

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

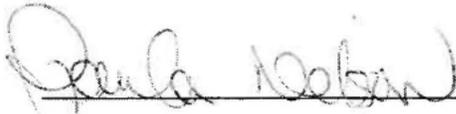
203324Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3. Administrative Information

PATENT CERTIFICATIONS

In the opinion and to the best knowledge of Avedro, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.



Pamela Nelson
Vice President, Regulatory Affairs



Date

1.3. Administrative Information

2. FIELD COPY CERTIFICATION

Avedro hereby certifies that the following FDA district office has been notified in writing that the electronic archival copy of NDA 203324 (Sequence 0007) for corneal collagen cross-linking can be accessed through the FDA network for the field copy technical sections described in 21 CFR 314.50 (1)(3):

New England District Office
One Montvale Ave, 4th Floor
Stoneham, MA 02180

Please find attached a copy of the written notification, dated 16 September 2013.



Pamela Nelson
Vice President, Regulatory Affairs

9/16/13
Date

EXCLUSIVITY SUMMARY

NDA # 203324/Original 1

SUPPL #

HFD #

Trade Name Photrexa Viscous, Photrexa and the KXL System

Generic Name riboflavin

Applicant Name Avedro, Inc.

Approval Date, If Known April 15, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

Please note: The applicant has Orphan Designation for the indication of keratoconus; therefore they will get 7 years exclusivity.

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?
YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 010415 Flamotide Injection
NDA# 009515 Hyrye Injection
NDA# 008036 Riboflavin

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 – UVX-001

Investigation #2 – UVX-002

Investigation #3 – UVX-003

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 078933 YES NO
! Explain:
The applicant's predecessor in interest (Peschke Meditrade) provided substantial support for the study

Investigation #2
IND # 077882 YES NO
! Explain:
The applicant's predecessor in interest (Peschke Meditrade) provided substantial support for the study

Investigation #3
IND # 077882 YES NO
! Explain:

The applicant's predecessor in interest (Peschke Meditrade) provided substantial support for the study

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:
The applicant's predecessor in interest (Peschke Meditrade) provided substantial support for the study. Peschke Meditrade sold the data and rights to UVX-001, UVX-002 and UVX-003 to Avedro in May 2010. Sponsorship of IND 77,882 was transferred to Avedro, Inc. on May 7, 2010.

Investigation #2 !
!
YES ! NO
Explain: ! Explain:
The applicant's predecessor in interest (Peschke Meditrade) provided substantial support for the study. Peschke Meditrade sold the data and rights to UVX-001, UVX-002 and UVX-003 to Avedro in May 2010.

Investigation #3 !
!
YES ! NO
Explain: ! Explain:
The applicant's predecessor in interest (Peschke Meditrade) provided substantial support for the

study. Peschke Meditrade sold the data and rights to UVX-001, UVX-002 and UVX-003 to Avedro in May 2010.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Jacquelyn Smith
Title: Senior Regulatory Project Manager
Date: June 21, 2016

Name of Office/Division Director signing form: Renata Albrecht
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

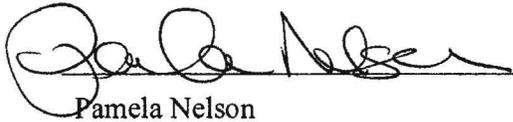
JACQUELYN E SMITH
06/21/2016

RENATA ALBRECHT
06/21/2016

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Avedro, Inc. 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.



Pamela Nelson

Vice President, Regulatory Affairs

11 / 8 / 11

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203324/ Original 1 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Photrexa Viscous, Photrexa Established/Proper Name: riboflavin Dosage Form: ophthalmic solution Device: KXL System		Applicant: Avedro, Inc. Agent for Applicant (if applicable):
RPM: Jacquelyn Smith		Division: Division of Transplant and Ophthalmology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input checked="" type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 15, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None RTF/May 4, 2012; CR/March 14, 2014; CR; /March 29, 2015

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input checked="" type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR/ March 29, 2015; CR/March 14, 2014; RTF/May 4, 2012;
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4/11/16
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	RS/ 10/16/15; RS/ 9/29/14; 9/16/13
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4/13/16
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	RS/ 10/16/15; RS/ 9/29/14; 9/16/13
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	4/13/16
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	2/2/16 1/29/16
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 4/8/16; 3/17/15; 3/9/15 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) <input checked="" type="checkbox"/> SEALD 2/23/15 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁵/Memo of Filing Meeting) (<i>indicate date of each review</i>) 	12/6/13
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) 3/29/16
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 4/27/16
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing (indicate date of mtg)	<input type="checkbox"/> No mtg 3/20/15
• If not the first review cycle, any end-of-review meeting (indicate date of mtg)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (indicate date of mtg)	<input type="checkbox"/> No mtg
• EOP2 meeting (indicate date of mtg)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	2/24/15
• 48-hour alert or minutes, if available (do not include transcript)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (indicate date for each review)	<input type="checkbox"/> None
Division Director Summary Review (indicate date for each review)	<input type="checkbox"/> None 4/15/16; 3/29/15; 3/14/14
Deputy Division Director Review (indicate date for each review)	<input type="checkbox"/> None 3/7/14
Cross-Discipline Team Leader Review (indicate date for each review)	<input type="checkbox"/> None 4/15/16; 3/27/15; 3/10/14
PMR/PMC Development Templates (indicate total number)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	
• Clinical review(s) (indicate date for each review)	4/15/16; 3/24/15; 3/7/14
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	Clinical review/ 3/7/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 3/27/15; 3/14/14; 2/22/14
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/10/16; 3/15/15
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/12/15; 2/28/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 1/17/14
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/26/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 4/13/16; 3/5/15; 2/20/14
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	<input type="checkbox"/> Not needed 2/18/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review) Division of Ophthalmic ENT Devices	<input type="checkbox"/> None 2/18/16; 1/11/16; 3/27/15 (6); 3/26/15 (2); 3/24/15 (6); 2/1/16; 2/10/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	4/13/16; 3/5/15; 2/20/14 (included in OPQ reviews)
<input checked="" type="checkbox"/> Review & FONSI (indicate date of review)	4/13/16; 3/5/15; 2/20/14 (included in OPQ reviews)
<input checked="" type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	4/13/16; 3/5/15; 2/20/14 (included in OPQ reviews)
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: 4/11/16 (see 4/13/16 OPQ review) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

