFID provides adequate assurance of safety in light of the potential uses of the laser outside the proposed settings. This issue
will be covered in more detail in Dr. Dexiu Shi’s review. However, it is also mentioned among the Major Issues at the end of this document.

The major components of the KXL System include the following:

- Optics Head with UV source
- KXL console with user interface
- Wireless remote control (with replaceable batteries)

![Figure 2-1. Overview Illustration of System](image-url)
### Table 1: KXL System Specifications

<table>
<thead>
<tr>
<th>SPECIFICATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical</strong></td>
<td>Battery Powered: 12V 35 Ah SLA</td>
</tr>
<tr>
<td></td>
<td>Line voltages 100-240 volts AC</td>
</tr>
<tr>
<td></td>
<td>Current</td>
</tr>
<tr>
<td></td>
<td>Single Phase</td>
</tr>
<tr>
<td></td>
<td>RMS, 50/60 Hz</td>
</tr>
<tr>
<td></td>
<td>Remote 2x AAA batteries</td>
</tr>
<tr>
<td><strong>User accessible Fuses</strong></td>
<td>250 V~</td>
</tr>
<tr>
<td><strong>Energy Delivery</strong></td>
<td>UV Radiation</td>
</tr>
<tr>
<td></td>
<td>3 mW/cm²</td>
</tr>
<tr>
<td></td>
<td>365 nm</td>
</tr>
<tr>
<td><strong>External Interfaces</strong></td>
<td>USB 2.0</td>
</tr>
<tr>
<td><strong>Physical Dimensions</strong></td>
<td>Length: 60 cm</td>
</tr>
<tr>
<td></td>
<td>Width: 9 cm</td>
</tr>
<tr>
<td></td>
<td>Height: 34 cm (all dimensions with arm retracted)</td>
</tr>
<tr>
<td><strong>Weight (crated system)</strong></td>
<td>NW 45 Kg</td>
</tr>
<tr>
<td></td>
<td>GW 120 Kg</td>
</tr>
<tr>
<td><strong>Battery Life</strong></td>
<td>16 hours</td>
</tr>
<tr>
<td>(normal operating conditions)</td>
<td></td>
</tr>
<tr>
<td><strong>Environmental Operating Conditions</strong></td>
<td>The system operates under the following atmospheric conditions (no condensation).</td>
</tr>
</tbody>
</table>

### Table 1: KXL System Specifications (Continued)

<table>
<thead>
<tr>
<th>SPECIFICATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambient temperature</strong></td>
<td>+10 to +40°C</td>
</tr>
<tr>
<td><strong>Relative humidity</strong></td>
<td>30% to 75%</td>
</tr>
<tr>
<td><strong>Transport and Storage Conditions</strong></td>
<td>The instrument withstands the following transport and storage conditions without damage or performance deterioration.</td>
</tr>
<tr>
<td><strong>Ambient temperature</strong></td>
<td>-15 to +70°C</td>
</tr>
<tr>
<td><strong>Relative humidity</strong></td>
<td>10% to 100% including condensation</td>
</tr>
</tbody>
</table>
Treatment Parameters

To begin preparing for treatment, the user enters the induction period for the instillation of the Photrex or Photrex (riboflavin ophthalmic solution) in minutes and seconds using the screen shown in Figure 12.

Figure 12: KXL System Set Induction Period Screen

The user sets the UV treatment parameters including total energy and UV power as shown in Figure 13. Please note that the RFID activation cards supplied in the United States will not allow treatment unless the Total Energy is set to 5.4J/cm² and the UV Power is set to 3 mW/cm².

(device description, pg. 21)

The sponsor provided Table 8 (below) to address differences between the specifications of the device used during clinical trials (the UV-X Illumination System) and the device proposed for marketing (the KXL System)
<table>
<thead>
<tr>
<th></th>
<th>Phase III</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UVA System</strong></td>
<td>UV-X Illumination System</td>
<td>KXL System</td>
</tr>
<tr>
<td><strong>Device Type</strong></td>
<td>LED illumination device (Class II)</td>
<td>LED illumination device (Class II)</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>Wavelength: 365 ( \text{nm} )</td>
<td>LED: Wavelength: 365 ( \text{nm} )</td>
</tr>
<tr>
<td><strong>Device Configuration</strong></td>
<td>Illumination system at end of an arm, attached to a floor stand or a patient bed</td>
<td>Illumination system at end of an articulated arm on top of a floor stand, wireless remote control and a system console</td>
</tr>
<tr>
<td><strong>Light Emission</strong></td>
<td>Continuous wave (CW)</td>
<td>Continuous wave (CW)</td>
</tr>
<tr>
<td><strong>Illumination Intensity</strong></td>
<td>3.0 mW/cm(^2)</td>
<td>3.0 mW/cm(^2)</td>
</tr>
<tr>
<td><strong>Illumination Diameter(s)</strong></td>
<td>Variable steps 7.0, 9.0 and 11.0 mm</td>
<td>Fixed at 9.0 mm</td>
</tr>
<tr>
<td><strong>Treatment Time</strong></td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td><strong>Patient Positioning</strong></td>
<td>On bed</td>
<td>On bed</td>
</tr>
<tr>
<td><strong>Targeting System</strong></td>
<td>N/A</td>
<td>Laser crosshairs</td>
</tr>
<tr>
<td><strong>Focal Plane Setting</strong></td>
<td>Subjective (homogeneity of UV pattern)</td>
<td>Objective (crossed laser beams)</td>
</tr>
<tr>
<td><strong>Electric Power</strong></td>
<td>100V to 240 V</td>
<td>100 V to 240 V</td>
</tr>
<tr>
<td><strong>Intensity Check</strong></td>
<td>UV light meter delivered with UV-X System</td>
<td>Integrated UV light meter</td>
</tr>
<tr>
<td><strong>Laser and LED Safety Compliance</strong></td>
<td>IEC 60825-1</td>
<td>IEC 60825-1 IEC 62471</td>
</tr>
<tr>
<td><strong>Electrical Safety Compliance</strong></td>
<td>IE 60601-1</td>
<td>IE 60601-1</td>
</tr>
</tbody>
</table>

Both systems are LED based illumination systems with a wavelength of 365 \( \text{nm} \). Both systems are continuous wave systems with an illumination intensity of 3.0 mW/cm\(^2\) and a treatment time of 30 minutes. The illumination diameter is 9.0 mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm steps. The patient is positioned on a bed for treatment in a supine position with both systems. The KXL System includes an alignment focusing beam that allows for alignment of the treatment area. The UV-X System was aligned subjectively by the user. The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used an external light meter. Both systems comply with IEC 60601-1 and IEC 60825-1, and the KXL System also complies with IEC 62471.

Avedro conducted testing which compared the spectral output of the UV-X system and the KXL system to evaluate their equivalence. The results were provided in Appendix 3.
Reviewer Comments: The differences cited in the table and text above were discussed with Dr. Dexiu Shi who is reviewing the laser. Dr. Shi addressed the other differences noted in the table and text in addition to the sponsor’s belief that the laser should be classified as a “Class I Laser”. The deficiency below addresses remaining clinical concerns.

Deficiency: You provide a listing of 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) in Table 8, Section 3.2R. This table indicates that the potential illumination diameters used in the trial include “Variable steps 7.0, 9.0 and 11.0 mm” while the device proposed to be marketed has an illumination diameter “Fixed at 9.0 mm”. Please address the following so that we may evaluate the impact that variability of this parameter may have had on study safety and effectiveness results and their applicability to expected postmarket device performance:

1) Please clarify how investigators were expected to choose the appropriate illumination diameter for use.
2) Please clarify how many subjects in each study were treated with each illumination diameter.
3) Please provide analyses of safety and effectiveness results stratified by illumination diameter used.
4) Please discuss how the labeling will instruct users regarding appropriate device use in light of a fixed diameter (for example, selection of patient population).

Finally, please 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 approval including, but not limited to: device description, laser settings and/or parameters, software, and instructions for use. This information is requested so that we may assess whether these differences could impact the safety or effectiveness of the device.

Drug Product:
Avedro’s riboflavin ophthalmic solutions, Photrexa and Photrexa (b)(4) are sterile, phosphate buffered saline solutions containing 0.12% riboflavin (Vitamin B2) in either 20% dextran or 0% dextran, respectively. The drug products are supplied as pre-filled 3-mL (b)(4) glass syringe packaged in a sealed secondary light-block pouch. Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photosensitizer.
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Photrex</th>
<th>Photrex 3 mL</th>
<th>Function</th>
<th>Quality Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin 5'-Phosphate Sodium</td>
<td>0.12%</td>
<td>0.12%</td>
<td>Active ingredient</td>
<td>USP; EP</td>
</tr>
<tr>
<td>Dextran 500</td>
<td></td>
<td></td>
<td></td>
<td>USP; EP</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td></td>
<td></td>
<td></td>
<td>USP; EP; JP</td>
</tr>
<tr>
<td>Sodium Phosphate, Monobasic</td>
<td></td>
<td></td>
<td></td>
<td>USP; EP</td>
</tr>
<tr>
<td>Sodium Phosphate, Dibasic</td>
<td></td>
<td></td>
<td></td>
<td>USP; EP</td>
</tr>
<tr>
<td>Sterile Water for Injection</td>
<td></td>
<td></td>
<td></td>
<td>USP</td>
</tr>
</tbody>
</table>

"Photrex and Photrex are filled into 3 mL multi-compendial (USP/NF and EP) clear glass syringes with plastic rigid tip cap and stoppered with a rubber stopper.” (from description and composition of drug)

Reviewer Comments: The drug component of this combination product is under review by CDER.

Dosage and Administration (per draft drug labeling):

Proposed Indications for Use:

(per form 356b): 

(per drug labeling):
Reviewer Comment: Although the NDA was initially submitted for a drug product with the proprietary name [obscured] in the most recent submission the sponsor appears to be requesting the following proprietary names for their Riboflavin product: Photrexa and Phototektra. This request is being made since “At a teleconference held on 22 May 2012 between Avedro and the Division of Medication Error Prevention and Analysis (DMEPA), Avedro was notified of DMEPA’s preliminary findings that the proposed proprietary name, [obscured], was unacceptable.”

Reviewer Comment: With regard to the proposed IFU for keratoconus: The orphan designation is for keratoconus. The studies enrolled subjects with progressive keratoconus. The risk/benefit considerations could be different between these 2 populations since some keratoconus patients remain stable for years and some progress. This is included with the major issues listed at the end of this review.

**Regulatory History:**

Important Dates/Points Regarding Regulatory History:

1998 – Per sponsor, corneal collagen cross-linking performed internationally since 1998.

November 7, 2007 - Clinical studies using the drug/device system conducted in the U.S. under IND 77,882, which was originally submitted by Peschke Meditrade GmbH (Hünenberg, Switzerland)

May 7, 2010 - Sponsorship of IND 77,882 was transferred to Avedro

November 2010 - [obscured] (riboflavin ophthalmic solution) / KXL® System received CE mark as a commercial medical device and is commercially available throughout Europe.

September 2, 2011 – Orphan drug designation granted to riboflavin ophthalmic solution and UVA irradiation for corneal cross-linking for the treatment of keratoconus.

Sponsor states “there is no FDA approved therapy in the US for the treatment of keratoconus or corneal ectasia following refractive surgery, two orphan indications for which patients are eagerly awaiting a therapeutic treatment option. The [obscured] (riboflavin ophthalmic solution)/KXL® System addresses a significant unmet medical need in these two orphan patient populations.”
Reviewer Comment: This statement appears to neglect device approvals – for example, Intacs were approved through CDRH for some keratoconus patients.

December 2, 2011 - Orphan drug designation granted to riboflavin ophthalmic solution and UVA irradiation for corneal cross-linking for treatment of corneal ectasia following refractive surgery.

March 8, 2012: Avedro submitted NDA 203-324 for corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery and received a Refusal to File (RTF) letter dated 04 May 2012.

May 31, 2012: Meeting between Avedro and the Division of Transplant and Ophthalmology Drug Products

August 15, 2012: Type A meeting with the Division of Transplant and Ophthalmology Drug Products, Office of New Drug Quality Assessment (ONDQA), and Office of Compliance

October 19, 2012: Agency’s General Advice Letter; Avedro resubmits the NDA for review.” The current submission is an NDA (type 505(b)(2)).

Reviewer Comments: Based on the records reviewed within the current file, it does not appear that CDRH was invited to comment on the submission prior to September Fall 2013. It appears the “agreements” alluded to in the submission that occurred at the meetings were made without CDRH concurrence.

I. Bench/Animal Testing and other Supportive Information
An extensive literature review was provided discussing clinical and preclinical testing with corneal crosslinking.

From the “Nonclinical Overview”:

“With riboflavin-UVA cross-linking of corneal collagen, a cytotoxic threshold irradiance level was found at \[ \text{[b]}(\text{d}) \text{ mW/cm}^2 \] after combined treatment with riboflavin plus UVA irradiation. No cytotoxicity was observed with riboflavin alone. In eyes of rabbits treated with 0.1% riboflavin and illuminated with UVA, there was no endothelial damage at 4 hr. In the enucleated porcine eyes treated with 0.1% riboflavin and exposed UVA, a pronounced, highly organized anterior fluorescence zone of 182.5 \( \mu \text{m} \) was noted suggesting stabilization of the cornea due to collagen compaction.

At a riboflavin concentration of 0.1% in the presence of a UVA dose of 5.4 J/cm\(^2\) for 30 min results in collagen cross-linking thereby stabilizing the cornea in
certain ocular diseases, e.g., keratoconus and ectasia. Based on clinical experience with this methodology, no long-term adverse effects have been observed.”

II. Summary of Clinical Investigation(s)

Three clinical trials were conducted. The sponsor has proposed pooling results.

Study Design/Overview:
The clinical development program of riboflavin ophthalmic solution/UVA irradiation in the treatment of keratoconus and corneal ectasia following refractive surgery included 3 completed Phase 3 clinical trials (UVX-001, UVX-002, and UVX-003). Each study was a prospective, randomized, parallel-group, open-label, sham-controlled, 12-month trial to determine the safety and effectiveness of a single application of riboflavin ophthalmic solution/UVA irradiation for performing CXL in the eyes of subjects with keratoconus or corneal ectasia. All 3 studies were generally identical in design and conduct. However, UVX-001 had a mixed population of subjects with either keratoconus or corneal ectasia, UVX-002 enrolled only keratoconus subjects, and UVX-003 enrolled only corneal ectasia subjects. Further, UVX-001 was a single-center study, whereas UVX-002 and UVX-003 each involved 9 sites. All sites in the 3 studies were located in the US.

Subjects whose eye(s) had not developed any contraindications for performing the CXL treatment at Month 3 or later were given the option of having CXL performed on their untreated fellow eye (from both treatment groups) and untreated sham eyes (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.

Reviewer Comment: Crossover at 3 months means that availability of control data will potentially be limited to 3 months.

In the clinical trials described, the drug product was a sterile, phosphate-buffered saline solution for topical ophthalmic use containing 0.1% riboflavin (Vitamin B2) with and without 20% dextran. The UVA irradiation system was a portable electronic medical device. The device’s light emitting diode (LED) is used to deliver a metered dose of UVA light to a targeted treatment area for illuminating the cornea during CXL.

Reviewer Comments: Per the dosing regimen used in clinical studies, it appears patients received up to 38 drops.

Clinical studies using the drug/device system were conducted in the U.S. under IND 77,882, which was originally submitted by Peschke Medittrade GmbH (Huttenberg, Switzerland) on November 7th, 2007. Sponsorship of IND 77,882 was transferred to Avedro on May 7th 2010.
**Investigational Device:**
UVA irradiation at a wavelength of 365 nm at an intensity of 3 mW/cm² (±0.3 mW/cm²) for 30 minutes resulting in a total dose of 5.4 J/cm² was utilized. An analysis and safety justification of the frequency, duration, and intensity of this protocol was detailed by Spoerl et al (2007).

**Control:**
“Based on discussions between the previous Sponsor and the FDA, an unmasked sham control was used whereby subjects went through the same procedure but without UVA irradiation or epithelial debridement. For both treatment groups, the total dose of riboflavin solution with dextran over the 30-minute pretreatment and 30-minute irradiation periods was calculated to be approximately 32 drops, or 1.6 mL (1 drop = 50 μL, 1.6 mL = 1.6 mg riboflavin).”

**Randomization and Sample Size:**
In each study, eligible subjects were randomized in a 1:1 ratio into 1 of 2 treatment groups: the CXL group and the control (sham) group. Subjects with bilateral keratoconus or corneal ectasia had only 1 eye designated for study treatment (i.e., the study eye). The planned sample size was 160 subjects (80 eyes per treatment group) for UVX-002 and UVX-003. For UVX-001, the planned sample size was 320 subjects (160 per indication, with 80 eyes per treatment group); enrollment into this single-site study was terminated early because the investigator left the study site.

**Enrollment criteria:**
The following are excerpts from the enrollment criteria:

General:
subjects had to be $\geq 14$ years of age and have a diagnosis of corneal ectasia after refractive corneal surgery (UVX-001 and UVX-003) or progressive keratoconus (UVX-001 and UVX-002), with keratoconus defined as $\geq 1$ of the following changes over a maximum 24-month period before randomization:

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

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

Subjects were excluded if they had Intacs in the eye to be treated (keratoconus subjects); history of chemical injury in the eye to be treated; or history of corneal disease in the eye to be treated (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc).
Criteria for UVX-003:

9.3.1. Inclusion Criteria
To be included in the study, subjects had to be 14 years of age or older; provide written informed consent; and be willing and able to comply with the schedule of follow-up visits. Subjects who had 1 or both eyes meet all of the following criteria were considered eligible for this study:

1. Had a diagnosis of corneal ectasia after refractive corneal surgery (e.g., laser-assisted in-situ keratomileusis [LASIK], photorefractive keratectomy [PRK], or epi-LASIK)
2. Had central or inferior steepening on the Pentacam map.
3. Had axial topography consistent with corneal ectasia
4. Had a BSCVA worse than 20/20 (<55 letters on Early Treatment of Diabetic Retinopathy Study [ETDRS] chart)
5. Contact Lens Wearers Only:

Removal of contact lenses for the required period of time prior to the screening refraction:

<table>
<thead>
<tr>
<th>Contact Lens Type</th>
<th>Minimum Discontinuation Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft</td>
<td>3 Days</td>
</tr>
<tr>
<td>Soft Extended Wear</td>
<td>1 Week</td>
</tr>
<tr>
<td>Soft Toric</td>
<td>2 Weeks</td>
</tr>
<tr>
<td>Rigid gas permeable</td>
<td>2 Weeks</td>
</tr>
</tbody>
</table>

9.3.2. Exclusion Criteria
Subjects who met any of the following criteria were excluded from this study:

1. Corneal pachymetry at the screening exam that was < 400 microns at the thinnest point measured by Pentacam in the eye(s) to be treated when the riboflavin with dextran solution alone was to be used or < 300 microns when the riboflavin without dextran was to be used.

2. Previous ocular condition (other than refractive error) in the eye(s) to be treated that could have predisposed the eye for future complications, for example:
   a. History of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.)
   b. Clinically significant corneal scarring in the CXL treatment zone that was not related to corneal ectasia or prior refractive surgery or, in the investigator’s opinion, would interfere with the cross-linking procedure.

3. A history of chemical injury or delayed epithelial healing in the eye(s) to be treated.

4. Pregnancy (including plan to become pregnant) or lactation during the course of the study

5. Known sensitivity to study medications

6. Subjects with nystagmus or any other condition that would have prevented a steady gaze during the CXL treatment or other diagnostic tests.

7. Subjects with a current condition that, in the investigator’s opinion, would have interfered with or prolonged epithelial healing.

8. Took vitamin C (ascorbic acid) supplements within 1 week of the cross-linking or sham control procedure was completed.
Reviewer Comments:

1. Criteria listed above are abridged.
2. With regard to the proposed IFU for keratoconus: The orphan designation is for keratoconus. The studies enrolled subjects with progressive keratoconus. The risk/benefit considerations could be different between these 2 populations since some keratoconus patients remain stable for years and some progress. This is identified as a major issue at the end of this review.
3. Corneal scarring in the CXL treatment zone was a potential exclusion criterion.
4. In the postrefractive ectasia studies, subjects s/p either LASIK or PRK were enrolled. s/p LASIK was the predominant population. It is unclear if any subjects were enrolled s/p epi-LASIK. This should be made clear in the device labeling since an indication for “post-refractive ectasia” is a general term. Users should be made aware what conditions were actually studied.

Study Visits/Clinical Assessments:
Subjects were evaluated at 8 study visits: screening/baseline, Day 0 (randomization/treatment day), and 1 day, 1 week, and 1, 3, 6, and 12 months after treatment. (from UVX-001 protocol)

Safety assessments included the following:
- loss of visual acuity defined as loss of 2 or more lines in best spectacle-corrected visual acuity ([BSCVA] +0.2 logMAR change) or BSCVA worse than 20/40 (>0.3 logMar);
- quality of vision using the Refractive Status Vision Profile (RSVP) questionnaire; individual scores, subscores and composite score (observed values and change from baseline in the subscores and composite scores); a difference of ≥6 points was considered to be clinically significant;
- adverse events;
- subject symptoms;
- changes in epithelial thickness;
- slit lamp examination of the cornea and lens; and
- changes in Pentacam images.
From UVX-001 Protocol:

### Table 4: Schedule of Visits and Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>Treatment Visit</th>
<th>1 Day</th>
<th>1 Week</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ocular History</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication History</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSCVA&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>UCVA&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Manifest Refraction</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Confocal microscopy</td>
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<td>X</td>
<td></td>
<td></td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Intracocular Pressure Measurement&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Slit Lamp Exam&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Endothelial cell count&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Dilated Fundus Examination</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pentacam Pachymetry, Keratometry</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Corneal Topography</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Manual keratometry</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>OPD scan</td>
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<td>X</td>
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<tr>
<td>RSVP Questionnaire</td>
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<td>Subjective Complaint Questionnaire</td>
<td>X</td>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Sign Consent</td>
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<td></td>
<td>X</td>
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<tr>
<td>Complications</td>
<td></td>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup> Repeat measurements from the screening exam prior to study treatment were allowed if needed to provide accurate baseline measurements before CXL or sham treatment.

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

<sup>c</sup> Distance BSCVA was performed using an ETDRS eye chart; the total number of letters that were seen was recorded.

<sup>d</sup> UCVA was performed using an ETDRS eye chart; the total number of letters that were seen was recorded.