MEMORANDUM OF TELECONFERENCE

Meeting Date: September 9, 2015

Application Number: NDA 203324

Product Name: Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System

Indication: Corneal Collagen Cross-linking

Applicant Name: Avedro, Inc.

Meeting Chair: Edward Cox, MD, MPH

Meeting Recorder: Jacquelyn Smith, MA

FDA ATTENDEES

Edward Cox, MD, MPH	Director, Office of Antimicrobial Products (OAP)
Judit Milstein	Chief Project Management Staff, DTOP
Yan Wang, PhD	Statistics Team Leader, DTOP
Dongliang Zhuang, PhD	Statistics Reviewer, DTOP
Daphne Lin, PhD	Deputy Director, Office of Translational Sciences, Office of Biostatistics, Branch IV (OTS/OB/DBIV)
Jacquelyn Smith, MA	Senior Regulatory Project Manager, DTOP
Maryam Mokhtarzadeh, MD	Medical Officer, DSDB/DOED/ODE/CDRH,
Kesia Alexander, PhD	Deputy Director, DOED/CDRH
Damia Jackson, BA	Regulatory Project Manager, DOED/CDRH
Markham Luke, MD, PhD	Deputy Office Director, ODE/CDRH
Patricia Love, MD	Deputy Director, OC/OSMP/OCP

AVEDRO, INC ATTENDEES

David Muller, PhD	President and Chief Executive Officer
Pamela Nelson, MBA	Vice President, Regulatory Affairs

BACKGROUND:

Avedro requested this meeting to obtain clarification on what CDRH is looking for with respect to the literature request (question 5 in the clinical information request).

DISCUSSION:

The Agency confirmed that an agreement was made on the criteria to bridge the two devices (2a-e). The discussion then focused on the August 14, 2015, information request. Regarding questions 1-4 and 6-7, the Agency noted Avedro's e-mail response sent on August 21, 2015. CDRH stated that they will conduct analysis of the various subgroups based on the available data. The Agency recognizes that subset analyses may have limited value, but may inform labeling or other aspects of the review. If concerns arise based on the subset analyses, the Agency will reach out to Avedro for clarification. The Agency explained the impetus behind these questions is the Advisory Committee Meeting discussion and recommendations. Avedro responded that they previously conducted some of these analyses on the entire study cohort. Regarding Question 5 of the August 14, 2015, information request, the Agency identified three articles on how the KXL system has been used in clinical trials for crosslinking purposes. While there are clinically significant differences in treatment duration and UV output parameters between the KXL in the literature and KXL proposed in the NDA; the Agency believes the articles may support relevant clinical experience with certain aspects of the KXL system, namely the patient interface and physician interface. The Agency would like clarification from Avedro regarding how the system identified in the articles is similar to the one proposed for market in the NDA. Specifically, the Agency is looking for all sources of literature where there is experience helpful to support aspects of the device not studied in the NDA. Avedro responded that there is no publication reporting on use of the KXL system under similar UV output parameters as those proposed in the NDA (e.g., 3mW/cm²). Avedro further stated that since the UV treatment parameters reported in the literature (often in a procedure termed "accelerated crosslinking") are significantly different than those proposed for marketing, they were not sure what information can be gleaned to address the Agency's specific concerns as the outcomes will be different. The Agency stated that as they are aware that the device has been used overseas, clarification is being requested whether the device reported in the literature has similar patient/physician interfaces to the device proposed in the NDA. The Agency further explained they are interested in the practicalities of the use of the device.

Avedro stated that they understand that the Agency is looking for this to give them comfort on clinical use of the KXL device but cannot look to the literature for effectiveness.

The Agency responded they completely understand the significant limitations on interpretation of such data for effectiveness outcomes due to the differences in the treatment parameters. They would like for Avedro to provide the literature review with clarification regarding the aspects of the KXL system that are representative of the device proposed in the NDA in each article (i.e.,

similarities as related to patient/physician interface). Avedro responded that they understand and will look for literature to address the Agency's request. The Agency inquired as to approximately how many articles the sponsor is expecting to submit. Avedro replied that there are approximately thirty or more such publications.

Avedro asked the Agency what the timeframe was for completing their subset analysis. The Agency stated they anticipate being able to finish by the end of September and will reach out to Avedro if clarification of data is needed.

Avedro asked the Agency about the timeframe for receiving the three articles on the KXL system to perform crosslinking. The Agency responded that the articles will be forwarded via email immediately following the ongoing September 9, 2015 meeting.

The meeting was summarized as follows:

An agreement regarding the protocol for 2a-2e has been reached; the Agency will review once the data is submitted. The Agency will also conduct internal subset analyses of the existing clinical trials. Regarding the literature search, if Avedro has additional knowledge about the literature found (i.e., identifying features of the KXL system in each article that are representative of the device proposed in the NDA) then please provide that information for each article. Avedro will provide the requested information, if known. Avedro stated the devices are pretty much the same as far as interface, but some software differences may exist. The Agency asked for Avedro to provide detail regarding such similarities and differences, where known. This information will be used to support the global experience which has been built with the patient/physician interface with the KXL system.

ACTION ITEMS:

- The Agency expects to issue the minutes of the Type A meeting and related post-meeting comments to summarize activities to date. A meeting between Avedro and the Agency will be scheduled in October 2015 to provide Avedro with status update
- Avedro will submit a literature search.
- The Agency will discuss the subset analysis collected in an internal meeting prior to following up with Avedro.

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/s/

EDWARD M COX
04/15/2016

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Monday, April 11, 2016 3:21 PM
To: 'Pamela Nelson'
Subject: Draft labeling-NDA 203324

Hi Pam,

A promised, we are sending you the draft labeling for NDA 203324. Please review and respond back to us as soon as possible.

We are available at 8:00 AM tomorrow to discuss if you need clarification or have questions.



April 11, 2016

CDER PROPOSE...



April 11 2016

KXL_UV_Illumin...



carton container

revisions 2.d...

Regards,
Jacquelyn

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/s/

JACQUELYN E SMITH
04/11/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203324

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Avedro, Inc
203 Third Avenue, 5th Floor
Waltham, MA 02451

ATTENTION: Pamela Nelson
Vice President, Regulatory Affairs

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) resubmission, dated and received, October 16, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Riboflavin Ophthalmic Solution, 0.12 % and Riboflavin, with 20% Dextran, Ophthalmic Solution, 0.12 %.

We also refer to your correspondence, dated and received, November 12, 2015, requesting review of your proposed proprietary names, Photrexa and Photrexa Viscous.

We have completed our review of the proposed proprietary names, Photrexa and Photrexa Viscous and have concluded that these names are conditionally acceptable.

If any of the proposed product characteristics as stated in your November 12, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5413. For any other information regarding this application, contact Jacquelyn Smith, Regulatory Project Manager in the Office of New Drugs, at 301-796-1002.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/02/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: December 1, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 3

Document to be mailed: YES NO

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NDA 203324

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for riboflavin ophthalmic solution and the KXL System. We have the following information request.

Information Request

To help us better assess trends please amend Tables 2-13 in the Amendment of November 23, 2015 to supply the data for riboflavin 5'-phosphate to 3 significant figures.

In your Amendment dated February 14, 2015 you supplied the individual values for the monophosphates, diphosphates, etc. for validation lots 3-FIN-1570, 3-FIN-1572, 3-FIN-1574 and 3-FIN-1576, 3-FIN- 1578, and 3-FIN-1580 stored at 25°C/60% RH and 40°C/75% RH (Tables 3-14). Please update these tables with data going out to 24 or 30 months at 25°C/60% RH, as appropriate.

Please respond to this information request by December 15, 2015.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
12/01/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: November 10, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 4

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light. We have the following information request.

Information Request

You have provided adequate evidence that the UVX and KXL devices provide equivalent UVA exposure to the cornea, given the assumption that the distribution of patient eye movements is the same for both devices. However, (b) (4) there are several details of the comparative description of the optical systems that need further clarification.

Also, there are puzzling apparent differences between the UVX and KXL (b) (4) report that need to be explained.

Please address the following minor issues before we approve the substitution of the KXL device for the UVX device in this NDA:



(b) (4)

Please explain this apparent inconsistency.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
11/10/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: November 10, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 4

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light. We have the following information request.

Information Request

We reviewed your responses to the outstanding EMC and EMC labeling deficiencies. You have not adequately responded to our main remaining EMC concern. In addition, there is one remaining minor error in the EMC labeling. Please correct these outstanding issues.

1. The first issue was a change [REDACTED] (b)(4) that had not previously been evaluated for its effect on EMC. You submitted a long list of changes that were made in order to pass EMC testing. The device was tested after the modifications were made and passed the tests. However, the modification [REDACTED] (b)(4) was not yet complete and you said that after this last modification was made, the device would be retested for EMC and the results of the retest would be submitted. In the most recent submission, you did submit EMC test results. However, the dates on which the EMC tests were performed were March 13, 14, 17-21, and 24, 2014. The chronology is as follows:
 - March 13, 14, 17-21, and 24, 2014: EMC testing, including assessment of a list of changes. However, the list did not include the change [REDACTED] (b)(4)
 - September 29, 2014: Your submission that described the modification [REDACTED] (b)(4) and stated that the device would be retested for EMC and that the test results would be submitted.

Thus, you still have not submitted the promised results of EMC retesting. This response is not acceptable. Please submit the promised test results.

2. While the EMC labeling required by IEC 60601-1-2 (and all other IEC standards) is specified using the European convention of comma “(,)” for the decimal separator, you were asked to use the US convention of the point “(.)” for the decimal separator in manuals intended for US distribution. The revised Operator’s Manual that you submitted shows that the decimal separator in the EMC guidance tables has been changed to the point “(.)” in all applicable locations but one. Please make this change in the last header row of the last column in Table 5-4, to change “2,5 GHz” to “2.5 GHz”.

NDA 203324

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
11/10/2015



NDA 203324

GENERAL ADVICE

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013, received September 16, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the combination product, Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System.