<sup>e</sup> Intracocular pressure measurements were taken using Goldmann applanation tonometry at the slit lamp. Tonopen could have been used only if application tonometry was medically contraindicated.

<sup>f</sup> The slit lamp exam included a complete survey of the anterior segment. The cornea was examined in detail with specific recordings and gradings (0 to 4—clear) of the following information: overall corneal clarity and any abnormalities such as corneal infiltrates.

<sup>g</sup> Intracocular pressure measurements were taken using Goldmann applanation tonometry at the slit lamp. Tonopen could have been used only if application tonometry was medically contraindicated.

### Study Endpoints:

#### Primary Effectiveness Endpoint:

For each study, the primary efficacy endpoint was corneal curvature, as measured by $K_{\text{max}}$. $K_{\text{max}}$ was evaluated at baseline and at Months 1, 3, 6, and 12. Study success was defined as a difference of $\geq 1$ D in the mean change in $K_{\text{max}}$ from baseline to Month 12 between the CXL group and the control group. Based on discussions with the FDA, it was agreed that this endpoint was clinically meaningful and an appropriate primary endpoint for demonstration of efficacy.
Originally, the primary efficacy endpoint was planned as the difference between the CXL group and the control group in $K_{\text{max}}$ from baseline to Month 3. At the time the studies were initially planned, a review of the existing literature suggested that the primary efficacy endpoint could be analyzed at 3 months post-procedure. However, subsequent additional literature suggested that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize (Wittig-Silva et al. 2008; Wolleusak and Iomdina, 2009; Caporossi et al. 2010). This is consistent with the FDA’s comments to the previous Sponsor, whereby the FDA strongly recommended that the Sponsor evaluate later time points. Based on the findings of this additional literature, and consistent with FDA recommendations, the Applicant extended the time point of the primary efficacy endpoint analysis to 12 months. The definition of clinically meaningful benefit, as previously agreed with the FDA, did not change and continued to be a $\geq 1$ D difference in the mean change in $K_{\text{max}}$ between the CXL group and the control group. This extension of the primary efficacy endpoint analysis to 12 months occurred after all subjects completed the study but prior to any formal efficacy analyses and, therefore, did not have any impact on conduct of the study.

**Other Effectiveness Endpoints:**

In addition to the primary endpoint, mean change from baseline $K_{\text{max}}$ was evaluated both for subjects who only received riboflavin with dextran and subjects who did not achieve a corneal thickness $\geq 400$ microns after treatment with riboflavin with dextran and subsequently received riboflavin without dextran.

Other efficacy parameters included mean changes from baseline $K_{\text{max}}$ for all CXL-treated eyes (eyes randomized to CXL treatment, eyes randomized to sham and subsequently treated with CXL, and fellow eyes subsequently treated with CXL) and non-study CXL-treated eyes. The categorical distribution of $K_{\text{max}}$ values was evaluated in randomized CXL eyes, including the proportion of subjects who experienced a $\geq 1$ D change from baseline $K_{\text{max}}$. Mean changes from baseline in BSCVA and UCVA and categorical changes from baseline in BSCVA were evaluated by treatment group.

**Results:**

Safety data were obtained for 420 eyes; 243 eyes with keratoconus and 177 eyes with corneal ectasia. These observations were obtained from 336 subjects (177 keratoconus; 159 corneal ectasia) at Month 6 and 300 subjects (164 keratoconus; 136 corneal ectasia) at Month 12.

A total of 384 subjects from the 3 completed studies received riboflavin ophthalmic solution/UVA irradiation or sham (control) treatment in the randomized study eye: 205 subjects with keratoconus (102, CXL; 103, control), and 179 subjects with corneal ectasia following refractive surgery (91, CXL; 88, control).

Subjects whose eye(s) had not developed any contraindications for performing the CXL treatment at Month 3 or later were given the option of having CXL performed on their untreated fellow eye (from both treatment groups) and untreated sham eyes (from control group). As a result, a total of 512 eyes (293, keratoconus; 219, corneal ectasia) received any CXL treatment: 193 randomized study eyes (102, keratoconus; 91, corneal ectasia) and 319 non-study eyes (191, keratoconus; 128, corneal ectasia).
Reviewer Comment: Based on a request for additional information sent by another reviewer, the sponsor stated that “neither UVX-001, UVX-002 nor UVX-003 protocols required data be collected for untreated fellow eyes. There is limited data available for untreated fellow eyes across all three studies as Investigators were not required to collect this information….At the three month visit or later, non-randomized fellow eyes could have the CXL procedure performed and data was then collected on these treated eyes. In the UVX-001 study, follow-up data was collected on 2 untreated fellow eyes at 1 site. In the UVX-002 study, untreated fellow eye data was collected from 10 subjects at 5 sites. In the UVX-003 study, untreated fellow eye data was collected from 4 subjects at 2 sites.”

Table 1: Description of Studies Included in the Summary of Clinical Safety

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>No. Centers Initiated/Enrolled</th>
<th>Study dates: Start/End</th>
<th>Design/Control</th>
<th>Indication Regimen</th>
<th>Randomized</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVX-001</td>
<td>1/1</td>
<td>2008-01-05 / 2010-07-27</td>
<td>prospective, randomized, parallel-group, open-label, sham-controlled study</td>
<td>Keratoconus</td>
<td>160 / 58</td>
<td>29 / 20, 16 - 60 years, 38 white, 39 M / 19 F</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CXL</td>
<td>80 / 29</td>
<td>29 / 12, 16 - 60 years, 9 white, 3 Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sham</td>
<td>80 / 29</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Keratoconus</td>
<td>Corneal ectasia</td>
<td>160 / 49</td>
<td>24 / 20, 24 - 63 years, 39 white</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CXL</td>
<td>80 / 24</td>
<td>25 / 11, 5 black / 5 other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sham</td>
<td>80 / 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CXL</td>
<td>80 / 73</td>
<td>74 / 62, 14 black / 3 Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sham</td>
<td>80 / 74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CXL</td>
<td>80 / 67</td>
<td>63 / 48, 12 black / 7 Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sham</td>
<td>80 / 63</td>
<td></td>
</tr>
</tbody>
</table>

a Number of eyes  
b Safety population

Reference ID: 3720918
Reviewer Comments: Poolability across sites and studies had been identified as a potential concern by CDER reviewers, therefore unpooled results were requested for many analyses.

Accountability:
Overall, 205 keratoconus subjects (102, CXL; 103, control) and 179 corneal ectasia subjects (91, CXL; 88, control) were enrolled into the studies. For both indications, most (75-78%) subjects completed the studies. None of the subjects discontinued due to an adverse event (AE).
In the pooled keratoconus studies, 100 (98.0%) of the 102 randomized to the CXL group were on study at Month 6, and 90 (88.2%) were on study at Month 12. At each study visit (Months 1 through 12), ≥95.0% of subjects who were on study had a Kmax value at the respective visit. For the 103 subjects randomized to the sham group, all were on study at Month 1; 101 (98.1%) were on study at Month 3; 96 (93.2%) were on study at Month 6; and 76 (73.8%) were on study at Month 12. For the first 3 months, all subjects in the control group stayed with the randomized treatment. Thereafter, 57 (59.4%) of the 96 subjects on study at Month 6 and 75 (98.7%) of the 76 subjects on study at Month 12 crossed over to CXL treatment. At each study visit, ≥95.0% of subjects who were on study had a Kmax value at the respective visit.

In the pooled corneal ectasia studies, 88 (96.7%) of the 91 subjects randomized to the CXL group were on study at Month 6, and 76 (83.5%) were on study at Month 12. At each study visit (Months 1 through 12), ≥95.5% of subjects who were on study had a Kmax value at the respective visit. For the 88 subjects randomized to the sham group, all were on study at Month 1; 87 (98.9%) were on study at Month 3; 80 (90.9%) were on study at Month 6; and 60 (68.2%) were on study at Month 12. All subjects in the control group stayed with the randomized treatment through Month 3. Thereafter, 48 (60.0%) of the 80 subjects on study at Month 6 and 58 (96.7%) of the 60 subjects on study at Month 12 crossed over to CXL treatment. At each study visit, ≥97.5% of subjects who were on study had a Kmax value at the respective visit.

Reviewer Comment: Due to the potential for crossover, accountability is particularly low for the control group beyond Month 3. The sponsor states that “As a result of the potential to cross-over, none of the subjects in the control group of UVX-001 and only 2 subjects each in the control group of UVX-002 and UVX-003 had an observation for the randomized study eye at Month 12.” Of note, there appears to have been a >10% loss to followup rate in the experimental arm as well.
Treatment Administered:

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

<table>
<thead>
<tr>
<th>Randomization:</th>
<th>Primary (Study Eye)</th>
<th>Secondary Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL n (%)</td>
<td>Sham n (%)</td>
</tr>
<tr>
<td>Subjects Randomized to CXL (N=102)</td>
<td>102 (100.0)</td>
<td>---</td>
</tr>
<tr>
<td>Subjects Randomized to Sham (N=103)</td>
<td>---</td>
<td>103 (100.0)</td>
</tr>
<tr>
<td>Total CXL (N=293)</td>
<td>102 (34.8)</td>
<td>---</td>
</tr>
</tbody>
</table>

| Subjects Randomized to CXL (N=91) | 91 (100.0) | --- | 26 (28.6) | 65 (71.4) | --- | --- |
| Subjects Randomized to Sham (N=88) | --- | 88 (100.0) | 22 (25.0) | 8 (9.1) | 80 (90.9) | --- |
| Total CXL (N=219) | 91 (41.6) | --- | 48 (21.9) | --- | 80 (36.5) | 219 (100.0) |

Demographics:

_Reviewer Comments:_ See study summary tables above for summary of demographics.

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

Regarding “geriatric use”, the sponsor states: “No subjects enrolled in the clinical studies were 65 years of age or older. There were 2 patients of 62 years of age.”

Regarding pediatric use, in the Phase III studies, there were 16 patients between 14-18 years of age. The sponsor states: “safety and effectiveness of the KXL System has not been established in patients less than 14 years of age.”

_Reviewer Comment:_ Potential for pediatric use is a concern.
“The most frequent ocular risk factors at baseline were eye rubbing and ocular history. The type of contact lens worn most frequently by subjects in each treatment group was rigid gas permeable. The majority (69.2%) of keratoconus subjects were classified as having mild disease (disease severity was not reported for corneal ectasia). Mean BSCVA at baseline was comparable between treatment groups in the pooled keratoconus (33.2 letters, CXL; 32.8 letters, control) and corneal ectasia (37.0 letters, CXL; 38.1 letters, control) studies. Subject medical history was consistent with expectations for subjects with keratoconus and corneal ectasia.”

**Protocol Deviations:** (Complete deviation listings are included in each study report – many deviations occurred in each study. Below are the deviations which the sponsor draws attention to, presumably “major”):

For UVX-001:
A total of 30 subjects (15, keratoconus; 15, corneal ectasia) failed to meet the criterion for corneal thickness (≥400 microns) and received artificial tears in the primary CXL eye in addition to the riboflavin with dextran solution on Day 0.

For UVX-002:
None of the subjects failed to meet the criterion for corneal thickness (≥400 microns) and received artificial tears in the primary CXL eye in addition to the riboflavin with dextran solution on Day 0.

Two subjects, 1 per treatment group, inadvertently received the incorrect randomized study treatment on Day 0 (Subjects 01201 and 01202).

For UVX-003:
One subject failed to meet the criterion for corneal thickness (≥400 microns) and received artificial tears in the primary CXL eye in addition to the riboflavin with dextran solution on Day 0.

**Analysis Populations:**
In UVX-002, 2 subjects, 1 per treatment group, inadvertently received the incorrect randomized study treatment on Day 0. Therefore, it was necessary to define both an intent-to-treat (ITT) and Safety population for this study. The ITT population consisted of all treated subjects, analyzed according to randomized treatment. The Safety population consisted of all treated subjects, analyzed according to the treatment actually received. Most of the efficacy analyses were conducted using the ITT population. Since the Kmax analyses of all CXL-treated eyes and non-study CXL-treated eyes involved crossover from sham to CXL treatment, these analyses were conducted using the Safety (as treated) population. Exposure results were also summarized using the Safety population.

For UVX-001 and UVX-003, all analyses were performed on the ITT/Safety population.

**Statistical Methodology:**
The statistical methodology was the same for each study. For continuous variables, statistical summaries included the number of subjects, mean, standard deviation, median,
minimum, and maximum. For categorical variables, statistical summaries included counts and percentages.

No formal interim analyses were conducted. However, an informal, unplanned analysis of Month 3 data was conducted for each study by the original Sponsor. Although this unplanned analysis did not have any impact on the conduct of the study or analysis, a portion of Type I error was allocated, post hoc, for that review (0.001 of the overall alpha-level of 0.05).

Differences between treatment groups for mean change from baseline $K_{\text{max}}$ were analyzed using a 2-sample t-test. Although p-values were reported for each visit, the only one used for statistical inference in the final analysis was at Month 12 (alpha=0.049). Similar analyses were conducted for BSCVA and UCVA.

Per the sponsor, regarding last observation carried forward (LOCF) analyses:
“Efficacy analyses were primarily based on imputation of missing data using the last observation carried forward (LOCF) approach. Because the study design allowed subjects in the control group to cross over to receive the CXL treatment after Month 3, LOCF was necessary to allow comparisons between the CXL and control groups at later time points. Further, as discussed with the FDA, the LOCF approach was appropriate because keratoconus and corneal ectasia are either stable or progressive in nature (Krachmer et al, 1984; Tuft et al, 1994; Pallikaris et al, 2001; Binder et al, 2005; Li et al, 2007; Wagner et al, 2007; Weed et al, 2008; Romero-Jiménez et al, 2010), and therefore $K_{\text{max}}$ is expected to either increase (worsen) or remain the same over time if the disease is not treated. With the LOCF approach, the control group carries forward a value which is equal to or less than the expected $K_{\text{max}}$ value at the later time point; that is, LOCF would be expected to underestimate the progression of disease in the control group. As a result, the LOCF approach provides a very conservative measure of success of the crosslinking procedure, as this approach minimizes the differences between treatment and control groups, making it more difficult to demonstrate a $\geq 1$ D difference in mean change from baseline $K_{\text{max}}$.

In addition to analyses based on LOCF, sensitivity analyses were conducted using observed case data. Results were summarized using observed values at each visit through Month 12; however, the number of observations in the randomized study eye dropped markedly after Month 3 in the control group when the study eye could receive CXL treatment. As a result, few (if any) subjects in the control group had an observation for the randomized study eye at Month 12. Therefore, for analyses comparing the CXL and control groups, focus was placed on Month 6 results, the last time point with an evaluable number of subjects in the control group."

Reviewer Comment: The LOCF method is of questionable value. The assumptions regarding the predictability and rate of disease progression (and resulting effect on $K_{\text{max}}$) are unacceptable. Due to the potential for crossover and the number of subjects who elected to do so, it appears that the data must be evaluated at 3 months post-treatment, when actual data is available (with reasonable accountability) for the control arm. This concern is included with major issues at the conclusion of this review.
Treatment administered:

All CXL-treated eyes received the same UVA irradiation treatment (365 nm at an irradiance of 3 mW/cm² for 30 minutes). Sham-treated eyes underwent the same UV irradiation procedure except the UVA light source was not illuminated during the procedure. For both indications, the mean number of drops of riboflavin with dextran administered prior to the UVA procedure (or mock procedure in sham eyes) and during the UVA procedure (or mock procedure in sham eyes) was approximately 16 and 15 drops, respectively. CXL-treated eyes that did not meet the requirement for corneal thickness ≥ 400 microns after UVA pre-treatment with riboflavin plus dextran received a second solution of riboflavin without dextran.

No subjects received CXL treatment more than once in the same eye. Subjects who received CXL in untreated fellow eyes (from CXL group) and untreated sham eye and untreated fellow eye (from control group) received CXL at least 3 months after the initial randomized treatment.

Table 3 summarizes the number of eyes treated with any CXL in the pooled keratoconus and corneal ectasia studies (i.e., primary study eyes randomized to CXL, primary study eyes randomized to control which subsequently received CXL, and fellow eyes in either treatment group which received CXL).

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

<table>
<thead>
<tr>
<th>Randomization:</th>
<th>Primary (Study Eye)</th>
<th>Secondary Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL n (%)</td>
<td>Sham n (%)</td>
</tr>
<tr>
<td>SUBJECTS WITH KERATOCONUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects Randomized to CXL (N=102)</td>
<td>102 (100.0)</td>
<td>---</td>
</tr>
<tr>
<td>Subjects Randomized to Sham (N=103)</td>
<td>---</td>
<td>103 (100.0)</td>
</tr>
<tr>
<td>Total CXL (N=293)</td>
<td>102 (34.8)</td>
<td>---</td>
</tr>
<tr>
<td>SUBJECTS WITH CORNEAL ECTASIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects Randomized to CXL (N=91)</td>
<td>91 (100.0)</td>
<td>---</td>
</tr>
<tr>
<td>Subjects Randomized to Sham (N=88)</td>
<td>---</td>
<td>88 (100.0)</td>
</tr>
<tr>
<td>Total CXL (N=219)</td>
<td>91 (41.6)</td>
<td>---</td>
</tr>
</tbody>
</table>

Safety Results:

Adverse Events:
The most frequently reported TEAEs, considered of mild intensity, were the expected sequelae following debridement of the cornea reported as corneal haze, corneal epithelium defect, corneal striae, punctate keratitis and eye pain. Headache, nasopharyngitis and dizziness were the only non-ocular treatment emergent adverse events (TEAEs) reported for ≥2% of subjects in the CXL group.
In keratoconus subjects, the most common ocular treatment-emergent adverse events (TEAEs) observed in the CXL group from baseline to Month 3 were corneal opacity (haze) (56.9%), punctate keratitis (24.5%), corneal striae (23.5%), corneal epithelium defect (22.5%), eye pain (16.7%), and vision blurred (15.7%) (Table 4). In corneal ectasia subjects, the most common ocular TEAEs observed in the CXL group were corneal opacity (haze) (68.1%), corneal epithelium defect (26.4%), eye pain (26.4%), punctate keratitis (19.8%), photophobia (18.7%), and vision blurred (16.5%). These events are expected sequelae following debridement of the cornea and occurred at a higher incidence than observed in control subjects, who did not undergo the debridement procedure or exposure to UVA light.

For both indications, the incidence of common TEAEs observed for any CXL-treated eye through Month 12 was generally consistent with that observed in the CXL group from baseline to Month 3 (Table 4). The incidence of visual acuity reduced tended to be higher in any CXL-treated eye, both for keratoconus (9.8%, CXL group through Month 3; 16.4%, any CXL-treated eye through Month 12) and corneal ectasia (11.0%, CXL group; 16.9%, any CXL-treated eye). More information on reduced visual acuity is presented in Section 5.6.

In all CXL-treated eyes, the incidence of corneal scar was 7.5% and 4.1% for keratoconus and corneal ectasia, respectively. The incidence of corneal oedema was low for both indications (1.0% keratoconus; 2.7%, corneal ectasia), as was the incidence of ulcerative keratitis (lower level terms of corneal melt, corneal ulcer, central corneal ulcer) (0.7%, keratoconus; 1.8%, corneal ectasia), corneal infiltrate (0.3%, keratoconus; 1.4%, corneal ectasia), and corneal disorder (lower level terms of corneal disorder, Descemet's membrane folds, corneal epithelium disorder, corneal endothelial disorder) (2.4%, keratoconus; 3.2%, corneal ectasia). None of the subjects experienced corneal perforation, recurrent erosion syndrome, bacterial keratitis, or Acanthamoeba keratitis. Subjects were excluded from the studies if they had a history of herpes zoster keratitis; therefore, reactivation of herpetic keratitis was not expected, and no cases were reported.
Table 4: Most Common (≥10%) Ocular Adverse Events in Any CXL-Treated Eye in the Pooled Keratoconus and Corneal Ectasia Studies (Safety Population)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Pooled Keratoconus Studies</th>
<th>Pooled Corneal Ectasia Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL Group (N=102)</td>
<td>Control Group (N=103)</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>23 (22.5)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Corneal opacityc</td>
<td>58 (56.9)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>Corneal striae</td>
<td>24 (23.5)</td>
<td>12 (11.7)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>6 (5.9)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>17 (16.7)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>11 (10.8)</td>
<td>0</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>25 (24.5)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>16 (15.7)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>10 (9.8)</td>
<td>9 (8.7)</td>
</tr>
</tbody>
</table>

a Results are presented as the number (%) of subjects with an event from baseline to Month 3.
b Results are presented as the number (%) of CXL-treated eyes with an event from baseline to Month 12.
c Almost all cases of corneal opacity were reported as haze.

For both indications, most TEAEs were mild or moderate in intensity, with most being mild. Severe ocular TEAEs that occurred in any CXL-treated eye consisted of eye pain (2 subjects), ulcerative keratitis (1 subject), eye irritation (1 subject), photophobia (1 subject), corneal epithelium defect (1 subject), corneal infiltrates (1 subject), and visual acuity decreased (1 subject). Of these, the eye pain (both cases), ulcerative keratitis, corneal epithelium defect, and corneal infiltrates were considered by the investigator to be related to epithelial defect (i.e., the debridement procedure); none were attributed to riboflavin or UVA light.

TEAEs generally resolved by the last study visit. Of the 178 CXL-treated eyes in keratoconus subjects with corneal opacity (haze), resolution occurred in 147 (82.6%) eyes; likewise, the event resolved in 118/148 (79.7%) eyes of corneal ectasia subjects. All but 2 of the severe events listed above resolved (eye irritation and photophobia).

For each indication, no clinically relevant differences were observed between studies in the AE profile for CXL-treated subjects. Further, no differences were observed in the AE profile for subjects who received riboflavin with dextran and those who required additional use of riboflavin without dextran prior to the UVA procedure.

Serious Adverse Events/Deaths:

5.5. Deaths, Other Serious Adverse Events, and Other Significant Events

No subjects died or prematurely discontinued study due to an AE. The incidence of serious adverse events (SAEs) that occurred from baseline to Month 3 was low in each treatment group.
regardless of indication: keratoconus (0%, CXL; 1.0%, control) and corneal ectasia (1.1%, CXL; 1.1%, control). These events consisted of suicide attempt (control, keratoconus), head injury (control, corneal ectasia), and corneal epithelium defect (CXL, corneal ectasia). The latter event is further described below.