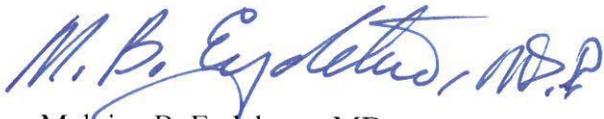
We also refer to your September 10, 2015 submission, containing Avedro's responses to the Information Request (IR) sent by the Agency to Avedro on August 14, 2015. The IR contained seven (7) items and requested analyses of Studies UVX-001, UVX-002, and UVX-003, as well as additional information from the literature, as discussed with Avedro during the teleconference on September 9, 2015.

We have reviewed your September 10, 2015, submission and have the following comments:

- The analyses specified in Items #1, #2, #3, #4 and #7 have been conducted by the Agency. We have no further questions for Avedro regarding these items.
- The literature review requested in Item #5, as discussed during the September 9, 2015, teleconference has been responded to by Avedro in the submission dated September 25, 2015. We have no additional literature requests regarding this item.
- For Item #6, requesting data from the Refractive Status and Vision Profile Questionnaire and the Subjective Complaint Questionnaire, you responded that all Adverse Events were obtained from clinician reports and that the primary endpoint was not based on these patient reported outcomes(PROs). Therefore, we are not requesting additional premarket assessment of information from the PROs used in this trial.

If you have any questions, call Ms. Jacquelyn Smith, MA, Senior Regulatory Project Manager, at 301-796-1600.

Sincerely,



Malvina B. Eydelman, MD
Director
Division of Ophthalmic, and
Ear, Nose, and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological
Health



Renata Albrecht, MD
Director
Division Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
10/27/2015

MEMORANDUM OF TELECONFERENCE

Meeting Date: October 15, 2015

Application Number: NDA 203324

Product Name: Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light

Indication: Corneal Collagen Cross-linking

Applicant Name: Avedro, Inc.

Meeting Chair: Edward Cox, MD, MPH

Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Edward Cox, MD, MPH	Director, Office of Antimicrobial Products (OAP)
Jacquelyn Smith, MA	Senior Regulatory Project Manager, DTOP

AVEDRO, INC ATTENDEES

David Muller, PhD	President and Chief Executive Officer
Pamela Nelson, MBA	Vice President, Regulatory Affairs

BACKGROUND:

The purpose of today's teleconference is to address the question of whether any further analyses are needed from Avedro regarding the additional clinical trial analyses (requested in the Agency's August 14, 2015 information request) as part of the planned resubmission of NDA 203324. The bulleted points below provide the minutes of this teleconference.

DISCUSSION:

- Over the last few months Avedro has engaged with CDER and CDRH to arrive at a common understanding of the items to provide in the resubmission for NDA 203324.

- The analyses requested in the August 14, 2015 information request have been performed within CDRH. No additional analyses are expected from Avedro regarding these items as part of the re-submission.
- Both Avedro and the Agency understand that both groups have worked to identify the information and analyses to support the review of the resubmission of NDA 203324; should additional questions come up during the review, Avedro and the Agency will work to address those questions. The review of the resubmission will provide the opportunity to further evaluate the safety and efficacy of the proposed product.
- Given the work done above by Avedro, CDRH, and CDER to prepare for the resubmission of NDA 203324, Avedro now plans to resubmit NDA 203324 for the Agency's review.

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/s/

EDWARD M COX
10/15/2015



NDA 203324

GENERAL ADVICE

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013, received September 16, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the combination product, Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System.

We also refer to your September 4, 2015, submission, containing the revised Type A Meeting Briefing Document that contains the revised protocol and acceptance criteria to address deficiencies 2.a.-2.e. in the March 29, 2015 Complete Response Letter (CRL).

During the June 11, 2015, Type A meeting, it was agreed that you may submit non-clinical data to address deficiencies 2.a.-2.e. in the CRL to bridge the KXL System to the UVX System. In addition, at the August 10, 2015, meeting there was discussion of getting further clarification on how to address 2.a.-2.e., including follow-up discussions on August 19, 20, and 26, 2015, with representatives from the Agency.

We acknowledge that your September 4, 2015 submission includes detailed description of the non-clinical tests you propose to conduct in order to comprehensively address items 2.a.-2.e. in the March 29, 2015, CRL. The proposed protocol includes a set of bench measurements and modeling studies to be conducted. Each specific test includes a description of the measurement or model setup, analytic procedures, data to be reported, and acceptance criteria necessary to address the deficiencies in 2.a.-2.e.

We have reviewed your September 4, 2015, submission and concluded that the protocol and acceptance criteria (methodologies, targets, and boundaries) are appropriate. A copy of the briefing book is attached for reference.

NDA 203324

Page 2

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager, at 301-796-1600.

Sincerely,



for

Malvina B. Eydelman, MD
Director
Division of Ophthalmic, and
Ear, Nose, and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological
Health



Renata Albrecht, MD
Director
Division Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

AVEDRO, INC.

**PHOTREXA™ VISCOUS (RIBOFLAVIN PHOSPHATES
OPHTHALMIC SOLUTION) 1.20 MG/ML 20% DEXTRAN AND
PHOTREXA™ (RIBOFLAVIN PHOSPHATES OPTHALMIC
SOLUTION) 1.20 MG/ML AND KXL™ SYSTEM FOR THE
TREATMENT OF PROGRESSIVE KERATOCONUS AND
CORNEAL ECTASIA FOLLOWING REFRACTIVE SURGERY**

NDA 203324

TYPE A MEETING

BRIEFING DOCUMENT

CDRH's agreements are predicated on the information provided in this briefing document and the adequacy of the data will be reviewed/assessed accordingly. Please be advised that unsolicited changes to the device/protocol/analyses may elicit additional comments.

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1. PURPOSE AND OBJECTIVES OF MEETING

The purpose of this meeting is to discuss the methodologies, targets, and boundaries that would be acceptable to FDA to address deficiencies 2(a)-2(e) in the Complete Response Letter, dated March 29, 2015 (Second CRL). Avedro and FDA discussed the CRL at the June 11, 2015, Type A meeting, and agreed that Avedro may submit non-clinical data to address deficiencies 2(a)-2(e) in the CRL to bridge the KXL System to the UVX System. As a next step, FDA agreed that Avedro may submit a second Type A meeting request in order to obtain clarity on the data that FDA will find acceptable to address these deficiencies.

This Type A meeting package includes detailed description of non-clinical tests that Avedro proposes to conduct in order to comprehensively address the questions raised by FDA in the CRL. The proposed protocols include a set of bench measurements and modeling studies that will be undertaken by Avedro. Each specific test includes a description of the measurement or model setup, analytic procedures, data to be reported, and acceptance criteria necessary to address the deficiencies in 2(a)-2(e) and bridge the KXL and UVX devices.

Avedro believes that execution of these protocols will quantitatively and definitively demonstrate that the UVX and KXL devices are clinically interchangeable. Avedro believes that this data will close all remaining questions relating to Avedro's New Drug Application (NDA 203324).

The specific questions relating to this objective are provided in Section 8.

Post meeting note:

Subsequent to the 10 August meeting, Avedro and FDA had multiple teleconferences to discuss the protocol whereby agreements were reached. Those agreements are incorporated herein in track changes mode as requested.

1.1. PROPOSED AGENDA

Avedro anticipates that the meeting will last for approximately 60 minutes and proposes the following agenda:

- Introductions (5 minutes)
- Question Review/Discussion (40 minutes)
- Summarize Agreements (10 minutes)

1.2.

1.3. LIST OF SPONSOR ATTENDEES

Name	Title
David Muller, Ph.D.	President and CEO, Avedro
Pamela Nelson	Vice President, Regulatory Affairs, Avedro
Desmond Adler, Ph.D.	Vice President, Engineering, Avedro
Geraldine Riera	Director, Regulatory Affairs, Avedro
(b) (4)	Regulatory Consultant
(b) (4)	Special Counsel, (b) (4)
(b) (4)	Consultant, (b) (4)

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7. **PROTOCOL OUTPUT**

Avedro believes that execution of these protocols will quantitatively and definitively demonstrate that the UVX and KXL devices are clinically interchangeable. Avedro believes that this data will close all remaining questions relating to Avedro's New Drug Application (NDA 203324).

8. QUESTIONS

8.1. Deficiencies 2(a)-2(e) in the Second CRL

The Divisions' original comment is presented below in bold, followed by a summary of Avedro's proposal and specific question(s) in italics.

8.1.1. Deficiency 2a

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 direction, 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 will provide all requested information.

8.1.2. Deficiency 2b

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. Explain any differences between the KXL map in the September 2013 submission and the KXL map in the September 29, 2014 resubmission that you provided

(b) (4)

Avedro's methodology to measure the UV irradiance at the device focal planes is provided in Section 4. Avedro will provide an explanation to the differences between the two KXL maps in the resubmission.

Does the Agency agree with the proposed measurement setup, analytical procedures, the type of data to be reported and equivalence acceptance criteria for the measurement of UV irradiance maps provided in Section 4?

Agency Response: Yes.

Does the Agency agree that providing this information and meeting the acceptance criteria will address Deficiency 2b?

Agency Response: Yes.

8.1.3. Deficiency 2c

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, 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.

Information of the features and procedures used to limit eye movement during the crosslinking procedure is provided in Section 3.1. Information on the effect of eye movements on the effective beam size and exposure pattern is provided in Section 3.2.

Regarding the Avedro proposal in Section 3,

- Does the agency agree with the proposed method, sample size, and equivalence acceptance criteria as identified in section 3?

Agency Response: Yes.

- Does the agency agree with the data presentation as a figure? Does the Agency require raw data to be submitted for the simulated method??

Agency Response: Yes.

Does the Agency agree that providing this information and meeting the equivalence criteria addresses Deficiency 2c?

Agency Response: Yes.

8.1.4. Deficiency 2d

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

As described in Section 6, Avedro proposes to conduct bench experiments to measure the actual focal plane position relative to the cornea for both the UVX and KXL devices.

(b) (4)

- Does the agency agree with the proposed method, sample size, and equivalence acceptance criteria as identified in section 4?

Agency Response: Yes.

- Does the agency agree with the data presentation as a figure? Does the Agency require raw data to be submitted for the figures??

Agency Response: Yes.

Does the Agency agree that providing this information and meeting the equivalence criteria addresses Deficiency 2d?

Agency Response: Yes.

8.1.5. Deficiency 2e

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 proposes to provide optical simulation data, generated using industry-standard modeling software, which quantitatively evaluates the UV irradiance in the X, Y, and Z directions across the cornea and sub-corneal structures. The model, as described in Section 5.1, includes a detailed description and explanation of the optical systems of both devices, and a descriptive table of all important optical components used in both devices.

- Regarding the Avedro proposal in section 5 the method will incorporate elements identified in the agency preliminary response. Avedro agreed to incorporate beam homogeneity, eye movement, focusing data and provide a 3D distribution of energy for each device.

Agency Response: Yes.

- Is the proposed method, including the addition stated above, acceptable?

Agency Response: Yes.