Two subjects, 1 per indication, had an ocular SAE in any CXL-treated eye during the 12-month study period. These events were severe ulcerative keratitis (verbatin: corneal ulcer, keratoconus) and moderate corneal epithelium defect (verbatin: epithelial ingrowth, corneal ectasia). The ulcerative keratitis developed 3 days after a subject in the control group received CXL treatment in the sham eye, and the event resolved approximately 5 months later. Treatment included a pressure patch, zymar, fortified vancomycin, Pred Forte, bacitracin, doxycycline, and Refresh. The corneal epithelium defect developed on Day 35 in a subject in the CXL group. The lasik flap was lifted to remove the epithelial growth, and the event resolved 1 week later. Neither of these SAEs was considered by the investigator to be related to riboflavin or UVA light, both were attributed to epithelial defect.

5.6. Loss of Visual Acuity

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

In keratoconus subjects, the greatest reduction in BSCVA observed in the primary study eyes at any time through Month 12 was −31 letters in the CXL group and −33 letters in the CXL group.

In corneal ectasia subjects, these values were −28 letters and −35 letters, respectively.

The proportion of subjects with visual acuity reduced reported as a TEAE at any time from baseline to Month 3 was comparable between treatment groups for keratoconus (9.8%, CXL; 8.7%, control) and was higher in the CXL group (11.0%) compared with the control group (1.1%) for corneal ectasia (Table 4). The incidence of visual acuity reduced reported for any CXL-treated eye through Month 12 was 16-17% for each indication. The relatively small difference in incidence between CXL-treated eyes from baseline to Month 3 versus Month 12 indicates that visual acuity reduced generally develops in the short-term and does not represent a late-onset complication.

For both indications, the majority of cases of reduced visual acuity resolved by the last study visit, all but 1 event was mild or moderate in intensity. A corneal ectasia subject had severe visual acuity reduced after receiving CXL in the sham study eye. The event developed with concurrent severe corneal infiltrates and moderate corneal epithelium defect. The reduced visual acuity resolved approximately 4.5 months after onset. In the opinion of the investigator, the visual acuity reduced, corneal infiltrates, and corneal epithelium defect were not related to UVA light or riboflavin. The 2 latter events were definitely related to epithelial defect, whereas the visual acuity reduced was not related.

For each indication, no clinically relevant differences were observed between studies for loss of visual acuity in CXL-treated subjects. Further, no differences were observed for loss of visual acuity in subjects who received riboflavin with dextran and those who required additional use of riboflavin without dextran prior to the UVA procedure.
5.7. Other Safety Assessments

For both indications, mean endothelial cell counts (cells/mm²) were comparable between treatment groups at baseline. Mean changes from baseline in endothelial cell density at Month 3 (the first planned time point) were not clinically relevant: keratoconus (–64 counts/mm², CXL; 23.6 counts/mm², control) and corneal ectasia (–44 counts/mm², CXL; –53 counts/mm², control). Mean changes in cell counts at Month 12 (the second planned time point) were 18.4 counts/mm² and –108 counts/mm² in the CXL group for keratoconus and corneal ectasia, respectively; observed case values were not evaluable in the control group at this time point. These results indicate the risk of endothelial damage was minimized in the UVX studies.

Pachymetry results showed transient reductions from baseline in mean corneal thickness at Months 1 and 3 in primary CXL-treated eyes, which lessened by Months 6 and 12. The incidence of elevated IOP reported as a TEAE was ≤1.0% in any CXL-treated eye for both indications. Other ophthalmic findings were not indicative of a safety concern for CXL treatment.

These findings are supported by several long-term studies reported in the literature. In the Siena Eye Cross Study, an open-label, nonrandomized phase 2 study in which 44 eyes with progressive keratoconus were followed for a minimum of 48 months after CXL treatment, no statistically significant reductions from baseline were observed in mean endothelial cell counts at Months 1, 2, 3, 6, 12, 24, 36, or 48. Further, no significant changes were observed in mean central corneal thickness or IOP throughout the study (Caporossi et al. 2010). In another prospective, nonrandomized study, mean endothelial cell count was evaluated in 28 eyes of 28 patients with progressive keratoconus up to 24 months after CXL treatment. At baseline, the mean cell count was 2651 counts/mm²; the count fell to 2485 counts/mm² and 2390 counts/mm² at Months 1 and 3, respectively, and then recovered to approximately 2500–2600 counts/mm² at Months 6, 12, and 24. No significant changes were observed in IOP (Vinciguerra et al. 2009). In 14 eyes of 14 patients with progressive keratoconus who were followed for 24 months after CXL treatment, no significant changes from baseline were observed in mean endothelial cell density at any evaluation time point (Months 1, 6, 12, and 24), and no significant changes were observed in corneal thickness (Months 6, 9, 12, and 24) or central foveal thickness (Months 3, 6, 9, 12, and 24) (Goldshleger et al. 2012).

Reviewer Comments: It is unclear that month 3 ECL counts are adequate in the control arm for comparison – longterm ECL counts to 1 year would be more compelling. The sponsor cited literature (included in this review under description of the primary efficacy endpoint) supporting the need for 1 year data.

Effectiveness Results:

For UVX-001: (summary results from study synopsis)

“CXL provided statistically significant and clinically meaningful improvements in Kmax in subjects with keratoconus and subjects with corneal ectasia following refractive surgery. For both populations, the difference between the CXL and control groups in mean change from baseline in Kmax progressively improved, in favor of CXL, from Month 3 through Month 12. The study met the definition of success for the primary efficacy endpoint, mean change from baseline Kmax (LOCF) ≥1 D between the CXL and control groups at Month 12. In keratoconus subjects, clinically meaningful improvements in Kmax (LOCF) were observed at Month 6 (–0.9 D vs. 0.5 D, difference of 1.4 D, \(p=0.0674\)) and Month 12 (–1.4 D vs. 0.5 D, difference of 1.9 D, \(p=0.0175\)) in favor of CXL. Similarly, clinically meaningful improvements in Kmax (LOCF) were observed at these time points in corneal ectasia subjects: Month 6 (–0.6 D vs. 1.0 D, difference of 1.6
D, p=0.0010) and Month 12 (–1.0 D vs. 1.0 D, difference of 2.0 D, p=0.0001). In both populations, the difference between treatment groups was statistically significant at Month 12, the prospectively-defined time point for statistical inference. To support the LOCF results, mean changes from baseline Kmax were also evaluated using observed case data through Month 6 (Note: Between-treatment comparisons using observed case data were not considered at Month 12, as no subjects in the control group had an observation for the randomized study eye at this time point). In both populations, progressive improvement in mean Kmax was observed in the CXL group. The difference in mean changes from baseline Kmax between the CXL and control groups exceeded 1.0 D at Month 6, both in keratoconus subjects (–1.0 D vs. 0.2 D, difference of 1.2 D, p=0.1517) and subjects with corneal ectasia (–0.8 D vs. 1.6 D, difference of 2.4 D, p=0.0002). Other efficacy results were clinically relevant and favored CXL treatment. The proportion of keratoconus subjects in the CXL group with a ≥1 D decrease (i.e., improvement) from baseline Kmax (LOCF) increased over time, ranging from 3.4% at Month 1 to 51.7% at Months 6 and 12. Likewise, the proportion of corneal ectasia subjects in the CXL group with a ≥1 D decrease from baseline Kmax ranged from 8.3% at Month 1 to 41.7% at Month 12. The proportion of CXL subjects who showed no change or had any worsening in Kmax (LOCF) progressively decreased over time, ranging from 79.3% at Month 1 to 24.1% at Month 12 in keratoconus subjects and from 87.5% (Month 1) to 29.2% (Month 12) in corneal ectasia subjects. Similar results were noted with observed case data. Mean changes from baseline Kmax (LOCF and observed values) in non-study CXL-treated eyes and all CXL-treated eyes were generally consistent with the Kmax findings of the primary efficacy analysis (randomized CXL eyes). Mean improvements in Kmax were observed at Month 12 in each analysis. 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 keratoconus subjects with a ≥15-letter improvement in BSCVA was generally comparable between treatment groups at Months 6 (LOCF and observed case) 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%).”
For UVX-002: (summary results from study synopsis)

**Efficacy Results:** In the ITT population, CXL provided statistically significant and clinically meaningful improvements in \( K_{\text{max}} \) in subjects with keratoconus. In the CXL group, mean \( K_{\text{max}} \) (LOCF) progressively decreased (i.e., improved) from baseline to Months 3, 6, and 12. In comparison, in the control group, mean increases (i.e., worsening) from baseline \( K_{\text{max}} \) were observed at these time points. The study met the definition of success for the primary efficacy endpoint, mean change from baseline \( K_{\text{max}} \) (LOCF) \( \geq 1 \) D between the CXL and control groups at Month 12. Clinically meaningful and progressive improvements in \( K_{\text{max}} \) (LOCF) were observed from Month 3 through Month 12 in favor of CXL. Month 3 (\(-0.6 \) D vs. \( 0.7 \) D, difference of \( 1.3 \) D, \( p=0.1142 \)), Month 6 (\(-1.1 \) D vs. \( 1.2 \) D, difference of \( 2.3 \) D, \( p=0.0129 \)), and Month 12 (\(-1.7 \) D vs. \( 1.2 \) D, difference of \( 2.9 \) D, \( p=0.0010 \)). The difference between treatment groups was statistically significant at Month 12, the prospectively-defined time point for statistical inference. LOCF results based on pooled data (i.e., all data from UVX-002 and keratoconus data from UVX 001) confirmed the findings of the individual UVX-002 study.

To support the LOCF results, mean changes from baseline \( K_{\text{max}} \) were also evaluated using observed case data through Month 6 (Note: Between-treatment comparisons using observed case data were not considered at Month 12, as only 2 subjects in the control group had an observation for the randomized study eye at this time point). In UVX-002, mean \( K_{\text{max}} \) (observed values) in the CXL group progressively decreased from baseline to Months 3 and 6, whereas in the control group, mean increases from baseline \( K_{\text{max}} \) were observed at these time points. The difference in mean change from baseline \( K_{\text{max}} \) between the CXL and control groups exceeded 1.0 D, in favor of CXL, at Month 3 (difference of \( 1.5 \) D, \( p=0.1051 \)) and Month 6 (difference of \( 3.1 \) D, \( p=0.0151 \)). Results from the pooled analysis (i.e., all data from UVX-002 and keratoconus data from UVX 001) confirmed these findings.

Other efficacy results were clinically relevant and favored CXL treatment. In the ITT population, the proportion of subjects in the CXL group with a \( \geq 1 \) D decrease (i.e., improvement) from baseline \( K_{\text{max}} \) (LOCF) progressively increased throughout the study, ranging from 12.3% at Month 1 to 50.7% at Month 12. The proportion of CXL subjects who showed no change or had any worsening in \( K_{\text{max}} \) (LOCF) progressively decreased over time, especially during the first 6 months of the study. At Month 12, the proportion of CXL subjects who showed no change or had any worsening in \( K_{\text{max}} \) was 30.1%. Similar results were noted with observed case data.

Mean changes from baseline in \( K_{\text{max}} \) observed with all CXL-treated eyes and non-study CXL-treated eyes were consistent with the results of the primary (randomized study eye) analysis.

In addition to improved corneal curvature, CXL was associated with clinically meaningful improvements in BSCVA. With both the LOCF and observed case analyses, mean improvements from baseline in BSCVA were greater in the CXL group compared with the control group at Month 6 (LOCF, \( p=0.0750 \); observed values, \( p=0.0064 \)). This effect was maintained through Month 12 in the LOCF analysis (\( p=0.0280 \)). The proportion of subjects with a \( \geq 15 \) letter improvement in BSCVA was several-fold higher in the CXL group than in the control group, in both the LOCF (Month 6, 14.5% vs. 2.8%; Month 12, 17.4% vs. 2.8%) and observed case (Month 6, 15.6% vs. 5.6%) analyses.
For UVX-003: (summary results from study synopsis)

**Efficacy Results:** CXL provided statistically significant and clinically meaningful improvements in \( K_{\text{max}} \) in subjects with corneal ectasia following refractive surgery. In the CXL group, mean \( K_{\text{max}} \) (LOCF) decreased (i.e., improved) from baseline to Months 3, 6, and 12. In comparison, in the control group, mean increases (i.e., worsening) from baseline \( K_{\text{max}} \) were observed at these time points. The study met the definition of success for the primary efficacy endpoint, mean change from baseline \( K_{\text{max}} \) (LOCF) \( \geq 1 \) D between the CXL and control groups at Month 12. Clinically meaningful improvements in \( K_{\text{max}} \) (LOCF) were observed at Month 6 (\(-0.5 \) D vs. \( 0.5 \) D, difference of \( 1.0 \) D, \( p=0.0084 \)) and Month 12 (\(-0.5 \) D vs. \( 0.5 \) D, difference of \( 1.0 \) D, \( p=0.0080 \)) in favor of CXL. The difference between treatment groups was statistically significant at Month 12, the prospectively-defined time point for statistical inference. LOCF results based on pooled data (i.e., all data from UVX-003 and corneal ectasia data from UVX-001) confirmed the findings of the individual UVX-003 study.

To support the LOCF results, mean changes from baseline \( K_{\text{max}} \) were also evaluated using observed case data through Month 6 (Note: Between-treatment comparisons using observed case data were not considered at Month 12, as only 2 subjects in the control group had an observation for the randomized study eye at this time point). In UVX-003, mean \( K_{\text{max}} \) (observed values) in the CXL group progressively decreased from baseline to Months 3 and 6, whereas in the control group, mean increases from baseline \( K_{\text{max}} \) were observed at these time points. The difference in mean change from baseline \( K_{\text{max}} \) between the CXL and control groups did not reach \( 1 \) D, in favor of CXL, at Month 3 (\(-0.2 \) D vs. \( 0.7 \) D, \( p=0.0397 \)) or Month 6 (\(-0.5 \) D vs. \( 0.1 \) D, \( p=0.2901 \)). However, with the pooled data (i.e., all data from UVX-003 and corneal ectasia data from UVX-001), the difference between treatment groups exceeded \( 1 \) D at Month 6 (\(-0.6 \) D vs. \( 0.7 \) D, difference of \( 1.3 \) D, \( p=0.0021 \)).

Other efficacy results were clinically relevant and favored CXL treatment. The proportion of subjects in the CXL group with a \( \geq 1 \) D decrease (i.e., improvement) from baseline \( K_{\text{max}} \) (LOCF) increased over time, ranging from 7.9\% at Month 1 to 28.6\% at Month 12. The proportion of CXL subjects who showed no change or had any worsening in \( K_{\text{max}} \) (LOCF) progressively decreased over time, ranging from 73.0\% at Month 1 to 41.3\% at Month 12. Similar results were noted with observed case data.

Mean changes from baseline in \( K_{\text{max}} \) observed with all CXL-treated eyes and non-study CXL-treated eyes were consistent with the results of the primary (randomized study eye) analysis.

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 \( \geq 15 \)-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 with a \( \geq 15 \) letter improvement in bSCVA was approximately 2-fold higher in the CXL group (11.9\% vs. 5.6\%).

To summarize:

For Keratoconus: Both studies (UVX-001 and UVX-002) met the definition of success for the primary efficacy endpoint, mean change from baseline \( K_{\text{max}} \) (LOCF) \( \geq 1 \) D between the CXL and control groups at Month 12. However, in UVX-001, while clinically meaningful improvements in \( K_{\text{max}} \) were first observed at Month 6 (\(-0.9 \) D vs. \( 0.5 \) D, difference of \( 1.4 \) D, \( p=0.0674 \)), the p value does not meet statistical significance until Month 12 (\(-0.9 \) D vs. \( 0.5 \) D, difference of \( 1.4 \) D, \( p=0.0674 \)). In UVX-002, clinically meaningful improvements in \( K_{\text{max}} \) were observed at Month 3 (\(-0.6 \) D vs. \( 0.7 \) D, difference of \( 1.3 \) D, \( p=0.1142 \)), Month 6 (\(-1.1 \) D vs. \( 1.2 \) D, difference of \( 2.3 \) D, \( p=0.0129 \)) and Month 12 (\(-1.7 \) D vs. \( 1.2 \) D, difference of \( 2.9 \) D, \( p=0.0010 \)). However we note the result was not statistically significant until Month 6. See table 11 below.

Reference ID: 3720918
For Postrefractive Corneal Ectasia: (UVX-001 and UVX-003)

Both studies met the definition of success for the primary efficacy endpoint, mean change from baseline Kmax (LOCF) $\geq 1$ D between the CXL and control groups at Month 12. In UVX-001, clinically meaningful improvements in Kmax were observed at Month 6 (–0.6 D vs. 1.0 D, difference of 1.6 D, $p=0.0010$) and Month 12 (–1.0 D vs. 1.0 D, difference of 2.0 D, $p=0.0001$) in favor of CXL. Similarly, clinically meaningful improvements in Kmax were observed at these time points in UVX-003: Month 6 (–0.5 D vs. 0.5 D, difference of 1.0 D, $p=0.0084$) and Month 12 (–0.5 D vs. 0.5 D, difference of 1.0 D, $p=0.0080$). P values reach statistical significance at months 3, 6 and 12 in both studies based on table 11 below.

<table>
<thead>
<tr>
<th>Visit</th>
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<th>UVX-001 CXL Group</th>
<th>UVX-001 Control Group</th>
<th>UVX-002 CXL Group</th>
<th>UVX-002 Control Group</th>
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<td>3.36</td>
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<td>1.2</td>
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<td>2.99</td>
<td>5.06</td>
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Reviewer Comments: Concerns regarding LOCF method have been mentioned above. The 3 month post-treatment data appears to be the most accurate way to evaluate study results due to the availability of control data prior to cross-over. The original efficacy endpoint was at 3 months post-treatment, but was extended after the study was concluded. Altering the timing of the endpoint to a later time would help the sponsor meet their primary efficacy endpoint across both indications studied, as noted above. However, the limitations of using data beyond 3 months include the potential for significant bias and the loss of significant control data.

Additional analyses have been requested by CDER reviewers and the value of these post-hoc analyses is unclear. It appears that, if considered, some of these analyses would allow the sponsor to meet their primary effectiveness endpoint for both populations (keratoconus is the population of concern based on the data presented above). However, there are many assumptions made. Based on the prespecified analyses (including the 3 month endpoint) it appears that the sponsor would not meet their primary effectiveness endpoint for both indications. One possible reason for this might have to do with a difference in the study populations in the two studies that enrolled subjects with “progressive keratoconus” subjects. While the treatment arm may have been fairly consistent with regard to the effect seen in each study, the control arm of one study may have shown more progression than seen in the second study. (Vague language is unavoidable when discussing these results because many of the new analyses project results to the 12 months timepoint based on 3 month data and it is impossible to ignore the significance of the assumption that progression would be inevitable, uniform and

| Table 11: Mean Changes from Baseline $K_{max}$ in the Randomized Study Eye (ITT Population, LOCF): UVX-001 (Corneal Ectasia Subjects), UVX-003, Pooled UVX-001 and UVX-003 |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|             | UVX-001         |                 | UVX-003         |                 | Pooled Studies  |
|             | CXL Group       | Control Group   | P-value$^a$     | CXL Group       | Control Group   | P-value$^a$     | CXL Group       | Control Group   | P-value$^a$     |
|            | (N=24)          | (N=25)          |                 | (N=97)$^b$      | (N=69)          |                 | (N=91)$^c$      | (N=88)          |                 |
| Baseline   |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| N          | 24              | 25              | 63              | 63              | 87              | 88              |
| Mean       | 50.3            | 55.0            | 55.1            | 54.7            | 55.4            | 54.8            |
| SD         | 6.26            | 5.45            | 7.09            | 6.77            | 6.86            | 6.40            |
| Min, Max   | 47.72           | 47.68           | 45.75           | 43.76           | 45.75           | 43.76           |
| Month 1    | N               | 24              | 25              | 63              | 63              | 87              | 88              |
| Mean Change from Baseline | 1.1              | 0.8              | 1.0              | 0.0              | 0.0005          | 1.0              | 0.3              | 0.0026          |
| SD         | 2.98            | 1.73            | 1.84            | 1.10            | 1.89            | 1.34            |
| Min, Max   | -5.6            | -3.7            | -3.6            | -2.2            | -5.6            | -3.7            |
| Month 3    | N               | 24              | 25              | 63              | 63              | 87              | 88              |
| Mean Change from Baseline | 0.1              | 1.0              | -0.2            | 0.6              | 0.386           | -0.1            | 0.7              | 0.0001          |
| SD         | 1.26            | 1.66            | 2.38            | 1.88            | 2.13            | 1.83            |
| Min, Max   | -3.3            | -1.7            | -9.7            | -3.12           | -9.7            | -3.12           |
| Month 6    | N               | 24              | 25              | 63              | 63              | 87              | 88              |
| Mean Change from Baseline | -0.6            | 1.0              | -0.5            | 0.5              | 0.0004          | -0.5            | 0.6              | 0.0001          |
| SD         | 1.61            | 1.69            | 1.95            | 2.28            | 1.85            | 2.14            |
| Min, Max   | -5.3            | -1.7            | -8.3            | -9.12           | -8.3            | -9.12           |
consistent over that time period). The ambiguity of the results underscores the need for an advisory panel for this first of a kind device.

Subgroup Analyses:

**4.3.7. Similarities and Differences in Subject Subgroups**

Subgroup analyses were conducted for the primary efficacy endpoint based on age (< median or ≥ median); gender (male or female); race (white or non-white); and baseline disease severity (mild or moderate/severe). Disease severity was only reported for keratoconus subjects.

In both the pooled keratoconus and corneal ectasia studies, mean improvements from baseline $K_{\text{max}}$ were observed in the CXL group at Month 6 and Month 12, regardless of age, gender, and race. Further, mean improvements from baseline $K_{\text{max}}$ were also observed in the CXL group at Month 6 and Month 12, regardless of disease severity, in the pooled keratoconus studies. Differences between the CXL and control groups in mean change from baseline $K_{\text{max}}$ were clinically meaningful ($\geq 1$ D), in favor of CXL, in all of the subgroups analyzed in the pooled keratoconus studies and most of the subgroups analyzed in the corneal ectasia studies, both at Month 6 (observed case analyses) and Month 12 (LOCF analyses). The magnitude of the treatment effect relative to sham tended to be greater in younger subjects versus older ones, females versus males, and non-whites versus whites. In the keratoconus studies, the magnitude of the treatment effect tended to be greater in subjects with moderate/severe disease versus mild disease. It should be noted however, that the subgroup analyses conducted for the UVX studies were not designed to identify independent predictors of response.