- Does the agency agree with the proposed analytical procedures?

Agency Response: Yes.

- Does the agency agree with the data presentation as a figure? Does the Agency require raw data to be submitted for the figures??

Agency Response: Yes.

Does the Agency agree that providing this information and meeting the equivalence criteria addresses Deficiency 2e?

Agency Response: Yes.

8.2. Regulatory

Question 5: Does the Agency agree that output from these protocols completely addresses deficiencies 2(a) through 2(e) in the Second CRL?

Agency Response: Yes.

Question 6: Does the Agency agree that addressing deficiencies 2(a)-2(e) establishes the bridge between the UVX and KXL devices and closes all remaining questions relating to NDA 203324?

Agency Response: No.

Question 7: Does the Agency agree that addressing deficiencies 2(a)-2(e) establishes the bridge between the UVX and KXL devices and closes all remaining non-clinical questions regarding device equivalence?

Agency Response: Yes.

CDRH's agreements are predicated on the information provided in this briefing document and the adequacy of the data will be reviewed/assessed accordingly. Please be advised that unsolicited changes to the device/protocol/analyses may elicit additional comments.

REFERENCES

Boettner EA. Spectral transmission of the eye. The University of Michigan Contract AF41 (609) - 2966.

Ginis, H, Pérez GM, Bueno JM, and Artal P. 2012. The Wide-Angle Point Spread Function of the Human Eye Reconstructed by a New Optical Method. *Journal of Vision* 12: 1–10. <http://jov.highwire.org/content/12/3/20.short> (July 12, 2013).

Tutt, R., Bradley A, Begley C, and Thibos LN. 2000. Optical and Visual Impact of Tear Break-up in Human Eyes. *Investigative Ophthalmology and Visual Science* 41(13): 4117–23.

Wollensak G, Aurich H, Wirbelauer C, and Sel S. 2010. Significance of the Riboflavin Film in Corneal Collagen Crosslinking. *Journal of cataract and refractive surgery* 36(1): 114–20. <http://www.ncbi.nlm.nih.gov/pubmed/20117714> (November 30, 2012).

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/s/

JACQUELYN E SMITH
09/30/2015



NDA 203324

MEETING MINUTES

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light.

The purpose of the August 10, 2015, Type A, meeting was to discuss the approach and methodology to address questions 2(a) through 2(e) in the Complete Response letter, dated March 29, 2015. Subsequent to the meeting, CDRH met with you on August 19, 20, and 26, 2015, to discuss the pre-clinical data necessary to address the device-to-device comparisons.

A copy of the official minutes, from each of the meetings, is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager at 301 796-1600.

Sincerely,

Malvina B. Eydelman, MD
Director
Division of Ophthalmic, and
Ear, Nose, and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological
Health

Sincerely,

Renata Albrecht, MD
Director
Division Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 10, 2015

Meeting Location: CDER WO22 1419

Meeting Type: Type A

Application Number: NDA 203324

Product Name: Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light

Indication: Corneal Collagen Cross-linking

Applicant Name: Avedro, Inc.

Meeting Chair: Renata Albrecht, M.D.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Renata Albrecht, MD	Director, Division of Transplant and Ophthalmology Products (DTOP)
Lori Kotch, PhD	Pharmacology/Toxicology Supervisor, DTOP
Aaron Ruhland, PhD.	Pharmacology/Toxicology Reviewer, DTOP
William Boyd, MD.	Medical Team Leader, DTOP
Martin Nevitt, MD	Medical Officer, DTOP
Diana Willard	Chief, Project Management Staff, DTOP
Judit Milstein	Chief Project Management Staff, DTOP
Yan Wang, PhD	Statistics Team Leader, DTOP
Dongliang Zhuang, PhD	Statistics Reviewer, DTOP
Daphne Lin, PhD	Deputy Director, Office of Translational Sciences, Office of Biostatistics, Branch IV (OTS/OB/DBIV)
Jacquelyn Smith, MA	Senior Regulatory Project Manager, DTOP
Markham Luke, MD PhD	Deputy Office Director, Office of Device Evaluation, CDRH
Malvina Eydelman, MD	Director, Division of Ophthalmic and Ear, Nose and Throat Devices (DOED), Office of Device Evaluation, CDRH
Maryam Mokhtarzadeh, MD	Medical Officer, CDRH/ODE/DOED
Dexiu Shi, PhD	Physicist, CDRH/ODE/DOED/DSDB

Bradley Cunningham, MS	Chief, Center for Devices and Radiological Health, Office of Device Evaluation, Division of Ophthalmic and Ear, Nose and Throat Devices (DSDB)
Damia Jackson, BA Thinkh Nguyen, MS	Regulatory Project Manager, CDRH/ODE/DOED Director, Office of the Commissioner, Office of Special Medical Programs, Office of Combination Products (OC/OSMP/OCP)
Patricia Love, MD John Weiner, JD Katherine Schumann, MS	Deputy Director, OC/OSMP/OCP Associate Director, OC/OSMP/OCP Acting, Associate Director of Regulatory Affairs, Office of Antimicrobial Products (ADRA/OAP)
Xin Fang, PhD Bruce Drum, PhD	Statistics Reviewer, CDRH/OSB/DBS/CODB Physicist/Vision Science Reviewer, CDRH/ODE/DOED/DSDB
James Reese, PhD	Health Science Administrator, Office of Special Medical Programs, Office of Orphan Products Development (OSMP/OOPD)

AVEDRO, INC ATTENDEES

David Muller, PhD	President and Chief Executive Officer
Pamela Nelson, MBA	Vice President, Regulatory Affairs
Geraldine Riera	Director, Regulatory Affairs
(b) (4)	Regulatory Consultant
Desmond Adler, MD	Vice President, Engineering
(b) (4)	Senior Counsel, (b) (4)
(b) (4)	Special Counsel, (b) (4)
(b) (4)	Consultant, (b) (4)

BACKGROUND:

The purpose of the meeting was to discuss: (i) Avedro's proposed methodology and acceptance criteria provided in the July 17, 2015, Briefing Book to address Items 2a-2e from the March 29, 2015 Second Complete Response Letter (CRL), and the Agency's August 10, 2015, preliminary comments in response to Avedro's proposed methodology and acceptance criteria; and (ii) to reach agreement on a clear pathway forward to approval for the application.