Literature cited by the sponsor to support longterm outcomes:

Until recently, evidence supporting the long-term efficacy of CXL has been lacking. However, a growing number of reports have been published indicating that the effect of CXL is long-lasting in subjects with keratoconus or corneal ectasia following refractive surgery, with follow-up periods up to 4-5 years (Hafezi et al, 2007; Raissk-Wolf et al, 2008; Vinciguerra et al, 2009; Caporossi et al, 2010; Goldich et al, 2012; Richoz et al, 2013).

**Future Studies:**

In addition to the completed studies, 3 multicenter, randomized, placebo-controlled Phase 3 studies have been planned to evaluate the safety and efficacy of riboflavin ophthalmic solution/UVA irradiation in subjects with keratoconus (KXL-001, KXL-002, and KXL-005). These protocols will evaluate an accelerated treatment regimen of riboflavin ophthalmic solution followed by UVA irradiation for 4 minutes (at 30mW/cm2) as opposed to the 30-minute duration evaluated in the original Phase 3 studies. The primary efficacy endpoint (difference between treatments in the maximum corneal curvature, measured by maximum keratometry [Kmax]), safety evaluations, and duration of follow-up are the same as in the completed studies.

**Reviewer Comments:** It is unclear whether CDRH has been or will be consulted with regard to the submissions for these planned studies. Based on the many major issues identified in the current file, I recommend that CDRH be involved as early as possible in communications with the sponsor regarding these planned studies.

**Advisory Panel Meeting:**

No meeting is currently planned.
Reviewer Comments: This is raised as a concern among Major Issues listed at the end of this review. A panel appears to be warranted for the first-of-a-kind technology.

Potential panel questions may include:

1. Has the Applicant provided sufficient evidence to support the effectiveness based on study results at 3 months?
2. Is consideration of 6 month or 12 month data appropriate given the lower accountability due to crossover or, alternatively, the assumptions made about disease progression?
3. Has adequate long-term data been provided for approval? (i.e., the study was not designed to continue until refractive stability was achieved – is the literature adequate to supplement the study results regarding this issue? i.e., how long post-treatment does cross-linking continue?)
4. 16 subjects were studied between 14-18 years of age. Has adequate data been provided to support safety and effectiveness in a pediatric population for the proposed IFU?

Labeling
Contraindications
(per the drug labeling):

(0) (0)

(per device user’s manual):

(0) (0)

Warnings and Precautions:
(per drug labeling):

(0) (0)
Warnings (per device User’s Manual):

Precautions (per device User’s Manual):

Reviewer Comment: The following statement appears in the labeling under warning and precautions:

I recommend the following language be removed from this section

According to device User’s Manual, pg. 3-17, at the conclusion of treatment:

Reviewer Comment: may be inappropriate.

User’s Manual includes a section on “Pausing or Canceling a Treatment”.

Reviewer Comments: This appears to be a risk mitigation measure to ensure that a treatment can be paused, stopped and documented (i.e., laser parameters) prior to completion, if necessary.
The KXL System Operator’s Manual referenced by the sponsor (and included in Appendix 5.1) states on the cover page that it represents “Rev B” of the Operator’s Manual. However, the following from a page of the Operator’s Manual is included on page 1819 of the file “device-info-appendices” in the Attachment No. 8 to Appendix . Note this text also comes from a page with a footer stating it is from the KXL Operator’s Manual, Revision B – however this language does not appear in the separate Operator’s Manual in Appendix 5.1:

Reviewer Comment: Language should be removed from any product labeling. Furthermore, the discrepancy in the various versions of the Operator’s Manual cited in this submission will need to be clarified.

Additional General Device Labeling Issues (KXL System User’s Manual)

1) Device Labeling does not include a summary of the clinical supportive data:

a. No study data such as in drug labeling (package insert) such as the following sections: Adverse Reactions/Use in special Populations (pregnancy/nursing mothers/pediatrics/geriatrics/etc.)/Clinical Studies Section/Patient Counseling.

b. In addition to the above study info, we also need a more detailed description than currently appears in the drug labeling for the following study details:

i. enrollment criteria
1. need to define what types of postrefractive ectasia were studied in the trial with precaution regarding lack of data on any other type of ectasia (postrefractive or otherwise)

   ii. 3 month study results

   1. Also limitations of data beyond 3 months (accountability and otherwise, if later results are reported).

2) Clarifications of terminology/features

   a. User’s Manual Mentions the ability to cancel or pause treatment mid-application. Is there any data regarding the repercussions of such action? Has this been studied? Any additional information regarding incomplete treatments and/or treatment parameter adjustment if resuming at a later time?

   b. “Induction Period” inadequately described and defined

   c. Precautions regarding lack of longterm data and potential risks of UV (examples) to:

      i. Lens

      ii. Retina

      iii. Corneal Keratocytes

      iv. Endothelium

   d. “Advanced Settings” have not been described other than to state that they are only “only available to Avedro and Service personnel with a KXL Advanced Settings access card.”

3) In the postrefractive ectasia populations, subjects s/p either LASIK or PRK were enrolled. s/p LASIK was the predominant population. It is unclear if any subjects were enrolled s/p epi-LASIK. This should be made clear in the device labeling since an indication for “post-refractive ectasia” is a general term. Users should be made aware what conditions were actually studied.

4) Pediatric Use – this is a potential major concern with the submission and may impact labeling considerations

   a. 14 yrs and older (study included 16 subjects between the ages of 14-18)

5) Differences between the device used in the clinical studies and the device to be marketed have not been adequately described and may require additional labeling revisions (ex. All illumination diameters available in device studied are not available in the device to be marketed)
Labeling review is ongoing at this time.

Post-Approval Study

No proposal was identified in this submission for a PostApproval Study.

Reviewer Comments: Given the Major Issues listed at the end of this document, including significant concerns with regard to the abbreviated followup of the control arm due to the potential for crossover at 3 months post-treatment, a post approval study may be warranted.

Conclusions/Recommendations

Based on my review of the clinical data, I have significant concerns as outlined below. In addition, the sponsor should be asked to address the deficiencies listed at the end of this review. My review is ongoing, particularly with regard to the study results and labeling.

Major Issues/Concerns:

1. No advisory panel is planned. This submission appears to be a “first of a kind” and in light of the concerns surrounding the clinical data and the fact that this combination product is likely to generate press, a panel meeting may be appropriate.

2. The device used in the clinical trials is not identical to the device proposed for approval. Differences include a fixed illumination diameter in the device proposed for approval (9mm) and a variable illumination diameter in the device used in the trial (7, 9, 11 mm) Furthermore, it is unclear whether the discussion of device differences listed by the sponsor includes all potential differences including any differences in device design, software, laser specifications and settings, instructions for use, etc. (deficiency below)

3. With regard to the indication for keratoconus: The orphan designation is for keratoconus. The studies enrolled subjects with progressive keratoconus. The risk/benefit considerations could be different between these 2 populations since some keratoconus patients remain stable for years and some progress.

4. Due to the potential for subject crossover from the control arm to the treatment arm at 3 months, a variety of concerns arise including reduced accountability beyond the 3 month visit for the control arm and concern regarding the use of last observation carried forward (LOCF) analyses to supplement the month 12 data. In contrast, using the 3 month visit data without LOCF analyses (as initially intended based on the study design), the sponsor does not meet prespecified effectiveness endpoint targets for all indications. Regardless, longterm data would be valuable for this technology.

5. Three separate clinical studies are reported and the poolability across studies has not been established. Therefore, there are concerns regarding the limited sample size for each treatment group. [The planned sample size was 160 subjects (80 eyes per treatment group) for UVX-002 and UVX-003. For UVX-001, the planned sample size
was 320 subjects (160 per indication, with 80 eyes per treatment group); enrollment into this single-site study was terminated early because the investigator left the study site.

6. Potential for pediatric use is a concern.

7. The proposed IFU includes 2 orphan drug designations (keratoconus and postrefractive ectasia), however, CDRH has approved at least one product for keratoconus (i.e., Intacs) and therefore it is unclear whether this will present a conflict due to the status of the current submission as a combination product.

8. The regulatory history demonstrates that CDRH has not been involved in the progression of this file from IND to NDA over many years. The sponsor cites many “agreements” made between the agency and the sponsor over this time. The path forward is unclear in light of these “agreements” and the future clinical studies that have already been planned by the sponsor.

9. Issues discussed with laser expert reviewer to be addressed by Dr. Dexiu Shi: appropriateness of the Class I laser determination chosen by the sponsor; concerns regarding potential exposure of the patient, physician, or others; whether RFID provides adequate control over laser specifications or whether software or hardware revisions are needed to limit the specifications to those studied (deficiencies may be appropriate however I defer to Dr. Dexiu Shi to address these issues)

10. Preliminary labeling concerns are listed under labeling section however labeling review has not been completed due to the remaining outstanding issues. Of note, revised and updated device labeling will need to be requested from the sponsor due to (1) discrepancies in various sections of this NDA file with regard to information on specific page numbers on the same version of the operator’s manual, (2) the sponsor’s failure to update the device labeling to include the newly proposed name of the drug product (Photrexas) and (3) the lack of any clinical study data in the device labeling which should be modified to include (at minimum) clinical data consistent with the drug labeling, as a starting point.

Deficiencies

You provide a listing of 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) in Table 8, Section 3.2R. This table indicates that the potential illumination diameters used in the trial include “Variable steps 7.0, 9.0 and 11.0 mm” while the device proposed to be marketed has an illumination diameter “Fixed at 9.0 mm". Please address the following so that we may evaluate the impact that variability of this parameter may have had on study safety and effectiveness results and their applicability to expected postmarket device performance:
1) Please clarify how investigators were expected to choose the appropriate illumination diameter for use.
2) Please clarify how many subjects in each study were treated with each illumination diameter.
3) Please provide analyses of safety and effectiveness results stratified by illumination diameter used.
4) Please discuss how the labeling will instruct users regarding appropriate device use in light of a fixed diameter (for example, selection of patient population)

Finally, please 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 approval including, but not limited to: device description, laser settings and/or parameters, software, and instructions for use. This information is requested so that we may assess whether these differences could impact the safety or effectiveness of the device.
Optical Radiation Hazard
Memorandum

Date: February 9, 2014

To: Bradley Cunningham, MS, Branch Chief, CDRH/ODE/DOED/DSDB
    Maryam Mokhtarzadeh, MD
    Malvina Eydelman, DOED Division Director

From: Dexiu Shi, Ph.D., Physicist and Vision Scientist, CDRH/ODE/DOED/DSDB

Doc# NDA203324
Drug: riboflavin ophthalmic solution/KXL System
Device: KXL System
Sponsor: Avedro

Subject: Intercenter/combination products consult on device safety
Requested by Jacquelyn Smith, M.A., CDER/OND/OAP/DTOP, Senior Regulatory
Health Project Manager

INTRODUCTION:

Indications for Use:

Avedro is submitting an Initial New Drug Application for (riboflavin ophthalmic solution) / KXL® System

The KXL® System is a UVA irradiation system whereby an electronic medical device with a light emitting diode (LED) is used to deliver a dose of UVA light to a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. Corneal collagen cross-linking improves the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma. Exposure of the cornea to UVA after topical administration of riboflavin induces cross-linking of the corneal collagen fibrils with a resultant increase in tensile strength of the collagen fibrils.

The sponsor states that:

- The (riboflavin ophthalmic solution) / KXL® System was granted orphan drug designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.
- The (riboflavin ophthalmic solution) / KXL® System was granted orphan drug designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.

- There is no FDA approved therapy in the US for the treatment of keratoconus or corneal ectasia following refractive surgery, two orphan indications for which patients are eagerly awaiting a therapeutic treatment option. The (riboflavin ophthalmic solution)/KXL® System addresses a significant unmet medical need in these two orphan patient populations.

- The (riboflavin ophthalmic solution) / KXL® System received CE mark as a commercial medical device in November 2010 and is commercially available throughout Europe.

Reviewer Comment: Clinical Reviewer, Maryam Mokhtarzadeh, MD, identified that:

- Although the NDA was initially submitted for a drug product with the proprietary name in the most recent submission the sponsor appears to be requesting the following proprietary names for their Riboflavin product: Photrexa and Photextra This request is being made since "At a teleconference held on 22 May 2012 between Avedro and the Division of Medication Error Prevention and Analysis (DMEPA), Avedro was notified of DMEPA’s preliminary findings that the proposed proprietary name, was unacceptable  

- The proposed IFU includes 2 orphan drug designations (keratoconus and postrefractive ectasia), however, CDRH has approved at least one product for keratoconus (i.e., Intacs) and therefore it is unclear whether this will present a conflict due to the status of the current submission as a combination product.

REVIEW SUMMARY:

Devices Information

In section 3.2 Regional Information of Device-Information, the following information is provided:

The 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 (riboflavin ophthalmic solution). Irradiating the Photrexa or Photrexa creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System.
The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient’s cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with Photrexa or Photrexa (riboflavin ophthalmic solution) and a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

UVA treatment

This clinical study is to assess the efficacy and safety of the UV-X™ Illumination System for performing corneal collagen cross-linking (CCCL) for the treatment of corneal ectasia after refractive surgery and progressive keratoconus. The UV-X™ system is a combination product consisting of a UVA 365 nm wavelength light source and Riboflavin 0.1% ophthalmic solution, administered in conjunction with the UVA light as a photosensitizer.
For all listed three studies, irradiance at 3 mW/cm² is applied for 30 minutes while maintaining the total dose at 5.4 J/cm² at the corneal surface.

The following are the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA.

- Induction Period: 30 minutes
- Irradiance: 3 mW/cm²
- Total Energy: 5.4 J/cm²
- Exposure Time: 30 minutes

a. Regarding UVA radiation safety:

The sponsor states the KXL System complies with IEC 60601-1 and IEC 60825-1 (Safety of laser products) and the IEC 62471 (Photobiological safety of lamps and lamp systems) (page 83). However, the UVA light is for treatment, thus these IEC and/or ISO standards are not applicable. Since UVA light is for treatment, thus the IEC and/or ISO standards (e.g., IEC 60825-1, and ISO15004-2) for laser safety and light hazard protection are not applicable. Scientific literatures are used in my review of the evaluation of UVA eye safety.

- UVA treatment parameters

The UVA total energy is the product of the intensity of the UVA beam (irradiance) and the UVA irradiation time. A number of research studies (see table below) demonstrate that the overall cross-linking effect depends upon the total UVA radiant exposure (i.e. photobiological dose or total energy delivered):

<table>
<thead>
<tr>
<th>Author</th>
<th>UVA Intensity</th>
<th>Exposure Time</th>
<th>Total UVA Exposure Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wollensak et al</td>
<td>3 mW/cm²</td>
<td>30 min</td>
<td>5.4 J/cm²</td>
</tr>
<tr>
<td>Caporossi et al</td>
<td>3 mW/cm²</td>
<td>30 min</td>
<td>5.4 J/cm²</td>
</tr>
<tr>
<td>Vinciguerra et al</td>
<td>3 mW/cm²</td>
<td>30 min</td>
<td>5.4 J/cm²</td>
</tr>
<tr>
<td>Grewal et al</td>
<td>3 mW/cm²</td>
<td>30 min</td>
<td>5.4 J/cm²</td>
</tr>
<tr>
<td>Raiskup-Wolf et al</td>
<td>3 mW/cm²</td>
<td>30 min</td>
<td>5.4 J/cm²</td>
</tr>
<tr>
<td>Koppen et al</td>
<td>3 mW/cm²</td>
<td>30 min</td>
<td>5.4 J/cm²</td>
</tr>
</tbody>
</table>

Researches for corneal collagen cross-linking has been to use 0.1% riboflavin solution and 370 nm UVA at 3 mW/cm² irradiance for 30 minutes, which is equivalent to 5.4 J/cm² radiant exposure were supported by many literatures that it is below the damage thresholds of UVA for the corneal endothelium, lens, and retina. Therefore, the UVA dose density of 5.4 J/cm² has been used as a kind of “gold standard” for safety assessment for the similar cross-link study (i.e., 365 nm, 0.1% riboflavin). The total UVA energy in excess of 5.4 J/cm² will be potentially risk.

However, there have been multiple reports that suggest that the overall cross-linking effect depends on the UVA irradiance (i.e. Intensity (W/cm²)). There is the safety
concern that higher irradiance (> 3 mW/cm²) may induce potential radiation hazard to the eyes. In recent times, there has been a noticeable increase in studies for developing the accelerated treatment protocols over a significantly shorter exposure period. For example, this study is to assess the effectiveness and safety of irradiance at 9, 18 up to 30 mW/cm² while maintaining the total dose at 5.4 J/cm².

**Reviewer Comment:** The KXL Systems sold commercially in the United States uses a UVA light (365 nm) at an intensity of 3 mW/cm² for maximum exposure up to 30 minutes, thus the total energy will be within 5.4 J/cm². Accordingly, the proposed UVA treatment parameters are considered to be safe.

However, there is the safety concern that UVA exposure at higher irradiance (>3 mW/cm²) and/or higher total energy (>5.4 J/cm²) may induce potential radiation hazard to the eyes.

The sponsor indicates a Radio Frequency Identification (RFID) activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The detailed discussion on RFID is present at following section.

- **The Radio Frequency Identification (RFID)**

  The RFID reader reads RFID activation cards which are supplied with Photrex or Photrex (riboflavin ophthalmic solution) and determine the allowable ranges for user-selectable treatment parameters for the system. 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 to be marketed in the United States, the maximum allowable treatment parameters will be limited to 3 mW/cm² for 30 minutes and a maximum energy density of 5.4 J/cm².

  The sponsor claims that the RFID activation card to be used in the United States is a card (a specialized treatment card that contains a set of treatment parameters which provide limits for the allowable power density (mW/cm²) and maximum energy density (J/cm²)). Both Power and Energy parameters have lower, upper and incremental limits that will be customized for sales in the United States. Once the RFID activation card is scanned, the treatment parameters entered by the user (power and energy) are verified against the parameters stored in the RFID activation card. Only if all entered parameters are within the respective ranges allowed on the RFID activation card, the user is allowed to proceed with the treatment.

  On Page 21, 3.2.R

Page 5 – NDA 203324 – Consult Review on Device Safety

Reference ID: 3720918
The user confirms the entered treatment parameters as shown in Figure 14.

**Reviewer Comment:** The sponsor states that the RFID activation cards supplied in the United States will not allow treatment unless the Total Energy is set to 5.4 J/cm² and the UV.

The sponsor needs to clarify whether UV radiation intensity of the US version KXL system is locked at the lowest setting (i.e. 3 mw/cm²). If yes, please descibe the method, such as, software control and/or hardware safeguard to shut down or black the UVA beam once the UV radiation intensity is greater than 3 mw/cm² (deficiency#1).
Homogeneity of the UVA irradiance

Spoerl, et al pointed that for UVA exposure, if hot spots are present, the damage thresholds may be exceeded locally, leading to localized endothelial damage, although the average irradiance may be less than damage thresholds. Therefore, clinically used light sources should be homogeneous of the irradiance across the beam area.

Reference:


Device Description (page 9) indicates that KXL UVA radiation is generated by a UV LED (365 nm). 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. The sponsor states the UV Homogeneity Measurement is performed in accordance to KXL System Optical Assembly Calibration (WI-01102-01) to verify that the UV Beam has been properly focused. The acceptance criteria is defined as that the homogeneity (flatness) of the beam at the focal plane shall be % RMS. The KXL System
Optical Assembly UV Homogeneity Measurement Master Validation (VAL-00005) is provided in Appendix 2.24.

**Reviewer Comment:**

- The proposed Homogeneity Measurement Master Validation plan (VAL-00005) is acceptable. However, no test result was presented. The sponsor needs to provide the test results/evidence demonstrating the UVA treatment beam is homogeneous over entire cornea area.

- The sponsor states that “UVA radiation is generated by UV LED (365nm).” However, the UV LED may be hazardous to the device operator. The sponsor should explain any mitigation(s) used for protecting the eye safety for operators (deficiency #2).

b. **Illumination System**

To correctly position the UV beam onto the cornea, two targeting lasers are used:

**Reviewer Comment:** The KXL system used two targeting lasers for illumination. The sponsor claimed that both targeting lasers are eye-safe (Class I laser) based on IEC 60825-1:2007. They do not provide the technical characteristics of the two lasers (laser name/model, maximum output power). This basic information is necessary for the review of the laser safety (deficiency #3).

**Equivalency of UVX and KXL Systems (page 82)**

The sponsor states that:

The UV-X Illumination System was utilized during the Phase III clinical study reported in the NDA. Avedro, Inc. believes that the KXL System for which commercial approval is being requested is equivalent to the UV-X Illumination System which was used during the Phase III clinical study. Table 8 compares the specifications of the UV-X Illumination System with the KXL System.
Table 8: Comparison of UV-X Illumination System (Phase III) Specifications with the KXL System (Commercial) Specifications.

<table>
<thead>
<tr>
<th></th>
<th>Phase III</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVA System</td>
<td>UV-X Illumination System</td>
<td>KXL System</td>
</tr>
<tr>
<td>Device Type (Classification)</td>
<td>LED illumination device (Class II)</td>
<td>LED illumination device (Class II)</td>
</tr>
<tr>
<td>Wavelength</td>
<td>Wavelength: 365 [\text{nm}]</td>
<td>LED: Wavelength: 365 [\text{nm}]</td>
</tr>
<tr>
<td>Device Configuration</td>
<td>Illumination system at end of an arm, attached to a floor stand or a patient bed</td>
<td>Illumination system at end of an articulated arm on top of floor stand, wireless remote control and a system console</td>
</tr>
<tr>
<td>Light Emission</td>
<td>Continuous wave (CW)</td>
<td>Continuous wave (CW)</td>
</tr>
<tr>
<td>Illumination Intensity</td>
<td>3.0 mW/cm²</td>
<td>3.0 mW/cm²</td>
</tr>
<tr>
<td>Illumination Diameter(s)</td>
<td>Variable steps 7.0, 9.0 and 11.0 mm</td>
<td>Fixed at 9.0 mm</td>
</tr>
<tr>
<td>Treatment Time</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Patient Positioning</td>
<td>On bed</td>
<td>On bed</td>
</tr>
<tr>
<td>Targeting System</td>
<td>N/A</td>
<td>Laser crosshairs</td>
</tr>
<tr>
<td>Focal Plane Setting</td>
<td>Subjective (homogeneity of UV pattern)</td>
<td>Objective (crossed laser beams)</td>
</tr>
<tr>
<td>Electric Power</td>
<td>100V to 240 V</td>
<td>100 V to 240 V</td>
</tr>
<tr>
<td>Intensity Check</td>
<td>UV light meter delivered with UV-X System</td>
<td>Integrated UV light meter</td>
</tr>
<tr>
<td>Laser and LED Safety Compliance</td>
<td>IEC 60825-1</td>
<td>IEC 60825-1 IEC 62471</td>
</tr>
<tr>
<td>Electrical Safety Compliance</td>
<td>IE 60601-1</td>
<td>IE 60601-1</td>
</tr>
</tbody>
</table>

Major differences are follows:

<table>
<thead>
<tr>
<th></th>
<th>Phase III (UV-X)</th>
<th>Commercial (KXL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Illumination Diameter(s)</td>
<td>Variable steps 7.0, 9.0 and 11.0 mm</td>
</tr>
<tr>
<td>2</td>
<td>Targeting System</td>
<td>No target laser (aligned subjectively by the user)</td>
</tr>
<tr>
<td>3</td>
<td>Focal Plane Setting</td>
<td>Subjective (homogeneity of UV pattern)</td>
</tr>
<tr>
<td>4</td>
<td>Intensity Check</td>
<td>UV light meter delivered with UV-X System</td>
</tr>
</tbody>
</table>
On page 83, 3.2.R Regional Information, the sponsor states:

Both systems are LED based illumination systems with a wavelength of \(365\) nm. Both systems are continuous wave systems with an illumination intensity of \(3.0\) mW/cm\(^2\) and a treatment time of 30 minutes. The illumination diameter is \(9.0\) mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm steps. The patient is positioned on a bed for treatment in a supine position with both systems. The KXL System includes an alignment focusing beam that allows for alignment of the treatment area. The UV-X System was aligned subjectively by the user. The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used an external light meter. Both systems comply with IEC 60601-1 and IEC 60825-1, and the KXL System also complies with IEC 62471.

**Reviewer Comment:** How those differences may affect the SE is discussed at below:

1. The illumination diameters: The illumination diameter is \(9.0\) mm in the KXL System while the UV-X System had a variable aperture with 7.0, 9.0 and 11.0 mm. The illumination intensity is given in \(3\) mJ/cm\(^2\) which is the same value for UV-X and KXL system.

2. Target system: KXL uses two targeting lasers source with crosshairs. The UV-X System was aligned subjectively by the user. The target system used in KXL system was improved.

3. Focus plane setting: KXL uses crossed laser beam. The UV-X was set focus plane by observe the homogeneity of UV pattern to determine focus plan subjectively.

4. Intensity Check: The KXL System has an integrated UV light meter for measuring intensity while the UV-X System used an light meter.

Clinical reviewer has the concern with the potential illumination diameters used in the trial include “Variable steps 7.0, 9.0 and 11.0 mm” while the device proposed to be marketed has an illumination diameter “Fixed at 9.0 mm”. For KXL, the device functionality has been limited compared to what was used in the clinical study. It is not clear what the repercussions of a fixed illumination beam diameter might be and how the labeling might need to instruct users regarding this difference between the device available and the device studied. Please see Dr. Mokhtarzadeh’s deficiency.
Non-Clinical Laboratory Studies (page 82)

The following testing and validation materials are provided as appendices:

Appendix 1.1 - Product Requirements Specification
Appendix 1.2 - System Validation Test Plan (PSPEC-00032-NDA)
Appendix 1.3 - System Validation Test Report (PSPEC-00051-NDA)
Appendix 1.5 - System Verification Test Plan (PSPEC-00033-NDA)
Appendix 1.6 - System Verification Test Report (PSPEC-00052-NDA)

Review Comment:

On Page 4, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), it specified that:

6.2.6.4 Output power shall be controlled to [ ] %.
6.2.6.8 Power uniformity over the illuminated area shall be [ ] % RMS.

a. A tolerance range [ ] % is given for UVA output. Please provide your rationale for why this tolerance range is selected and/or the justification that the [ ] % illumination fluctuation will be safe for proposed treatment.

b. Please provide the test result to demonstrate power uniformity over the illuminated area is [ ] % RMS for KXL system (deficiency#4).

LABELING (KXL Operator’s Manual)

The sponsor provided two versions of KXL Operator’s Manual (i.e., ML-00002, 2011 and ML-00006, 2012) in Appendix 5.1. (device-info-appendices) We found there are discrepancies between these two versions, especially the Indications for Use/Intended Use are not identical. In version ML-00002, 2011 (page 3-1), [ ] is included:

[Blank Space]
**Reviewer Comment:** Sponsor should provide the explanation on the discrepancies and provide the final version of KXL Operator’s Manual for this study (deficiency#5).

### DEFICIENCIES:

Based on my review, the following engineering and laser and optical radiation safety deficiencies have been identified:

1. The sponsor states a Radio Frequency Identification (RFID) activation card will be used to determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²) and the treatment parameters that will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA are as follows:

   Induction Period: 30 minutes
   Irradiance: 3 mW/cm²
   Total Energy: 5.4 J/cm²
   Exposure Time: 30 minutes

   Please clarify whether UV radiation intensity of the US version KXL system is locked at the lowest setting (i.e. 3mW/cm²). If yes, please describe the method, such as, any software control and/or hardware safeguard to shut down or block the UVA beam once the UV radiation intensity is great than 3mW/cm².

2. On Page 4-5, section 6.2.6 Energy Delivery (Appendix 1.1 Product Requirements Specification), it specified that:

   6.2.6.4. Output power shall be controlled to % RMS.
   6.2.6.8. Power uniformity over the illuminated area shall be % RMS.

   Please address the following concerns:

   c. A tolerance range is given for UVA output. Please provide your rationale for why this tolerance range is selected and/or the justification that the % illumination fluctuation will be safe for proposed treatment.

   d. Please provide the test result to demonstrate power uniformity over the illuminated area is % RMS for KXL system.

3. You state that “UVA radiation is generated by UV LED (365nm).” Please address the following concerns:

   a. You only provided the Homogeneity Measurement Master Validation plan (VAL-00005) However, no test result was presented. Please explain the criteria of the homogeneity
and provide the test results to demonstrate the UVA treatment beam is homogeneous over 
entire cornea area.

b. Please be advised that (b)(4) may be hazard to the device operator. The 
sponsor should explain any mitigation(s) used for protecting the eye safety for operators

4. You state that the KXL system used two targeting lasers for illumination, and both targeting 
lasers are eye-safe (Class I laser) based on IEC 60825-1:2007. However, you do not provide 
the technical characteristics of the two lasers (laser name/model, maximum output power). 
Please provide this information. This basic information is necessary for the review of the 
laser safety.

In addition, it is unclear from your submission how the lasers and LEDs classification was 
determined; please provide detailed information for determination of laser/LEDs 
classification. This information will assist us in evaluating the laser and optical radiation 
safety analyses.

5. You provided two versions of KXL Operator’s Manual (i.e., ML-00002, 2011 and ML-00006, 
2012) in Appendix 5.1. (device-info-appendices) We found there are discrepancies between 
these two versions, especially the Indications for Use/Intended Use are not identical.

- On page 1-1, KXL Operator’s Manual (ML-00006), 2012, the following Indication for 
Use (IFU) statement is provided:

\[(b)(4)\]

(b)(4)
Please provide your explanation on the discrepancies and provide your final version of KXL Operator’s Manual for this study.
Software
MEMO OF
SOFTWARE REVIEW
of a MAJOR Level Of Concern device

NDA: 203324

DATE: 1/24/14

FROM: Joseph Jorgens III, Senior Biomedical and Software Engineer OSEL-DESE 301-796-2588
TO: Brad Cunningham ODE/DOED/DSDB Bldg 66 2430 301-796-6620
SUBJECT: Software review of Avedro, 230 Third Avenue Waltham, MA. Contact: Pamela Nelson, Vice President, Regulatory Affairs, (781) 768-3430

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Succinct Conclusion: Submission is Deficient

The information provided in this submission is insufficient to meet the software concerns as described in the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, and it is recommended that, from a software standpoint, additional information be acquired in order to complete the review of this submission.

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SUMMARY:

Avedro is submitting an Initial New Drug Application for (riboflavin ophthalmic solution)/KXL System

The System was designated a combination product and clinical studies using the drug/device system were conducted in the U.S. under IND 77,882, which was originally submitted by Peschke Meditrade GmbH (Htienenberg, Switzerland) on November 7th, 2007. Sponsorship of IND 77,882 was transferred to Avedro on May 7th 2010.

The system was granted orphan designation for the treatment of keratoconus on September 2nd, 2011 and for

Reference ID: 3720918
corneal ectasia following refractive surgery on December 2nd, 2011.

Keratoconus is a naturally-occurring degenerative ocular disorder characterized by progressive thinning and steepening of the central cornea, which leads to increasing myopia, irregular astigmatism, protrusion and eventual loss of best spectacle-corrected visual acuity (BCSVA).

Onset of keratoconus generally occurs during puberty or early adulthood and, if left untreated, patients experience progressive vision impairment.

Corneal ectasia is a complication of refractive surgeries including laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy (PRK). Corneal ectasia is a condition in which the cornea is weakened so that it protrudes under the force of intraocular pressure and bows outward. This results in loss of uncorrected visual acuity and loss of best spectacle corrected visual acuity.

Both keratoconus and corneal ectasia patients may progress to the point of requiring corneal transplantation.

Corneal collagen cross-linking has been demonstrated to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma and stabilizing corneal curvature, thus slowing or stopping the progression of keratoconus and corneal ectasia following refractive surgery. Additional clinical benefits are corneal flattening and improvement in both uncorrected and best spectacle corrected visual acuity.

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 Photrex or Photrex (riboflavin ophthalmic solution). Irradiating the Photrex or Photrex creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient’s cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with Photrex or Photrex (riboflavin ophthalmic solution) and a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.
Software Controlled Aspects of the Device

All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy.

SOFTWARE REVIEW

1. **Level of Concern: Acceptable**
   In Section 1.6.1 entitled Level of Concern, the firm provided the correct determination of the Level Of Concern and included their supporting rationale: MAJOR.

2. **Software Description: Acceptable**
   In Section 1.2 entitled Functional Components of the Device and Section 1.6.2 entitled Software Description, the firm provided an acceptable overview of the device features that are controlled by software, and a description of the intended operational environment, which included information on the programming language and the hardware platform.

3. **Device (including software) Hazard Analysis: Acceptable**
   In Appendix 1.28 entitled FMEA, the firm provided an acceptable description of the hazards presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4. **Software Requirements Specifications (SRS): Acceptable**
   In Appendices 1.10 and 1.11 entitled Software Requirements Specification the firm provided acceptable software requirements specifications, which documented the functional, performance, interface, design and development requirements.

5. **Architecture Design Chart: Acceptable**
   In Appendix 1.12 entitled Architecture Description, the firm provided an acceptable detailed depiction of functional units and software modules.

   In Appendices 1.14 – 1.16 entitled Design Description, the firm provided acceptable design specifications, which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.

7. **Traceability: Acceptable**
   In Appendix 1.17 entitled Traceability Matrices, the firm provided acceptable traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing.

8. **Software Development Environment Description: Acceptable**
   In Appendix 1.18 entitled Software Development Plan, the firm provided an acceptable description of the software development environment, which included a summary of the software life cycle development plan, an annotated list of the control/baseline documents generated during the development process.

9. **Verification and Validation Documentation: Acceptable**
   In Appendices 1.20 – 1.25 entitled Validation, Verification and Testing, the firm provided acceptable unit, integration and system level test protocols, including pass/fail criteria, test reports, summaries and tests results.

Reference ID: 3720918
10. **Revision Level History:** Acceptable  
In Appendix 1.26 entitled Software Revision History, the firm provided an acceptable revision history log documenting all major changes to the software during its development cycle and the release version numbers.

11. **Unresolved Anomalies (bugs):** Acceptable  
In Appendix 1.27 entitled Bug Listing, the firm provided an acceptable list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors.

12. **Cyber and Information security:** Not Acceptable  
The firm is incorporating an RFID activation card as part of this system. The Cybersecurity issues were not addressed. This should be done.

13. **Run-Time Error Detection:** Not Acceptable  
The firm did not include any information about what tools (such as a static analysis tool), if any, were used to detect software run-time errors. This should be provided.

**RECOMMENDATION: Deficiencies should be addressed**

For the reasons specified supra, it is recommended that the firm should be asked for the following additional information before final approval is considered.

I will be happy to discuss these matters with the firm directly if that is more desirable. The following verbiage is offered as a possibility for inclusion in any oral or written correspondence with the firm.

If you have questions concerning these additional information requests, please contact Joseph Jorgens III on 301-796-2588.

Prior to submitting the additional information, please familiarize yourself with the following software guidance documents:

  5/11/05

  (issued 9/9/1999)

- “General Principles of Software Validation; Final Guidance for Industry and FDA Staff” (issued 1/11/2002)  

FDA is developing guidance on CyberSecurity and has published a draft for public comment. While it does not constitute finalized recommendations and is not currently in effect, you may find the draft guidance, and comments in the associated public docket helpful.


You may also want to consider a review of the following consensus standards: IEC 62304:2006 (Medical device software – Software life-cycle processes) and ISO 14971:2000 (Medical devices - Application of risk management to medical devices).

For all the following information, please provide a table of contents with page numbers and tabbed sections, with each section repeating the question which is being addressed and clearly providing the answers to each of these additional information questions. If some of the information was provided in the original submission, please repeat that information in your response: do not just reference some previously submitted information.

12. Cyber and Information security
You did not provide information on Cybersecurity for your RFID activation card.

Please discuss in detail, information on your design considerations, including mitigations pertaining to intentional and unintentional cybersecurity risks including:

A specific list of all cybersecurity risks that were considered in your design.
A specific list and justification for all cybersecurity controls that you established, and the justification as to why such controls are adequate. Please provide the evidence that the controls perform as intended.

Please incorporate, as appropriate, the information identified here in your Hazard Analysis.

13. Run-Time Error Detection
What tools, (such as static analysis tools), if any, do you use to detect run-time errors. For any such tool used, please identify what error types the tool detects, your method and process of applying the tool(s), and a summary report and/or conclusion about the results.

Note: some common run-time errors are:

1. Un-initialized variables
2. Type mismatches
3. Memory leaks
4. Buffer over/under flow
5. Dead and unreachable code
6. Memory/heap corruption
7. Unexpected termination
8. Non-terminating loops
9. Dangerous Functions Cast
10. Illegal manipulation of pointers
11. Division by zero
12. Race conditions
Electromagnetic compatibility
Memorandum

Date February 1, 2014
From Senior Electronics Engineer (Jeffrey L. Silberberg), CDRH/OSEL/DESE
Subject EMC consult for NDA203324 Avedro KXL UV irradiation system
To Brad Cunningham, CDRH/ODE/DOED/DSDB

Scope
This is in response to your request for an EMC review of the subject submission.

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

Recommendations
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.

1. On page 60 and 61 of the device-information document, there is a table of “recognized standards” with which the KXL System is claimed to comply. However, for many of the standards listed, there is 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 important. Also, FDA does not recognize EN standards, and there are several on the list. Conformity with IEC 60601-1-2 is claimed. However, the EMC test report cites EN 60601-1-2. While the two standards are essentially identical, please be consistent in your claims of conformity. Finally, please submit an FDA Form 3654 for each standard to which conformity is claimed.

2. The immunity pass/fail criteria specified in the EMC test report do 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 have not specified the performance that you determined to be the Essential Performance of the KXL System. It’s possible that this could be derived from the specification of Criterion A; however, please specify the Essential Performance explicitly. Any future EMC testing to IEC 60601-1-2 that you submit 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.

3. There are 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 shows that the testing was performed only at VAC/Hz. We note 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.

4. The EMC test reports identified the modifications below that were made to the KXL System in order to pass the tests. Please affirm that all of these modifications will be included in all production units.

Reference ID: 3720918
5. IEC 60601-1-2:2007 specifies requirements for testing and for labeling. In order to demonstrate conformity with the standard, 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. The system technical description is required to include the items below.

      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.

   b. The system Instructions for Use is required to include the items below.

      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; and

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

6. The KXL System incorporates wireless remote control and RFID. We were not able to find information on the effective radiated power of either wireless device, nor was I able to find information on the communication service or protocol used by the wireless remote control. Please provide this information and also address all the issues raised in the 2013 FDA guidance Radio Frequency Wireless Technology in Medical Devices (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm077210.htm), including performing wireless coexistence testing or submitting a justification as to why wireless coexistence testing is not needed.

7. 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, mistakes and accidents do happen. 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”.

Reference ID: 3720918
Background

The KXL System is an electronic medical device intended to deliver ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of [riboflavin ophthalmic solution]. According to the sponsor, irradiating [riboflavin] creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The KXL System is shown in Figure 1.

While the sponsor does not specify the intended use environments explicitly, it can be assumed that the system will be used in hospitals, clinics, and doctors’ offices.

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 exposure time, and UV intensity) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with [riboflavin ophthalmic solution] and a radio-frequency identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user selectable power density levels and the maximum allowable dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

![Figure 1 - The KXL System](image)

The UV irradiance dose is the product of the intensity of the irradiance and the exposure time. The following are the

Reference ID: 3720918
treatment parameters that the sponsor claims will be allowed by the RFID activation card in KXL Systems sold commercially in the United States on the basis of this NDA.

Induction Period: 30 minutes
Irradiance: 3 mW/cm²
Exposure Time: 30 minutes

Although the submission might include appendices that describe wider treatment parameters that are available on devices sold outside of the United States, the sponsor claims that all devices sold commercially in the United States will have treatment specifications limited by the RFID activation card to those listed here.

Table 1 shows excerpts from the KXL System specifications.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical</strong></td>
<td>Battery Powered: 12V 35 Ah SLA</td>
</tr>
<tr>
<td></td>
<td>Line voltages 100-240 volts AC, Current</td>
</tr>
<tr>
<td></td>
<td>Single Phase RMS, 50/60 Hz, Remote 2x AAA batteries</td>
</tr>
<tr>
<td><strong>User accessible Fuses</strong></td>
<td>250 V~</td>
</tr>
<tr>
<td><strong>Energy Delivery</strong></td>
<td>UV Radiation</td>
</tr>
<tr>
<td></td>
<td>3 mW/cm²</td>
</tr>
<tr>
<td></td>
<td>365 nm</td>
</tr>
<tr>
<td><strong>External Interfaces</strong></td>
<td>USB 2.0</td>
</tr>
<tr>
<td><strong>Battery Life</strong></td>
<td>(normal operating conditions) 16 hours</td>
</tr>
</tbody>
</table>

The KXL System is a portable system with an articulating arm that houses the illumination system at the end. The articulating arm allows movement of the system for alignment of the UV Beam to the patient’s cornea. The articulating arm sits on top of a floor stand that houses an internal battery that powers the system. The battery is recharged by a system internal charger from a standard AC outlet. The complete optics assembly can be moved in x, y, and z. A wireless remote controls all system movements.

A system console houses the user interface and the RFID reader. The user interface controls all treatment parameters that are set through a touch screen PC running Windows Embedded Standard. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable dosage (in J/cm²) for the system. According to the sponsor, the software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console and there are more than zero treatments remaining.

The Optics Head houses the UVA irradiation mechanism. UVA radiation is generated by UV LED. The LED is manufactured to emit UVA radiation at a wavelength of 365 nm. 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. Both lasers are controlled

Treatment parameters entered by the user (power, time and energy) are verified against the parameters stored in the RFID activation card. Only if all three entered parameters are within the respective ranges allowed on the RFID activation card, the user is allowed to proceed with the treatment.

The RFID activation card is programmed with an initial number of treatments for which it may be used. When scanned, the number of treatments remaining is decremented by one until the card is empty. An RFID activation card can only be used if it is identified by the system’s cryptography software module as a certified Avedro-created tag and if its country code matches that of the KXL System. A given multi-use RFID activation card will be accepted only if it contains at least one remaining treatment. Once a multi-use RFID activation card has been scanned, the user is given a visual indication of the number of treatments remaining on the card.

Therefore, it is not possible to simply store and re-write the current number of treatments remaining on a given multi-use disposable RFID activation card.
Since cards cannot be written by the KXL System, when a multi-use card is scanned, a previously unlocked memory block on the card is irreversibly locked. Since blocks can never be unlocked, this method prevents a malicious user from “rolling back” the number of treatments remaining on a given card. Since there are 64 blocks on a given tag, the number of treatments per card is limited to 64.

The position of the KXL System head can be manually adjusted and located appropriately over the patient’s eye by the physician. The position can then be fine-tuned using the wireless remote control, in an X, Y and Z direction. (See Figure 2.)

The joystick controls X and Y directions; the two buttons control the movement along the Z axis.

![Wireless remote control](image)

**Figure 2 - Wireless remote control**

The approximate sequence of operation is as follows:

- Device power is turned on by the user. The system then checks for startup errors and if the system is starting up correctly, a system calibration is performed. The system checks whether a partial treatment has been detected. If not, the system prepares for a new treatment.

- To begin preparing for treatment, the user enters the induction period for the instillation of the riboflavin ophthalmic solution in minutes and seconds.

- The user sets the UV treatment time in minutes and seconds and the UV power.

- The user is instructed to scan an RFID treatment activation card using the RFID reader.

- The user is prompted to sync the alignment remote with the KXL System and does so by pressing the sync button on the alignment remote.

- The patient’s eye is prepared for treatment by the physician removing the epithelium. The KXL System then instructs the doctor to apply the riboflavin ophthalmic solution.

- The KXL System tracks the induction time and notifies the user that the induction is complete.
The UV treatment is then performed.

The KXL System tracks the treatment time, turns off the UV and notifies the user when the treatment has been completed.

Once the treatment has been completed, the system may be powered off.

Detailed review

1. On page 60 and 61 of the device-information document, there is a table of “recognized standards” with which the KXL System is claimed to comply. However, for many of the standards listed, there is 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 important. Also, FDA does not recognize EN standards, and there are several on the list. Conformity with IEC 60601-1-2 is claimed. However, the EMC test report cites EN 60601-1-2. While the two standards are essentially identical, the sponsor should be consistent in the claims of conformity. Finally, the sponsor should be asked to submit an FDA Form 3654 for each standard to which conformity is claimed.

2. The immunity pass/fail criteria specified in the EMC test report do 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, the sponsor has not specified the performance that was determined to be the Essential Performance of the KXL System. It’s possible that this could be derived from the specification of Criterion A; however, the sponsor should be asked to specify the Essential Performance explicitly. Any future EMC testing to IEC 60601-1-2 submitted by the sponsor 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.