The meeting began with opening remarks and introduction of the attendees. A complete list of the preliminary comments is attached. The meeting discussion begins thereafter.

Questions

Avedro's methodology to measure the UV irradiance at the device focal planes is provided in Section 4. Avedro will provide an explanation to the differences between the two KXL maps in the resubmission.

Question 1: Does the Agency agree that the measurement setup, analytical procedures, data to be reported and equivalence acceptance criteria for the measurement of UV irradiance maps provided in Section 4 will address Deficiency 2b?

Agency Response:

We acknowledge that you will submit information as requested. Please be advised that we may identify additional deficiencies during our review.

Methods  (b) (4) appear to be acceptable.
 (b) (4)

Therefore, in order to allow a quantitative comparison of both beam shape and irradiance distribution for the UVX and KXL devices, please provide XY irradiance maps from at least 2 UVX and 2 KXL devices, and ensure that horizontal and vertical profiles are averaged separately, not combined, and standard deviations of the profiles are provided along with the means. See the comments on deficiency 2c below regarding measurements of irradiance distributions that incorporate eye movements.

Information of the features and procedures used to limit eye movement during the crosslinking procedure is provided in Section 3.1. Information on the effect of eye movements on the effective beam size and exposure pattern is provided in Section 3.2.

Question 2: Does this information address Deficiency 2c?

Agency Response:

 (b) (4)

(b) (4)
(b) (4) Please take into account these important issues (b) (4)
when addressing the deficiency identified in the March 2015 complete response letter.

As described in Section 6, Avedro proposes to conduct bench experiments to measure the actual focal plane position relative to the cornea for both the UVX and KXL devices.

Question 3: Does the Agency agree that the measurement setup, analytical procedures, data to be reported and equivalence acceptance criteria of the measurement of the focal plane position provided in Section 6 will address Deficiency 2d?

Agency Response:

We requested information to assess the focal plane of the KXL device compared to the UVX device. Based on the information you provide, your proposed bench experiment design appears reasonable; however, you do not identify, or describe, a calibration procedure to establish the “true” distance from device housing to best focus for each device. We believe such a procedure is necessary to determine whether the focusing procedures for the two devices place best focus at different depths relative to the front corneal surface. Please develop a calibration procedure accordingly. Also, please clarify, for both devices, whether the surface of best focus for the beam is planar or follows the curvature of the cornea. The shape of the surface of best focus should also be incorporated into the simulations described in response to deficiency 2e.

Avedro proposes to provide optical simulation data, generated using industry-standard modeling software, which quantitatively evaluates the UV irradiance in the X, Y, and Z directions across the cornea and sub-corneal structures. The model, as described in Section 5.1, includes a detailed description and explanation of the optical systems of both devices, and a descriptive table of all important optical components used in both devices.

Question 4: Does the Agency agree that the measurement setup, analytical procedures, data to be reported and equivalence acceptance criteria of the optical ray trace modeling focal provided in Section 5 will address Deficiency 2e?

Agency Response:

You propose to provide optical simulation data to address our request for a comparative analysis of UV distribution. In general, your proposed optical simulation modeling accounts for most of the important optical factors; however, there are other factors, which we believe are important to consider when assessing the UV distribution of the KXL for comparison to the UVX device. Specifically, please consider incorporating the beam homogeneity, eye movement, and focusing data acquired in your responses to deficiencies 2b, 2c, and 2d above. The principal outcome of the analysis should be a 3D distribution of energy absorbed in the corneal stroma for each device. Please revise your testing procedures to incorporate these additional optical factors.

Regulatory

Question 5: Does the Agency agree that output from these protocols completely addresses deficiencies 2(a) through 2(e) in the Second CRL?

Agency Response:

This will be a review issue.

Question 6: Does the Agency agree that addressing deficiencies 2(a)-2(e) establishes the bridge between the UVX and KXL devices and closes all remaining questions relating to NDA 203324?

Agency Response:

The response to this question needs further discussion internally. A response will be provided at a later time, as indicated in the June 11, 2015 Meeting Minutes.

MEETING DISCUSSION:

Avedro opened with statements firmly expressing disappointment and frustration over the interactions with the Agency that have occurred over the past few years regarding the NDA file. Avedro referenced the agreement four years ago with CDRH regarding the information needed to demonstrate comparability between the two device constituent parts and stated that that agreement has not been honored. Avedro stated that they were disappointed to receive the second CRL after an Advisory Committee voted to approve this orphan product. In addition, Avedro stated that they believe they have provided the Agency with all the information the Agency requested during the Agency's review of the NDA. Avedro noted that corneal collagen cross-linking (CXL) is approved in over 60 countries around the world, including China. Avedro stated US is the only country that does not have CXL approved, and also stated that CXL is occurring in the United States (U.S.) with devices and drugs that are not approved and patients are getting injured. Avedro further explained that 400 patients a month, in the U.S., are getting corneal transplants because they do not have access to approved cross-linking in the U.S.