3. There are 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 shows that the testing was performed only at VAC/Hz. I note that the AC input specifications of the KXL System are 100-240 VAC. The sponsor should be asked to perform these tests as specified by IEC 60601-1-2, i.e. repeat them at 100 VAC.

4. The EMC test reports identified the modifications below that were made to the KXL System in order to pass the tests. The sponsor should be asked to affirm that all of these modifications will be included in all production units.

5. IEC 60601-1-2:2007 specifies requirements for testing and for labeling. In order to demonstrate conformity with the standard, in addition to evidence of meeting the testing requirements of the standard, the sponsor needs to submit evidence of meeting the labeling requirements. This includes the items listed below. I was not able to find any of these items in the Operator’s Manual.

   a. The system technical description is required to include the items below.

      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. The system Instructions for Use is required to include the items below.

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; and

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

6. The KXL System incorporates wireless remote control and RFID. I was not able to find information on the effective radiated power of either wireless device, nor was I able to find information on the communication service or protocol used by the wireless remote control. The sponsor should be asked to provide this information and also address all the issues raised in the 2013 FDA guidance Radio Frequency Wireless Technology in Medical Devices (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm077210.htm), including performing wireless coexistence testing or submitting a justification as to why wireless coexistence testing is not needed.

7. I was 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, mistakes and accidents do happen. 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. The sponsor should be asked 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”.

Jeffrey L. Silberberg
Senior Electronics Engineer
CDRH/OSM/DESE
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
03/25/2015
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

eConsult Cover Sheet

Consult Number: CON1421346

Document Number: GEN1400864

Applicant: Avedro

Trade Name:

Consult Type: Electrical Safety

Requestor: Maritze Ortega [MXO]
maritze.ortega@fda.hhs.gov ; 301-796-5625

Requestor Home: CDRH\ ODE\ DOED

Requested Consultant: Sandy Weininger [SXW]

Gatekeeper / Consultant: Sandy Weininger [SXW] Weininger - S

sandy.weininger@fda.hhs.gov ; 301-796-2582

Consultant Home: CDRH\ OSEL\ DBP

Date Requested: October 28, 2014

Due Date: January 6, 2015

Instructions: the ELESFT consult to one of our electrical equipment safety reviewers.

Scope of Review:

You have requested an electrical safety review of a combination product, (riboflavin ophthalmic solution) / KXL® System that irradiates the cornea with ultraviolet light An electrical safety review is concerned with the safe use of electrical energy – starting with establishing safe requirements, performing comprehensive risk identification, analysis, and control, and verifying that the device performs as specified (from an electrical function perspective).

I did NOT evaluate laser safety as part of this review.

NDA 203324 Avedro Vedera KXL system – electrical safety review
**Recommendation:**

Sponsor 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. Sponsor has performed adequate safety and functional testing, using both internal and recognized (i.e. standards) methods and acceptance criteria. Sponsor 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.

**Device description:**

The KXL System is an electronic medical device which delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of riboflavin ophthalmic solution. Irradiating riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. Figure 1 provides an illustration of the KXL System. Controlling the timing, intensity, and direction of this UV energy is the essential performance for the device.

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. The complete optics assembly can be moved in x, y, and z axes via wireless remote controls all system movements.

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 exposure time, and UV intensity) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with riboflavin ophthalmic solution and a Radio Frequency Identification (RFID) activation card. A system console houses the user interface and the RFID reader. The user interface controls all treatment parameters that are set through a touch screen PC running Windows Embedded Standard. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

To correctly position the UV beam onto the cornea, two targeting lasers are used.

Both lasers are controlled.
Figure 1. System components

Electrical System Safety and Performance considerations

Safety Controls
Relevant electrical safety product requirements that have their implementation verified to assure safe operation:

6.2 Performance Requirements

6.2.1 PRS-10: Battery capacity shall allow for at least 16 hours of continuous operation (2 work days) without recharging.

6.2.2 PRS-11: The system shall monitor the battery status and request a recharge and/or inhibit a treatment if necessary.
6.2.3 PRS-12: The battery charger shall be able to power the system in addition to charging the battery.

6.2.4 PRS-13: The battery charger shall be universally operable on line voltages from 100VAC to 240VAC, 50/60Hz

6.2.5 PRS-14: The power cord shall be detachable.

6.2.6 Energy Delivery

6.2.6.4 PRS-18: Output power shall be controlled to \(30\)\(^\circ\)\(\%\).

6.2.6.5 PRS-19: The lower and upper limits of user-selectable power density levels shall be determined by RFID treatment authorization cards. Maximum range shall be between 3mW/cm\(^2\) and 45mW/cm\(^2\).

6.2.6.6 PRS-20: The lower and upper limits of user-selectable illumination duration shall be determined by RFID treatment authorization cards. Maximum range shall be between 1 min and 30 min.
2.3 System Block Diagram

Discussion:

Successful testing using IEC 60601-1 (General standard for electromedical safety) provides the primary assurance of safe operation considering basic physical hazards, such as mechanical and electrical shock, fire, vibration, safe surface temperature, and fluid ingress protection. This considers who might touch the instrument and where – thus assuring that neither the patient nor operators are exposed to hazardous energy. The primary risks from this device, other than basic physical hazards, are the exposure of the eyes (patient or operator) to unintended UV radiation. This electrical safety review is concerned with assuring that the device controls the UV LEDs according to specification and dependably considering any malfunctions that may occur and not that the treatment times and amplitude (for example) are correct.
An insulation diagram indicates how the patient/operator is isolated from the mains power (wall) and secondary circuits of the product. There are quite a few additional areas of concern for a product in terms of meeting insulation requirements, other than patient and circuit isolation but patient isolation is critical to a design. The isolation diagram proves that you have two levels of protection available so if a single fault occurs the user or patient will be safe from an electrical shock hazard or another type of hazard.

Note that sponsor is using the 2nd edition of IEC 60601-1 with amendments for electrical safety. FDA currently recognizes the 3rd edition (see Recognition Number 19:4: AAMI / ANSI ES60601-1:2005/(R)2012 and A1:2012, c1:2009/(R)2012 and a2:2010/(R)2012 (consolidated text) medical electrical equipment - part 1: general requirements for basic safety and essential performance (iec 60601-1:2005, mod). The test report starts on p 1399 of the device-info-appendix. Testing was performed in 2011, prior to the date of recognizing the 3rd edition. Sponsor has in place a risk management process conforming to ISO 14971 that complements the product testing and one of the differences between the 2nd and 3rd editions (the other being the identification of essential performance). This allows for a case to be made that the 2nd edition testing + a risk management process is acceptable. Separate test certificates and rest reports were submitted for the battery charger.

Update: sponsor has provided a more recent test report for IEC 60601-1, 3rd edition, dated April 2, 2014. This removes the special case cited above. Information is adequate.

**Risk Management summary**

Sponsor describes their using a risk management process that conforms to ISO 14971. Sponsor reports that a FEMA (failure modes and effects analysis) was used to evaluate the Avedro Vedera
KXL system, consisting of 24 major components. 91 failure modes were evaluated in hardware, software and consumable components, with an average risk index of 15.5 and a highest risk index of 36, prior to mitigation. With mitigation, the average risk index is 5.9, and the highest risk index is 8. No residual risks (after mitigation) were classified as "moderate" or "high", with a risk index of 10 or higher. With the implemented mitigations, all failure modes were reported to be acceptable for use. Sponsor appropriately included hazards arising from electrical energy (e.g. leakage currents, electric shock, ingress protection, excessive surface temperatures) sources and lack of performance (e.g. emergency shutdown procedures, battery failure) and asserts that all risks associated with the use of the device have been assessed and properly mitigated.
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/s/

JACQUELYN E SMITH
03/25/2015
MEMO OF

SOFTWARE REVIEW
of a MAJOR Level Of Concern device

NDA: 203324

DATE: 1/24/14

FROM: Joseph Jorgens III, Senior Biomedical and Software Engineer OSEL-DESE  301-796-2588
TO: Brad Cunningham ODE/DOED/DSDB  Bldg 66 2430 301-796-6620
SUBJECT: Software review of Avedro, 230 Third Avenue Waltham, MA. Contact: Pamela Nelson, Vice President, Regulatory Affairs, (781) 768-3430

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Succinct Conclusion: APPROVE

The information contained within this submission is sufficient to meet the software concerns as described in the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, and it is recommended that, from a software standpoint, this submission be approved.

-------------------------------------------------------------------------------------------------------------------------------------------------------

SUMMARY:

Avedro is submitting an Initial New Drug Application for (riboflavin ophthalmic solution)/KXL System

The System was designated a combination product and clinical studies using the drug/device system were conducted in the U.S. under IND 77,882, which was originally submitted by Peschke Meditrade GmbH (Htiernenberg, Switzerland) on November 7th, 2007. Sponsorship of IND 77,882 was transferred to Avedro on May 7th 2010.

The system was granted orphan designation for the treatment of keratoconus on September 2nd, 2011 and for corneal ectasia following refractive surgery on December 2nd, 2011.
Keratoconus is a naturally-occurring degenerative ocular disorder characterized by progressive thinning and steepening of the central cornea, which leads to increasing myopia, irregular astigmatism, protrusion and eventual loss of best spectacle-corrected visual acuity (BCSVA).

Onset of keratoconus generally occurs during puberty or early adulthood and, if left untreated, patients experience progressive vision impairment.

Corneal ectasia is a complication of refractive surgeries including laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy (PRK). Corneal ectasia is a condition in which the cornea is weakened so that it protrudes under the force of intraocular pressure and bows outward. This results in loss of uncorrected visual acuity and loss of best spectacle corrected visual acuity.

Both keratoconus and corneal ectasia patients may progress to the point of requiring corneal transplantation.

Corneal collagen cross-linking has been demonstrated to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma and stabilizing corneal curvature, thus slowing or stopping the progression of keratoconus and corneal ectasia following refractive surgery. Additional clinical benefits are corneal flattening and improvement in both uncorrected and best spectacle corrected visual acuity.

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 Photrex or Photrex (riboflavin ophthalmic solution). Irradiating the Photrex or Photrex creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient’s cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

The KXL System is used in conjunction with Photrex or Photrex (riboflavin ophthalmic solution) and a Radio Frequency Identification (RFID) activation card. The RFID activation card uniquely identifies the system console and determines the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage (in J/cm²). The software allows treatment only if a valid treatment authorization card has been identified by the RFID reader of the system console.

Software Controlled Aspects of the Device
All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy.

SOFTWARE REVIEW

1. **Level of Concern: Acceptable**
   In Section 1.6.1 entitled Level of Concern, the firm provided the correct determination of the Level Of Concern and included their supporting rationale: MAJOR.

2. **Software Description: Acceptable**
   In Section 1.2 entitled Functional Components of the Device and Section 1.6.2 entitled Software Description, the firm provided an acceptable overview of the device features that are controlled by software, and a description of the intended operational environment, which included information on the programming language and the hardware platform.

3. **Device (including software) Hazard Analysis: Acceptable**
   In Appendix 1.28 entitled FMEA, the firm provided an acceptable description of the hazards presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4. **Software Requirements Specifications (SRS): Acceptable**
   In Appendices 1.10 and 1.11 entitled Software Requirements Specification the firm provided acceptable software requirements specifications, which documented the functional, performance, interface, design and development requirements.

5. **Architecture Design Chart: Acceptable**
   In Appendix 1.12 entitled Architecture Description, the firm provided an acceptable detailed depiction of functional units and software modules.

   In Appendices 1.14 – 1.16 entitled Design Description, the firm provided acceptable design specifications, which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.

7. **Traceability: Acceptable**
   In Appendix 1.17 entitled Traceability Matrices, the firm provided acceptable traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing.

8. **Software Development Environment Description: Acceptable**
   In Appendix 1.18 entitled Software Development Plan, the firm provided an acceptable description of the software development environment, which included a summary of the software life cycle development plan, an annotated list of the control/baseline documents generated during the development process.

9. **Verification and Validation Documentation: Acceptable**
   In Appendices 1.20 – 1.25 entitled Validation, Verification and Testing, the firm provided acceptable unit, integration and system level test protocols, including pass/fail criteria, test reports, summaries and tests results.

10. **Revision Level History: Acceptable**
    In Appendix 1.26 entitled Software Revision History, the firm provided an acceptable revision history log documenting all major changes to the software during its development cycle and the release version numbers.
11. **Unresolved Anomalies (bugs): Acceptable**
   In Appendix 1.27 entitled Bug Listing, the firm provided an acceptable list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors.

12. **Cyber and Information security: Acceptable**
   In the firm’s response to the Agency’s deficiency letter in Agency Request 13, the Cybersecurity issues were adequately addressed.

   The firm stated that they do not use any static analysis tool to detect software run-time errors. Because this section is intended to inform the firm that we are now interested in the use of static analysis tools and to collect data on their current use, this response is Acceptable.

**RECOMMENDATION: APPROVAL**

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.
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/s/

JACQUELYN E SMITH
03/25/2015
LABEL AND LABELING MEMO
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: March 17, 2015
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 203324
Product Name and Strength: Photrea (riboflavin 5'-phosphate ophthalmic solution), 0.146%

Photrea Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%

Rx or OTC: Rx
Applicant/Sponsor Name: Avedro
Submission Date: October 15, 2014
OSE RCM #: 2014-2135
DMEPA Team Leader: Yelena Maslov, PharmD
1 REASON FOR REVIEW
This memo is written to update the recommendations for the labels and labeling for Review #2014-2135 for the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, and carton labeling for Photrexa and Photrexa Viscous, NDA 203324. We are updating our recommendations because Office of Product Quality (OPQ) made a determination regarding the established name and strength of the product and it differs from the established name and strength we used in Review #2014-2135.

2 CONCLUSION & RECOMMENDATIONS
DMEPA concludes that the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, and carton labeling can be improved to increase the readability and prominence of important information on the labels and to reduce the potential for formulation selection errors.

We do not have any recommendations for the prescriber information labeling at this time.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

2.1 RECOMMENDATIONS FOR AVEDRO

A. Photrexa and Photrexa Viscous Syringe Labels

i. There is no sufficient differentiation between the syringe labels for the two products. The only difference is the product names (Photrexa vs. Photrexa Viscous) and small wave-looking graphic above the letter ‘e’ in the root name, Photrexa. Thus, we recommend you provide additional differentiation between the labels to help prevent wrong product selection errors through coloring, boxing, or other means.

ii. If space permits, revise the layout of the proprietary name, established name and strengths to be as follows:

- Photrexa
  (riboflavin 5’-phosphate ophthalmic solution)
  0.146%
  or
- Photrexa Viscous
  (riboflavin 5’-phosphate in 20% dextran ophthalmic solution)
iii. If space permits, add the statement

B. Photrexa and Photrexa Viscous Tyvek® Pouch and Foil Pouch Labeling

i. See A.i, A.ii, and A.iii and revise Tyvek® pouch and foil pouch labeling accordingly.

ii. Your product has not been provided an exception, therefore, we request you add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

C. Photrexa and Photrexa Viscous Carton Labeling

i. Add the product barcode as required per 21CFR 201.25(b)(1)(ii).

ii. Ensure that the proprietary name, established name, and strength statements are the most prominent information on the labeling. We recommend increasing the size of the proprietary name, established name and strength, and significantly decreasing the size of the company name and logo. If additional space is necessary, consider reducing the size of the colored graphics.

- Photrexa
  (riboflavin 5'-phosphate ophthalmic solution)
  0.146%
  or

- Photrexa Viscous
  (riboflavin 5'-phosphate in 20% dextran ophthalmic solution)
  0.146%

iii. Bold the statements to increase the prominence of the route of administration and how the product should be used.

iv. Remove the following confusing statement from the upper right corner “for Administration”. Additionally, remove the duplicate proprietary
name and revise the net quantity statement
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 2 presents relevant product information for Photrexa and Photrexa Viscous that Avedro submitted on October 24, 2014.

<table>
<thead>
<tr>
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APPENDIX B.  N/A

APPENDIX C.  PREVIOUS DMEPA REVIEWS

C.1  Methods
We searched the L:Drive on February 27, 2015 using the terms, riboflavin to identify reviews previously performed by DMEPA.

C.2  Results
Our search identified a proprietary name review OSE RCM# 2014-40632 and 2014-40633\(^1\) completed on January 13, 2015 for Photrex and Photrex Viscous which found the names to be acceptable.

Our search also identified a label, labeling and packaging review OSE RCM# 2013-2338\(^2\) completed on December 19, 2013. We confirmed that our previous recommendations were not implemented.


APPENDIX D. N/A

APPENDIX E. N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis,\(^3\) along with postmarket medication error data, we reviewed the following Photrea and Photrea Viscous labels and labeling submitted by Avedro on October 15, 2014.

- Syringe Labels
- Tyvek\textsuperscript{®} Pouch Labeling
- Foil Pouch Labeling
- Carton Labeling
- Package Insert (no image included)

G.2 Label and Labeling Images

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/s/

YELENA L MASLOV
03/17/2015
LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: March 6, 2015
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 203324
Product Name and Strength: Photorexa (Riboflavin), Ophthalmic Solution
Photorexa Viscous (Riboflavin with 20% Dextran), Ophthalmic Solution
Product Type: Singe Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Avedro
Submission Date: October 15, 2014
OSE RCM #: 2014-2135
DMEPA Primary Reviewer: Rachna Kapoor, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

Reference ID: 3712359
1 REASON FOR REVIEW
This review evaluates the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, carton labeling, and insert labeling for Photrex (Riboflavin) and Photrex Viscous (Riboflavin with 20% Dextran) Ophthalmic Solutions, NDA 203324, for areas of vulnerability and could lead to medication errors.

2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
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<td>FDA Adverse Event Reporting System (FAERS)</td>
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<td>Previous DMEPA Reviews</td>
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<td>Human Factors Study</td>
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<td>ISMP Newsletters</td>
<td>E (N/A)</td>
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<tr>
<td>Other</td>
<td>F (N/A)</td>
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<td>Labels and Labeling</td>
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N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
DMEPA evaluated proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, and carton labeling and we find that it is important to ensure that Photrex is well differentiated from Photrex Viscous due to the use of 20% dextran to add viscosity to Photrex, so that these products are not confused. Although this may be an important issue for this product, it may be even more important for generic products that will not contain a proprietary name to ensure that they are well-differentiated from each other. Thus, we recommend that a statement “Contains Dextran, 20%” should appear on the Photrex Viscous labels and labeling in addition to other differentiation features. Additionally, labels and labeling can be improved to increase the prominence and readability of important information on the label to promote the safe use of the product.
4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, and carton labeling can be improved to increase the readability and prominence of important information on the labels and to reduce the potential for formulation selection errors.

We do not have any recommendations for the prescriber information labeling at this time.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

4.1 RECOMMENDATIONS FOR AVEDRO

A. Photrex and Photrex Viscous Syringe Labels
   i. There is no sufficient differentiation between the syringe labels for the two products. The only difference is the product name (Photrex vs. Photrex Viscous) and the statement “in 20% dextran”. Thus, we recommend you provide additional differentiation between the labels to help prevent wrong product selection errors through coloring, boxing, or other means.

   ii. Revise the strength to be as follows:

       4.38 mg/3 mL

       (1.46 mg/mL)

   iii. If space permits, add the statement

B. Photrex Viscous Syringe Label Only
   i. Add the statement “Contains Dextran, 20%”.

C. Photrex and Photrex Viscous Tyvek® Pouch and Foil Pouch Labeling
   i. See A.i and A.ii and revise Tyvek® pouch and foil pouch labeling accordingly.

   ii. Your product has not been provided an exception, therefore, we request you add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

D. Photrex and Photrex Viscous Tyvek® Pouch Labeling Only
   i. See A.iii and revise Tyvek® pouch labeling accordingly.
E. Photrexa Viscous Tyvek® Pouch and Foil Pouch Labeling Only

i. Under the strength statement, add the statement “Contains Dextran, 20%” that will reinforce the difference between Photrexa and Photrexa Viscous.

F. Photrexa and Photrexa Viscous Carton Labeling

i. Add the product barcode as required per 21CFR 201.25(b)(1)(ii).

ii. Ensure that the proprietary name, established name, and strength statements are the most prominent information on the labeling. We recommend increasing the size of the proprietary name, established name and strength, and significantly decreasing the size of the company name and logo. If additional space is necessary, consider reducing the size of the colored graphics.

iii. The proprietary name, established name, and strength should appear as follows:

   Photrexa or Photrexa Viscous

   Riboflavin or Riboflavin with 20% Dextran

   4.38 mg/3 mL

   (1.46 mg/mL)

   iv. Bold the statements to increase the prominence of the route of administration and how the product should be used.

   v. Remove the following confusing statement from the upper right corner “for Administration”. Additionally, remove the duplicate proprietary name and revise the net quantity statement

G. Photrexa Viscous Carton Labeling Only

i. Add the statement “Contains Dextran, 20%”.

Reference ID: 3712359
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Photrex and Photrex Viscous labels and labeling submitted by Avedro on October 15, 2014.

- Syringe Labels
- Tyvek® Pouch Labeling
- Foil Pouch Labeling
- Carton Labeling
- Package Insert (no image included)

G.2 Label and Labeling Images

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/s/

RACHNA KAPOOR
03/06/2015

YELENA L MASLOV
03/09/2015
CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: March 13, 2014

TO: Jacquelyn Smith, Regulatory Project Manager
    William Boyd, M.D., Medical Officer
    Division of Transplantation and Ophthalmic Products

FROM: Roy Blay, Ph.D.
    Good Clinical Practice Assessment Branch
    Division of Good Clinical Practice Compliance
    Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
    Team Leader
    Good Clinical Practice Assessment Branch
    Division of Good Clinical Practice Compliance
    Office of Scientific Investigations

    Kassa Ayalew, M.D., M.P.H.
    Acting Branch Chief
    Good Clinical Practice Assessment Branch
    Division of Good Clinical Practice Compliance
    Office of Scientific Investigations

SUBJECT: Evaluation of a Clinical Inspection

NDA: NDA 203324

APPLICANT: Avedro, Inc.

DRUG: Riboflavin ophthalmic solution/KXL system

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of corneal ectasia after corneal refractive surgery and/or progressive keratoconus

Reference ID: 3471696
I. BACKGROUND:

The Applicant submitted this NDA to support the use of riboflavin ophthalmic solution/KXL system for the treatment of corneal ectasia after corneal refractive surgery and/or progressive keratoconus.

The pivotal study inspected in support of the indication at Dr. R. Doyle Stulting’s site was UVX-001 entitled “Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Corneal Ectasia or Progressive Keratoconus”

Dr. Stulting’s clinical site was selected for inspection because it enrolled relatively large numbers of subjects and had significant impact on study results. Please note that a large number of subjects discontinued the UXV-001 study prematurely because the investigator (Dr. Stulting) left the site; the study was then terminated by the IRB. The proportion of subjects who discontinued the study was 17% and 56% in the treatment and control groups, respectively.

II. RESULTS (by Site):

<table>
<thead>
<tr>
<th>Name of CI, Location</th>
<th>Protocol #/ Site #/ # of primary eyes</th>
<th>Inspection Dates</th>
<th>Final Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Doyle Stulting, M.D. Woolfson Eye Institute 875 Johnson Ferry Road, Suite 100 Atlanta, GA 30343 At Emory University: Study Coordinator: Kristin West</td>
<td>UVX-001/ Site # 01/ 107 primary eyes</td>
<td>27 Jan – 10 Mar 2013</td>
<td>Pending Preliminary=VAI</td>
</tr>
</tbody>
</table>

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
PENDING = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.
a. **What was inspected:** At this site for Protocol UVX-001, 117 subjects were screened, and 107 subjects were enrolled. Those subjects who were enrolled following Dr. Stulting’s departure from Emory University were terminated prior to their completion of the study. The records of 21 subjects were reviewed, and of these subjects, seven were terminated prior to the 12 month visit. These records were reviewed at Dr. Stulting’s current clinical site, not at Emory University where the study began. The investigation determined that the records at the current site are copies because all original records were retained at Emory. Records reviewed included, but were not necessarily limited to, informed consent forms (ICFs), medical histories, treatment schedules, and adverse events.

b. **General observations/commentary:** Dr. Stulting originally conducted this study as a sponsor-investigator IND and hired as the monitor. Dr. Stulting wrote the protocol, arranged for data analysis, trained the technologists and sub-investigators, obtained monitoring, and submitted documentation to the IRB. Prior to the first subject’s enrollment, the Peschke Group became the sponsor and the single site trial evolved into a multicenter trial with Dr. Stulting serving as the medical monitor. After the first subject was enrolled, the Peschke Group ceased financial support; however the study continued, and, according to Dr. Stulting, “without proper monitoring”. In March 2010, Dr. Stulting retired from Emory University. He requested closure of the study in an amendment submitted to the Agency on June 23, 2010, and also requested closure of the study from the IRB via the same amendment. The IRB withdrew the study based on Dr. Stulting’s failure to close the study prior to leaving Emory. Subsequent communications between Emory and Dr. Stulting have occurred only through legal representation.

A Form FDA 483 was issued to Dr. Stulting at the conclusion of the inspection noting numerous deficiencies. These deficiencies included, but were not limited, to the following:

i. **Lack of adherence to protocol**
   1. Subjects were randomized to the study despite not exhibiting stable refraction, a protocol requirement.
   2. Subject was randomized to the study based on the findings of two nonconsecutive examinations to determine contact lens stability. The protocol required that randomization be based on the results of the two most recent consecutive examinations.
   3. Subjects were treated based on preoperative evaluations that took place more than 30 days prior to treatment despite the protocol requirement that such evaluations take place within 30 days of treatment.
4. Subjects discontinued the use of contact lenses 12 and 6 days prior to the first refraction, respectively. The protocol required the discontinuation of contact lenses two weeks prior to the first refraction.

5. Subject was randomized into the study with an I-S ratio of 0.346 despite an inclusion criterion requiring an I-S ratio of greater than 1.5 diopters.

6. Subject had a randomized eye treated and the fellow eye treated despite the protocol requirement that fellow eye treatment occur within six months of treatment of the randomized eye.

7. The protocol required the instillation of two drops of riboflavin to increase corneal thickness to greater than 400 microns. Of the 21 subjects whose records were reviewed, 12 had the cross-linking procedure performed with the corneal thickness less than 400 microns. The investigator stated that artificial tears were used in place of riboflavin for all treated subjects; however, the protocol was not amended to reflect this change.

ii. Inadequate informed consent

1. Subject signed an ICF with hand-written revisions not previously approved by the IRB.

2. Subject signed an ICF; however, screening procedures had already been performed.

3. Subjects did not provide all required signatures on the ICF.

4. Subject did not date the ICF.

5. Subjects lacked complete ICFs on file.

6. None of the 107 enrolled subjects were re-consented with the updated versions of the ICF.

iii. Inadequate records

Subject lacked a medical history to document a history of keratoconus and progression of the disease.

iv. Inadequate adverse event reporting

Subject attempted suicide twice. These two SAEs were not reported to the IRB by the investigator; however, they were reported to the IRB after Dr. Stulting’s departure.

c. Assessment of data integrity: The FDA field investigator stated that there was no evidence of inaccurate data capture and that the primary efficacy endpoint and other
endpoint data were verifiable. Other than the above observations, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dr. Stulting’s clinical site was inspected in support of this NDA. This site was issued a Form FDA 483. The preliminary classification for this inspection is Voluntary Action Indicated (VAI) based on preliminary communications with the field investigator. The review division may wish to consider whether the deficiencies as described above for this clinical site would have a significant impact on the evaluation of safety or efficacy for this trial. Observations include deviations from protocol, inadequate informed consent, inadequate records, and inadequate adverse event reporting. Otherwise, based on the inspection findings available to date, the study appears to have been conducted adequately, and the data submitted by this site appear acceptable in support of the respective indication.

Note: This preliminary classification is based on communications with the field and documentation available to date. The establishment inspection report (EIR) has not been received from the field and is pending final review. A further inspection summary addendum will be generated upon review of the EIR should conclusions change from the pending classifications stated here.

The review division plans to issue a Complete Response (CR) letter to the sponsor in response to various deficiencies in the application. OSI has provided the division with a written recommendation for inclusion in the letter requesting a reassessment by the sponsor of the monitoring practices at Dr. Stulting’s site.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigation
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
JANICE K POHLMAN
03/14/2014
Entering and signing for Roy Blay and myself

KASSA AYALEW
03/14/2014
Memorandum

Date: March 21, 2014

To: Jacquelyn Smith, M.A., Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Products (OPDP)

Subject: NDA 203324
Riboflavin phosphates ophthalmic solution

OPDP acknowledges receipt of your consult request dated October 16, 2013, for the proposed labeling for Riboflavin phosphates ophthalmic solution. Reference is made to the March 14, 2014 Complete Response letter. For this reason, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DTOP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Christine Corser at Christine.corser@fda.hhs.gov or (301) 796-2653.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE G CORSER
03/21/2014
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 21, 2014

TO: Jacquelyn Smith, Regulatory Project Manager
    William Boyd, M.D., Medical Officer
    Division of Transplantation and Ophthalmic Products

FROM: Roy Blay, Ph.D.
    Good Clinical Practice Assessment Branch
    Division of Good Clinical Practice Compliance
    Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H
    Team Leader
    Good Clinical Practice Assessment Branch
    Division of Good Clinical Practice Compliance
    Office of Scientific Investigations

    Kassa Ayalew, M.D., M.P.H.
    Acting Branch Chief
    Good Clinical Practice Assessment Branch
    Division of Good Clinical Practice Compliance
    Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 203324

APPLICANT: Avedro, Inc.

DRUG: Riboflavin ophthalmic solution/KXL system

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of corneal ectasia after corneal refractive surgery and/or progressive keratoconus
CONSULTATION REQUEST DATE: October 9, 2013
CLINICAL INSPECTION SUMMARY DATE: February 24, 2014
DIVISION ACTION GOAL DATE: March 1, 2014
PDUFA DATE: March 16, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of riboflavin ophthalmic solution/KXL system for the treatment of corneal ectasia after corneal refractive surgery and/or progressive keratoconus.

The pivotal studies are as follows:

UVX-001 entitled “Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Corneal Ectasia or Progressive Keratoconus”, and

UVX-002 entitled “Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Progressive Keratoconus”, and

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

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

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

**Key to Classifications**
- NAI = No deviation from regulations.
- VAI = Deviation(s) from regulations.
- OAI = Significant deviations from regulations. Data unreliable.
- Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.
1. Francis Price, Jr., M.D.
Price Vision Group and Cornea Research Foundation of America
9002 N. Meridian St. Suite 100
Indianapolis, IN 46260

a. What was inspected: At this site for Protocol UVX-002, 32 subjects were screened, 26 subjects were enrolled, and 22 subjects completed the study. For Protocol UVX-003, 25 subjects were screened, 21 subjects were enrolled, and 20 subjects completed the study. The informed consent forms for all subjects for both studies were reviewed. The records of 21 subjects for Protocol UVX-002 were audited. Inclusion and exclusion criteria were reviewed for all subjects. Communications between the clinical investigator, the sponsor, and the IRB were also reviewed. Examination results for screening, sham, sham follow-ups, corneal collagen cross-linking (CXL) and CXL follow-ups were audited. The records of 12 enrolled subjects and two screened, but not enrolled, subjects were reviewed for Protocol UVX-003 with source documentation compared to the data line listings. Review included verification of eligibility, BSCVA, EDTRS, pentacam results for screening, treatment, and all follow-up visits, monitoring and adverse events reports, and drug accountability.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection with a single observation noting that Subjects [redacted] in Protocol UVX-002, and Subject [redacted] in Protocol UVX-003, did not sign the most recently approved version of the informed consent form. The revised version of consent form indicated a change in sponsorship of the study.

c. Assessment of data integrity: This occurrence of failure to obtain the most current version of informed consent would not appear to adversely affect safety and/or efficacy considerations. Other than this single observation, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. David Hardten, M.D., FACS
Minnesota Eye Consultants, P.A.
710 E. 24th St., Suite 100
Minneapolis, MN 55404

a. What was inspected: At this site for Protocol UVX-002, 27 subjects were screened, 16 subjects were enrolled, and 14 subjects completed the study. For Protocol UVX-003, 21 subjects were screened, 15 subjects were enrolled, and 12 subjects completed the study. All subjects signed informed consent forms prior to enrollment in the studies. Source document data were compared with data line listings. Among the records reviewed for each subject included Pentacam printouts showing source measurements including Kmax, source documents for examinations, BCVA charts and results at screening and three months, randomization documentation, adverse event reporting, and protocol deviations.
b. **General observations/commentary**: A Form FDA 483 was issued at the conclusion of the inspection noting that all adverse events (AEs) for Subject were not reported; specifically, three AEs (all rated as mild) including “orange blobs” in VA OS when eye closed, ocular pain following treatment, and flashing lights OS peripherally. Also, there were some discrepancies between source data and line listings as follows:

<table>
<thead>
<tr>
<th>Subject</th>
<th>Source</th>
<th>Line Listing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 month BCVA - 47</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>3 month pupil center - 476</td>
<td>446</td>
</tr>
<tr>
<td></td>
<td>Screening BSCVA - 45</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Screening BSCVA - 19</td>
<td>15</td>
</tr>
</tbody>
</table>

c. **Assessment of data integrity**: The review division may wish to consider whether these additional reported adverse events or data discrepancies would have a significant impact on the evaluation of safety or efficacy for this trial. Otherwise, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Peter Hersh, M.D.
Cornea and Laser Eye Institute
300 Frank W. Burr Blvd., Suite 71
Teaneck, NJ 07666

a. **What was inspected**: At this site for Protocol UVX-002, 63 subjects were screened, 54 subjects were enrolled, and 53 subjects completed the study. For Protocol UVX-003, 37 subjects were screened, 30 subjects were enrolled, and 29 subjects completed the study. All subjects signed informed consent forms prior to enrollment for both studies. The records of 19 of the enrolled subjects were reviewed for Protocol UVX-002 and for 29 subjects for Protocol UVX-003. Selected source documents were compared to the case report forms (CRFs) and line listings. Records reviewed included, but were not limited to, financial disclosure, inclusion/exclusion criteria, IRB, sponsor and monitor correspondence, protocol deviations, delegation of responsibilities, the primary efficacy endpoint, study drug and device accountability, and adverse event reporting.

b. **General observations/commentary**: A Form FDA 483 was not issued at the conclusion of the inspection. An updated Financial Disclosure form reported the receipt by Dr. Hersh of consulting fees and an equity interest in the form of 30,000 shares of stock options from the sponsor.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
4. Eric D. Donnenfeld, M.D.  
Ophthalmic Consultants of Long Island  
2000 North Village Ave., Suite 402  
Rockville Centre, NY 11570

**a. What was inspected:** At this site for Protocol UVX-002, 20 subjects were screened, and 11 subjects enrolled and completed the study. For Protocol UVX-003, 25 subjects were screened, 19 subjects were enrolled, and 18 subjects completed the study. The records of 11 subjects were audited for Protocol UVX-002, and the records of 19 subjects were audited for Protocol UVX-003. The informed consent forms for all subjects enrolled in both studies were reviewed.

Records reviewed for Protocol UVX-002 included, but were not necessarily limited to, inclusion and exclusion criteria, financial disclosure, monitoring communications, adverse event reporting, and primary efficacy data were reviewed for all subjects. Communications between the clinical investigator and the sponsor and IRB were also reviewed. Examination results for screening, sham, sham follow-ups, corneal collagen cross-linking (CXL) and CXL follow-ups were audited.

Records reviewed for Protocol UVX-003 included, but were not limited to, inclusion and exclusion criteria, randomization, protocol deviations, adverse events, eye examinations, primary efficacy data, and test article accountability.

**b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection noting that adverse events were experienced by subjects that were documented in subject source records but not reflected in the sponsor’s data line listings. Specifically, Subject [redacted] in Protocol UVX-002 experienced an epithelial defect in OS while Subjects [redacted] in Protocol UVX-003 experienced epithelial defects in OS and OD, respectively.

The following deviations from Protocols UVX-002 and UVX-003 as documented in the CRFs were not reported to the sponsor:

For Protocol UVX-002

i. For Subject [redacted] on 08/11/08, the fellow eye was not instilled with the riboflavin ophthalmic solution every two minutes for 30 minutes as required by protocol. During the pretreatment period, the 22 minute dose time was 4 minutes after the 20 minute dose time. During the irradiation period, the 26 minute dose time was 3 minutes after the 24 minute dose time; and the 30 minute dose time was 1 minute after the 28 minute dose time.

ii. For Subject [redacted], the fellow eye was treated more than six months after the initial eye: the initial eye was treated [redacted] and the fellow eye treated on
For Protocol UVX-003

i. For Subject (b)(6), during treatment of the treatment and fellow eyes, the riboflavin ophthalmic solution was not instilled in the eye every 2 minutes for 30 minutes as required by protocol. During the pretreatment period (b)(6) the 14 minute dose time was 3 minutes after the 12 minute dose time. During the pretreatment period on 11/19/08, the 20 minute dose time was 3 minutes after the 18 minute dose time. During the irradiation period (b)(6) the 16 minute dose time was 3 minutes after the 14 minute dose time; and the 30 minute dose time was 1 minute after the 28 minute dose time.

ii. For Subject (b)(6) during treatment of the treatment eye, the riboflavin ophthalmic solution was not instilled in the eye every 2 minutes for 30 minutes as required by protocol. During the pretreatment period, the 10 minute dose time was 3 minutes after the 8 minute dose time.

iii. For Subject (b)(6), during treatment of the fellow eye, the riboflavin ophthalmic solution was not instilled in the eye every 2 minutes for 30 minutes as required by protocol. During the irradiation period, the drops were instilled for 27 minutes.

Dr. Donnenfeld, in his written response dated February 7, 2014, stated that because the cornea was purposely abraded as part of treatment, it was not considered to be an adverse event by him. Dr. Donnenfeld further stated that such debridement was typically noted in the Adverse Event Log to capture any instances where wound closure did not occur within one week. As the noted subjects did heal within one week, there was no adverse event to record.

Dr. Donnenfeld acknowledged that Subject (b)(6) did have the fellow eye treated more than six months after the study eye in violation of the protocol and that this deviation was not reported to the IRB. He stated that the staff has been reeducated on the need to report such deviations to the IRB.

Dr. Donnenfeld acknowledged that the times of eye drop instillation were not always recorded for the four subjects described above; however, after review of the treatment process with his staff, he noted the staff’s response that subjects did receive the eye drops in a timely manner.

Dr. Donnenfeld reiterated that his site strives for adherence to all study procedures and regulatory guidelines and that redundant measures are in place to assure quality data recording and timely reporting of protocol deviations.

c. Assessment of data integrity: The review division may wish to consider whether the failure to report epithelial defects and protocol deviations as described above would have a significant impact on the evaluation of safety or efficacy for this trial. Otherwise, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
5. Avedro, Inc.
230 Third Avenue
Waltham, MA 02451

a. **What was inspected:** The sponsor’s responsibilities with regards to the conduct of Protocols UVX-002 and UVX-003 were inspected. The inspection included a review of the progress of the studies from the original sponsor, Peschke Meditrade with its accompanying CRO, to the transfer of responsibilities to the current sponsor, Avedro, with the involvement of its CRO. Multiple key vendors were identified by Avedro as being responsible for development of electronic case report forms (eCRFs), database design and management, data management, and biostatistics.

The inspection included, but was not limited to, review of adverse event documentation practices, the use of eCRFs and accompanying audit trails, data entry and management, safety monitoring activities, documentation of training requirements for data entry staff and monitors, CRO correspondence, and investigational device calibration records.

b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection noting that there were numerous instances where there were no Monitoring Visit reports or documentation of review by Avedro for initial and interim monitoring visits (IMVs) as required by the Study Monitoring Plan or Study Data Entry Plan: three examples were noted at Dr. Stulting’s site, 11 examples at Dr. Donnenfeld’s site, 12 examples at Dr. Hersh’s site, 10 examples at Dr. Price’s site, and 12 examples at Dr. Hardten’s site. Most of these examples of missing documentation occurred between the time that Avedro terminated its contract monitoring data entry arrangements with its CRO and the time that Avedro resumed these activities in-house. At the time of inspection, Avedro noted that 97% of all study visits had been completed and that they re-monitored 100% of the study data and ensured appropriate reporting of adverse events.

c. **Assessment of data integrity:** The review division may wish to consider whether these protocol deviations as described above would have a significant impact on the evaluation of safety or efficacy for this trial. While these monitoring issues were noted at the sponsor’s site, there is no indication to date that these issues adversely affected the collection of safety and efficacy data. Otherwise, the studies appear to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication.

6. R. Doyle Stulting, M.D.
Current contact information:
Woolfson Eye Institute

Inspection is ongoing at this time.
III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Price, Hardten, Hersh, and Donnenfeld were inspected in support of this NDA. Inspection of Dr. Stulting’s clinical investigator site is ongoing. In addition, a sponsor inspection of Avedro, Inc., was also conducted. Drs. Price, Hardten, and Donnenfeld, and the sponsor were issued Form FDA 483s. The preliminary classification for all of these inspections is Voluntary Action Indicated (VAI) based on preliminary communications with the field investigators. The review division may wish to consider whether the deficiencies as described above for each of the clinical sites would have a significant impact on the evaluation of safety or efficacy for this trial. Observations were made regarding missing monitoring reports or documentation of review of those reports at the sponsor; however, there does not appear to have been an impact on collection of efficacy or safety data at the clinical sites. Otherwise, based on the inspection findings available at this time, the studies appear to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication.

Note: Preliminary classifications are based on communications with the field and documentation available to date. The establishment inspection reports (EIRs) have not been received from the field and are pending final review. An inspection summary addendum will be generated when the report from Dr. Stulting’s inspection becomes available and will be updated if conclusions change from the pending classifications stated here upon review of the submitted reports.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Reference ID: 3459151
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROY A BLAY
02/22/2014

JANICE K POHLMAN
02/22/2014

KASSA AYALEW
02/22/2014
Label, Labeling and Packaging Review

Date: December 19, 2013
Reviewer: Aleksander Winiarski, PharmD
Division of Medication Error Prevention and Analysis
Acting Team Leader: Morgan Walter, PharmD, MBA
Division of Medication Error Prevention and Analysis
Drug Name and Strength: Riboflavin Ophthalmic Solution and Dextran 20%,
Riboflavin Ophthalmic Solution
Application Type/Number: NDA 203324
Applicant/sponsor: Avedro
OSE RCM #: 2013-2338

*** This document contains proprietary and confidential information that should not be released to the public.***
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1 INTRODUCTION
This review evaluates the proposed container label, carton, and insert labeling for Riboflavin Ophthalmic Solutions, NDA 203324 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY
NDA 203324 was resubmitted on September 16, 2013 after receiving a refusal to file decision from the Agency on May 4, 2013 citing chemistry, manufacturing and control (CMC) deficiencies, and required English translation of submitted publications.

1.2 PRODUCT INFORMATION
The following product information is provided in the September 16, 2013 submission:

- Active Ingredient:
- Indication of Use:
- Route of Administration: Ophthalmic
- Dosage Form: Solution
- Strength:
- Dose and Frequency:
- How Supplied: 3 mL glass syringe
- Storage:

Reference ID: 3425344
• Container and Closure systems: Each carton contains a bulk pack of 10 syringes, in single-use foil pouches. Each foil pouch contains a 3 mL glass syringe of Riboflavin/Dextran or Riboflavin contained within a Tyvek® pouch.

2 METHODS AND MATERIALS REVIEWED
DMEPA reviewed the labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING
Using the principles of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Syringe Labels submitted September 16, 2013 (Appendix B)
- Tyvek Pouch Labeling submitted September 16, 2013 (Appendix C)
- Foil Pouch Labeling submitted September 16, 2013 (Appendix D)
- Carton Labeling submitted September 16, 2013 (Appendix E)
- Syringe sample provided on December 11, 2013 (No image)
- Insert Labeling submitted September 16, 2013

3 MEDICATION ERROR RISK ASSESSMENT
The following sections describe the results and our risk assessment of Riboflavin/Dextran and Ribovlavin product design as well as the associated label and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT
We note that the two formulations are packaged in separate bulk cartons each containing 10 single use syringes. This presents a challenge as the use of one of the products may be inadvertently omitted during the process. Conversely storing the syringes together may present a potential for wrong formulation selection errors due to identical packaging and product design. During meetings with the Division DMEPA raised this potential issue and stated that the current packaging configuration may present a risk of wrong selection errors, especially because the packaging for both formulations is identical and because each formulation may only differ with the presentation of the approved proprietary name and established name (with Dextran vs. without). The Deputy Director acknowledged the potential for these errors, but was not concerned with the packaging configuration and stated that both formulations will not always be used during the procedure, therefore he concluded that separate packaging is appropriate. Additionally, he acknowledged DMEPA’s question regarding any safety concerns in the event that each formulation would be confused for the other and stated that there is no safety concern with the resulting potential wrong formulation selection error.

Therefore, DMEPA acknowledges that although there is risk for formulation selection errors to occur, these errors do not pose a safety risk and thus appropriate labeling changes to differentiate the formulations can be used to minimize the potential for medication errors to occur. For example, the Riboflavin solution (without Dextran) is only used at one step in the procedure, therefore a prominent statement on the labeling identifying the intended step in the product use process may help to minimize wrong formulation selection.

However the risk may be minimized with appropriate labeling which states the correct route and site of administration that is “for topical ophthalmic use only”.

We note that the proposed syringe cap color (gray) is inconsistent with the American Academy of Ophthalmology’s (AAO) policy statement “Color Code for Topical Ocular Medications” which recommends the uniform use of a color-coding system for the caps and labels of topical ocular medications.

Additionally, the container label and carton labeling colors are orange and green for each of the formulation which is also inconsistent with AAO’s policy.

We acknowledge that color schemes should differentiate the product packaging but should not be inconsistent with the AAO color code assignments.

Additionally we note that the presentation of the Dosage and Administration information in the insert labeling may lead to confusion and we propose that it is reorganized either into a bulleted, numbered, or table format which will clarify each step in the use process.

We provide additional recommendations in sections 5.1 and 5.2 to further improve clarity of important prescribing information, and readability of labels and labeling.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the labels and to reduce the potential for formulation selection errors.

5 RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

Based on this review, DMEPA provides the following comments for the Division’s consideration:

A. General – use of the proprietary name in the insert labeling

1. The proprietary names Photrex and Photrex are undergoing a proprietary name review and have not yet been approved. Therefore, we suggest using the terms “Tradename1” and “Tradename2” as place holders in the insert labeling until the Applicant receives approval for their proprietary names.
B. Dosage and Administration Section of the Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI).

1. The presentation of the dosing information is difficult to follow and may lead to confusion in the current paragraph format. Consider re-organizing the presentation of the Dosage and Administration information either into a bulleted, numbered, or table format which will clarify each step in the use process. Similar to:

C. Syringe Cap Color

1. The proposed syringe cap color (gray) is inconsistent with the American Academy of Ophthalmology’s (AAO) color code. Grey color has been assigned to non-steroidal anti-inflammatory products. Please consider referring the Applicant to AAO’s policy on the “Color Code for Topical Ocular Medications”\(^2\).

5.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General – All Labels and Labeling

1. Do not use the proposed proprietary names on your labels and labeling until your receive an approval from the Agency. Until you receive an approval for your proprietary names, you may use the terms "Tradename1" and "Tradename2" as placeholders for placement and editing purposes.

2. The colors used in the submitted packaging, orange or green for each of the formulations, are inconsistent with American Academy of Ophthalmology’s (AAO) policy statement, “Color Code for Topical Ocular Medications”\(^3\). Revise the colors to ensure that packaging between the formulations is appropriately differentiated; however ensure that the selected colors are not in contradiction with the AAO’s policy statement.

B. Riboflavin/Dextran Syringe Labels

1. Ensure that the proprietary name, established name, and strength statements are the most prominent information on the label. Due to limited space on the syringe label include only the minimum requirements as per small label rules in 21CFR 201.10(i) such as the proprietary name, established name, strength, lot/expiration, and name of the manufacturer, parker, or distributor of the drug to appear similar to:

<table>
<thead>
<tr>
<th>Proprietary name</th>
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</thead>
<tbody>
<tr>
<td>Established name</td>
</tr>
<tr>
<td>xx %</td>
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</tbody>
</table>

   Avedro inc.
   Lot: Exp:

C. Riboflavin Syringe Labels

1. See B1 above.

D. Riboflavin/Dextran Tyvek Pouch and Foil Pouch Labeling

1. According to the submitted description of the container closure system the dimensions of the Tyvek Pouch are 3” x 11.5” and the Foil pouch are 5”x10”. However, the dimensions of the submitted labeling for both pouches are 63 mm x 30 mm. To improve readability, increase the size of the labeling to closer match the sizes of the pouch containers.

2. Revise the presentation of the proprietary name, established name, and strength statement to appear in the customary order as in B1 above. Additionally, relocate the net quantity statement (3 mL) to the bottom portion of the label, away from the strength statement.

---

3. To reduce clutter, consider removing the statements (0-6)
   List the inactive ingredients of the solution on the side of the panel, as appropriate.

4. Relocate the storage information and usual dosage statements to above the lot number and minimize their size.

5. Remove (0-6) as those are not customary on U.S. labels and labeling and create clutter.

6. Your product has not been provided an exception, therefore we request you add the product barcode to each individual labeling as required per 21CFR 201.25(b)(1)(ii).

7. Revise the statements (0-6) and bold this statement.

E. Riboflavin Tyvek Pouch and Foil Pouch Labeling
1. See D1 through D7 above.

2. Riboflavin (without dextran) formulation, under the strength statement add and bold a statement that will prompt the user to use this formulation in the appropriate step during the procedure, similar to: For use when measured corneal thickness is less than 400 microns.

F. Riboflavin/Dextran Carton Labeling
1. Revise the presentation of the proprietary name, established name, and strength statement to appear in the customary order as in B1 above.

2. Ensure that the proprietary name, established name and strength are the most prominent information on the label by increasing their size, and significantly decreasing the size of the company logo. If additional space is necessary consider reducing the size of the colored graphics.

3. Add the product barcode as required per 21CFR 201.25(b)(1)(ii).

4. Remove the following confusing statement from the upper right corner “for Administration”. Additionally remove the duplicate proprietary name and revise the net quantity statement (0-6).

5. Remove (0-6) as that is not customary information on US labeling.

6. See D7 above.

G. Riboflavin Carton Labeling
1. See D7, E2 and F1 though F5.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.
APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEKSANDER P WINIARSKI
12/19/2013

MORGAN A WALKER
12/19/2013
# RPM FILING REVIEW
(Including Memo of Filing Meeting)
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

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<th>Application Information</th>
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<tr>
<td><strong>NDA # 203324</strong></td>
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<tr>
<td><strong>BLA#</strong></td>
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<tr>
<td><strong>NDA Supplement #</strong>:S-</td>
</tr>
<tr>
<td><strong>BLA Supplement #</strong></td>
</tr>
<tr>
<td><strong>Efficacy Supplement Type SE-</strong></td>
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</tbody>
</table>

**Proprietary Name**: Photrex and Photrexa

**Establish/Prop Name**: riboflavin

**Dosage Form**: ophthalmic solution

**Strengths**: 20% dextran and 0% dextran

**Applicant**: Avedro, Inc.

**Agent for Applicant (if applicable)**: N/A

**Date of Application**: September 16, 2013

**Date of Receipt**: September 16, 2013

**Date clock started after UN**: N/A

**PDUFA Goal Date**: March 16, 2014

**Action Goal Date (if different)**: N/A

**Filing Date**: November 15, 2013

**Date of Filing Meeting**: October 15, 2013

**Chemical Classification**: (1,2,3 etc.) (original NDAs only)

**Proposed indication(s)/Proposed change(s)**

**Type of Original NDA**

AND (if applicable)

**Type of NDA Supplement**

- [ ] 505(b)(1)
- [x] 505(b)(2)
- [ ] 505(b)(1)
- [ ] 505(b)(2)

**Review Classification**

- [ ] Standard
- [ ] Priority
- [ ] Tropical Disease Priority Review Voucher submitted

**Resubmission after withdrawal?** [ ]

**Resubmission after refuse to file?** [x]

**Part 3 Combination Product?** [x]

- [ ] Convenience kit/Co-package
- [ ] Pre-filled drug delivery device/system (syringe, patch, etc.)
- [ ] Pre-filled biologic delivery device/system (syringe, patch, etc.)
- [ ] Device coated/impregnated/combined with drug
- [ ] Device coated/impregnated/combined with biologic
- [ ] Separate products requiring cross-labeling
- [ ] Drug/Biologic
- [ ] Possible combination based on cross-labeling of separate products
- [x] Other (drug/device/biological product)

Version: 5/10/13

Reference ID: 3418741
## Collaborative Review Division (if OTC product): N/A

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<td>Are the proprietary, established/proper, and applicant names correct in tracking system?</td>
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<td>Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov/CDER/Offices/BusinessProcessSupport/resm163969.html">http://inside.fda.gov/CDER/Offices/BusinessProcessSupport/resm163969.html</a></td>
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### Application Integrity Policy

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<td>If yes, explain in comment column.</td>
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### User Fees

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<tr>
<td>Is Form 3397 (User Fee Cover Sheet) included with authorized signature?</td>
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</table>

Version: 5/10/13
Reference ID: 3418741
User Fee Status

If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.

Payment for this application:

☐ Paid
☑ Exempt (orphan, government)
☐ Waived (e.g., small business, public health)
☐ Not required

If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.

Payment of other user fees:

☐ Not in arrears
☑ In arrears

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<td>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</td>
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<td>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</td>
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<td>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></td>
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<td>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</td>
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Exclusivity

Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: [http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm](http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm)

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</table>

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Reference ID: 3418741
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  

| X |

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)

| X |

If yes, # years requested:

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?  

| X |

If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?

| X |

If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.

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If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

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| If electronic submission, does it follow the eCTD guidance? 
| If not, explain (e.g., waiver granted). |
| Index: Does the submission contain an accurate comprehensive index? |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: |

| X |


Version: 5/10/13

Reference ID: 3418741
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<td>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</td>
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<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
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<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
<td>X</td>
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- Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].
- Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.

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<th>Clinical Trials Database</th>
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<td>Is form FDA 3674 included with authorized signature?</td>
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- If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”
If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant.

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Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].

Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge…”

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Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR).

If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.

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If yes, date consult sent to the Controlled Substance Staff:

For non-NMEs: Date of consult sent to Controlled Substance Staff:

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<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREA</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Does the application trigger PREA?

If yes, notify PeRC RPM (PeRC meeting is required)²

Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.

² [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm)
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</td>
<td>X</td>
</tr>
<tr>
<td>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</td>
<td>X</td>
</tr>
<tr>
<td>If no, request in 74-day letter</td>
<td></td>
</tr>
<tr>
<td>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</td>
<td>X</td>
</tr>
<tr>
<td>If no, request in 74-day letter</td>
<td></td>
</tr>
<tr>
<td>BPCA (NDAs/NDA efficacy supplements only):</td>
<td>X</td>
</tr>
<tr>
<td>Is this submission a complete response to a pediatric Written Request?</td>
<td></td>
</tr>
<tr>
<td>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name</td>
<td>YES</td>
</tr>
<tr>
<td>Is a proposed proprietary name submitted?</td>
<td>X</td>
</tr>
<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</td>
<td></td>
</tr>
<tr>
<td>REMS</td>
<td>YES</td>
</tr>
<tr>
<td>Is a REMS submitted?</td>
<td>X</td>
</tr>
<tr>
<td>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</td>
<td></td>
</tr>
<tr>
<td>Prescription Labeling</td>
<td>NOT APPLICABLE</td>
</tr>
<tr>
<td>Check all types of labeling submitted.</td>
<td></td>
</tr>
<tr>
<td>Package Insert (PI)</td>
<td></td>
</tr>
<tr>
<td>Patient Package Insert (PPI)</td>
<td></td>
</tr>
<tr>
<td>Instructions for Use (IFU)</td>
<td></td>
</tr>
<tr>
<td>Medication Guide (MedGuide)</td>
<td></td>
</tr>
<tr>
<td>Carton labels</td>
<td></td>
</tr>
<tr>
<td>Immediate container labels</td>
<td></td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
</tr>
<tr>
<td>Is Electronic Content of Labeling (COL) submitted in SPL format?</td>
<td>X</td>
</tr>
<tr>
<td>If no, request applicant to submit SPL before the filing date.</td>
<td></td>
</tr>
<tr>
<td>Is the PI submitted in PLR format?</td>
<td>X</td>
</tr>
</tbody>
</table>

3 http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm


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Reference ID: 3418741
<table>
<thead>
<tr>
<th>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? <strong>If requested before application was submitted</strong>, what is the status of the request?</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
</tr>
<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</td>
</tr>
<tr>
<td>All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?</td>
</tr>
<tr>
<td>X</td>
</tr>
<tr>
<td>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)</td>
</tr>
<tr>
<td>X</td>
</tr>
<tr>
<td>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?</td>
</tr>
<tr>
<td>X</td>
</tr>
</tbody>
</table>

**OTC Labeling**

- Check all types of labeling submitted.

<table>
<thead>
<tr>
<th>OUTER CARTON LABEL</th>
<th>IMMEDIATE CONTAINER LABEL</th>
<th>BLISTER CARD</th>
<th>BLISTER BACKING LABEL</th>
<th>CONSUMER INFORMATION LEAFLET (CIL)</th>
<th>PHYSICIAN SAMPLE</th>
<th>CONSUMER SAMPLE</th>
<th>OTHER (SPECIFY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

If no, request in 74-day letter.

Are annotated specifications submitted for all stock keeping units (SKUs)?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

If no, request in 74-day letter.

If representative labeling is submitted, are all represented SKUs defined?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

If no, request in 74-day letter.

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Other Consults**

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Meeting Minutes/SPAs**

If yes, specify consult(s) and date(s) sent:

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-of Phase 2 meeting(s)?</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Date(s): 12/7/11

If yes, distribute minutes before filing meeting
<table>
<thead>
<tr>
<th>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date(s): 2/28/13</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, distribute minutes before filing meeting</strong></td>
<td></td>
</tr>
<tr>
<td>Any Special Protocol Assessments (SPAs)?</td>
<td>X</td>
</tr>
<tr>
<td>Date(s):</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, distribute letter and/or relevant minutes before filing meeting</strong></td>
<td></td>
</tr>
</tbody>
</table>
ATTACHMENT

MEMO OF FILING MEETING

DATE: October 15, 2013

BLA/NDA/Supp #: 203324

PROPRIETARY NAME: Photrex and Photrexa

ESTABLISHED/PROPER NAME: riboflavin

DOSAGE FORM/STRENGTH: ophthalmic solution

APPLICANT: Avedro, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: Avedro submitted this NDA on September 16, 2013, and it was received electronically on September 16, 2013. It is a priority review.

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM:</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Jacquelyn Smith</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPMS/TL:</td>
<td></td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>William Boyd</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer:</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>William Boyd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>William Boyd</td>
<td></td>
</tr>
<tr>
<td>Social Scientist Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OTC Labeling Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Clinical Microbiology (for antimicrobial products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td>Review Area</td>
<td>Reviewer</td>
<td>TL:</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Gerlie Gieser</td>
<td>Y</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Dongliang Zhuang</td>
<td>Y</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Maria Rivera</td>
<td>Y</td>
</tr>
<tr>
<td>Statistics (carcinogenicity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenicity (assay/assay validation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Quality (CMC)</td>
<td>George Lunn</td>
<td>Y</td>
</tr>
<tr>
<td>Quality Microbiology (for sterile products)</td>
<td>Denise Miller</td>
<td>Y</td>
</tr>
<tr>
<td>CMC Labeling Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility Review/Inspection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC/OSI/DSC/PMSB (REMS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FILING MEETING DISCUSSION:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### GENERAL
- **505(b)(2) filing issues:**
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
  - **YES □ NO**
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?
  - **YES □ NO**

Describe the scientific bridge (e.g., BA/BE studies):

- **Per reviewers, are all parts in English or English translation?**
  - **YES □ NO**
  - If **no**, explain:

- **Electronic Submission comments**
  - **Not Applicable**

  **List comments:**

### CLINICAL
- **Not Applicable**
- **FILE**
- **REFUSE TO FILE**

**Comments:**
- Review issues for 74-day letter

- **Clinical study site(s) inspections(s) needed?**
  - **YES □ NO**
  - If **no**, explain: The application contains no clinical
It is a 505(b)(2) and references NDA 018604, NDA 021478, NDA 018828, NDA 019909, NDA 020089, NDA 018603 and published literature.

- **Advisory Committee Meeting needed?**
  - Yes
  - No
  - To be determined

  **Comments:**

  *If no, for an NME NDA or original BLA, include the reason.* For example:
  - This drug/biologic is not the first in its class
  - The clinical study design was acceptable
  - The application did not raise significant safety or efficacy issues
  - The application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease

- **Abuse Liability/Potential**
  - Not Applicable
  - FILE
  - REFUSE TO FILE

  **Comments:**

  **If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?**

  **Comments:**

  **CLINICAL MICROBIOLOGY**
  - Not Applicable
  - FILE
  - REFUSE TO FILE

  **Comments:**

  **CLINICAL PHARMACOLOGY**
  - Not Applicable
  - FILE
  - REFUSE TO FILE

  **Comments:**

  **Clinical pharmacology study site(s) inspections(s) needed?**
  - Yes
  - No

  **BIOSTATISTICS**
  - Not Applicable
<table>
<thead>
<tr>
<th>Comments:</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</strong></td>
<td><strong>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</strong></td>
</tr>
<tr>
<td>□ Not Applicable</td>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>□ FILE</td>
<td>□ FILE</td>
</tr>
<tr>
<td>□ REFUSE TO FILE</td>
<td>□ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
<td>□ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td>Comments:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</strong></td>
<td><strong>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</strong></td>
</tr>
<tr>
<td>□ Not Applicable</td>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>□ FILE</td>
<td>□ FILE</td>
</tr>
<tr>
<td>□ REFUSE TO FILE</td>
<td>□ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
<td>□ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td>Comments:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRODUCT QUALITY (CMC)</strong></td>
<td><strong>PRODUCT QUALITY (CMC)</strong></td>
</tr>
<tr>
<td>□ Not Applicable</td>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>□ FILE</td>
<td>□ FILE</td>
</tr>
<tr>
<td>□ REFUSE TO FILE</td>
<td>□ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
<td>□ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td>Comments:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental Assessment</strong></td>
<td><strong>Environmental Assessment</strong></td>
</tr>
<tr>
<td>• Categorical exclusion for environmental assessment (EA) requested?</td>
<td>• Categorical exclusion for environmental assessment (EA) requested?</td>
</tr>
<tr>
<td>□ YES</td>
<td>□ YES</td>
</tr>
<tr>
<td>□ NO</td>
<td>□ NO</td>
</tr>
<tr>
<td>If no, was a complete EA submitted?</td>
<td>If no, was a complete EA submitted?</td>
</tr>
<tr>
<td>□ YES</td>
<td>□ YES</td>
</tr>
<tr>
<td>□ NO</td>
<td>□ NO</td>
</tr>
<tr>
<td>If EA submitted, consulted to EA officer (OPS)?</td>
<td>If EA submitted, consulted to EA officer (OPS)?</td>
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<tr>
<td>□ YES</td>
<td>□ YES</td>
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<tr>
<td>□ NO</td>
<td>□ NO</td>
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<tr>
<td>Comments:</td>
<td>Comments:</td>
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</table>

<table>
<thead>
<tr>
<th>COMMENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality Microbiology (for sterile products)</strong></td>
<td><strong>Quality Microbiology (for sterile products)</strong></td>
</tr>
<tr>
<td>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</td>
<td>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</td>
</tr>
<tr>
<td>□ Not Applicable</td>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>□ YES</td>
<td>□ YES</td>
</tr>
<tr>
<td>□ NO</td>
<td>□ NO</td>
</tr>
<tr>
<td>Comments:</td>
<td>Comments:</td>
</tr>
</tbody>
</table>
**Facility Inspection**

- Establishment(s) ready for inspection?
  - Yes
  - No

- Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?
  - Yes
  - No

**Facility/Microbiology Review (BLAs only)**

- Not Applicable
- File
- Refuse to file

**CMC Labeling Review**

**APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)**

- Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?
  - Yes
  - No

- If so, were the late submission components all submitted within 30 days?
  - Yes
  - No

- What late submission components, if any, arrived after 30 days?

- Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?
  - Yes
  - No
<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a comprehensive and readily located list of all clinical sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>included or referenced in the application?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a comprehensive and readily located list of all manufacturing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>facilities included or referenced in the application?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Renata Albrecht, M.D.

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V):

**21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

<table>
<thead>
<tr>
<th>REGULATORY CONCLUSIONS/DEFICIENCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒ The application is unsuitable for filing. Explain why:</td>
</tr>
<tr>
<td>☒ The application, on its face, appears to be suitable for filing.</td>
</tr>
</tbody>
</table>

**Review Issues:**

- ☒ No review issues have been identified for the 74-day letter.
- ☐ Review issues have been identified for the 74-day letter. List (optional):

**Review Classification:**

- ☐ Standard Review
- ☒ Priority Review

**ACTIONS ITEMS**

- ☒ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
- ☐ If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
- ☐ If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- ☐ BLA/BLA supplements: If filed, send 60-day filing letter

*Version: 5/10/13*

*Reference ID: 3418741*
<table>
<thead>
<tr>
<th>Task</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>If priority review:</td>
<td></td>
</tr>
<tr>
<td>- notify sponsor in writing by day 60 (For BLAs/BLA supplements:</td>
<td></td>
</tr>
<tr>
<td>include in 60-day filing letter; For NDAs/NDA supplements:</td>
<td></td>
</tr>
<tr>
<td>see CST for choices)</td>
<td></td>
</tr>
<tr>
<td>- notify OMPQ (so facility inspections can be scheduled earlier)</td>
<td></td>
</tr>
<tr>
<td>Send review issues/no review issues by day 74</td>
<td></td>
</tr>
<tr>
<td>Conduct a PLR format labeling review and include labeling issues</td>
<td></td>
</tr>
<tr>
<td>in the 74-day letter</td>
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<td>Update the PDUFA V DARRTS page (for NME NDAs in the Program)</td>
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<td>BLA/BLA supplements: Send the Product Information Sheet to the</td>
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<td>product reviewer and the Facility Information Sheet to the</td>
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<td>facility reviewer for completion. Ensure that the completed</td>
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<td>forms are forwarded to the CDER RMS-BLA Superuser for data entry</td>
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<td>into RMS-BLA one month prior to taking an action [These sheets</td>
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<td>may be found in the CST eRoom at:</td>
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<td><a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0</a></td>
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Reference ID: 3418741
Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

1. it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
2. it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
3. it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean any reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

1. The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
2. No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
3. All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely...
for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
12/06/2013