Avedro noted that they do not believe that the Agency's minutes of the June 11, 2015, Type A, meeting accurately reflects the discussion and agreements that occurred during the meeting. Avedro noted they were sent email requests and then told "never mind." Avedro noted that they were told that addressing Items 2.a.-2.e. from the March 29, 2015 Complete Response letter and linking the devices would be easier, but that has not proven to be so. Avedro stated they were told they would not need a new clinical study and now they were being asked to do the fixation study, and described the challenge and complexity of such a study and questioned the ability of such a study generating useful information, and asked about alternative approaches of addressing the question. Avedro further stated that at the June 11, 2015, Type A, meeting, it was agreed that Avedro would provide the methodology and acceptance criteria to address Items 2.a.-2.e. for the Agency's review. Avedro stated that they submitted the requested information in the July 17, 2015, briefing document, but do not believe that clear, concise feedback from the Agency was

received in the preliminary comments issued before the August 10, 2015 meeting. Avedro also stated that the lack of clear answers and guidance from the Agency is extremely frustrating and has created unnecessary delays on the path to approval.

Avedro added that the goal of this August 10, 2015, meeting is to obtain a clear path forward. Avedro further emphasized that this is an orphan product and that the company has committed to conducting a Phase 4 study. Avedro further stated that they have cooperated fully with the agency to respond to all information requested from the Agency, as far as they understood the requests. Avedro reiterated that despite their best efforts, it is still not clear what the Agency wants and without clear direction it is impossible to answer the Agency's requests. Avedro asked that the Agency be completely transparent about what information is required to move the NDA forward to approval.

Avedro stated that following the June 11, 2015, meeting, they were under the impression that an agreement was reached and that nonclinical information would be sufficient to answer questions 2.a.-2.e. to bridge the two devices.

Avedro asked in the July 17, 2015, Briefing Book whether the Agency agreed that adequately addressing deficiencies 2.a.-2.e. establishes the bridge between the UVX and the KXL devices and closes all remaining questions in the NDA. The Agency stated in the preliminary comments to #6, "The response to this question needs further discussion internally. A response will be provided at a later time, as indicated in the June 11, 2015 meeting minutes." Avedro stated that the Agency's response to Question #6 in the preliminary comments to Avedro's protocol suggests the Agency may still request more information. In addition Avedro said this topic was not discussed in the June 11, 2015 meeting.

Avedro believes the preliminary responses for the August 10, 2015 meeting conflict with what Avedro believed was agreed to at the June 11, 2015, that Avedro could submit non-clinical information to 2.a.-2.e. to bridge the two devices. Avedro further stated that all deficiencies would have had to be identified in the Complete Response letter.

Avedro reiterated that they are trying to move forward, and requested clear instruction from the Agency during today's meeting and that the following be reflected in the meeting minutes: whether the Agency agrees submission of the proposed non-clinical data for deficiencies 2.a.-2.e. is a complete response to the second CRL and that if the data are adequate, it will be an adequate bridge for the UVX and KXL devices. If further information will be required to move the file forward to approval, Avedro requests that the Agency tell them now and that these be clearly stated in the meeting minutes. Avedro also requested that the Agency provide information in a clear/transparent manner so they can respond. Avedro continued to state that they received conflicting messages throughout the review process and this places Avedro in an unfair position with no clear pathway forward to approval.

The Agency responded that if there are issues/disagreements with the meeting minutes, Avedro should let the Agency know. As the Agency stated in the June 11, 2015, Type A, meeting, the additional non-clinical information referenced in the March 29, 2015, second CRL was in

context of needing an additional future clinical trial. When Avedro stated that they were going to rely on existing clinical data, the Agency said that they would go back and look to see if additional subset analyses were needed. (Avedro acknowledged this discussion point.) The Agency is actively working to address this and is planning to send the assessment as noted in the June 11, 2015 minutes. Additionally, the Agency indicated that they would provide this proposal to Avedro before or at the same time of the final meeting minutes for today's meeting (August 10, 2015). It was agreed that Avedro would have the opportunity to review and comment on the information.

Avedro expressed concern regarding the Agency preliminary response use of the word "deficiencies" in the Agency's response to Question #1. The Agency stated that the August 10, 2015, meeting minutes will reflect that the use of the word deficiencies refers to additional questions on data submitted. The Agency further added that a complete response should contain responses to all the CRL deficiencies and that the Agency tries to identify the deficiencies up-front, but sometimes things are learned during the review process. The Agency clarified that it is not a preferred option to have to request additional information, but it can happen.

Avedro stated that it found the Agency's preliminary responses ambiguous and confusing. For example, the Agency's use of terminology such as "it appears to be" does not provide clear guidance. In addition, Avedro stated that the Agency agreements/disagreements to the methodology and acceptance criteria were not in the Agency's response. The Agency stated that since the Agency does not know the outcome (study results) of Avedro's proposed methods, the Agency can't completely agree to the criteria. Avedro disagreed. Avedro stated the purpose of submitting the protocol was to obtain agreement on the success criteria. Avedro further emphasized that it is about agreeing on the protocol design and acceptance criteria before conducting the experiments. This is consistent with the Agency guidance document which allows companies to obtain agreement with the Agency on acceptability criteria and it is done all the time. The Agency agreed that clarifying comments will be provided on the protocol and acceptance criteria.

With reference to Question #2, Avedro expressed confusion over the Agency's request for an eye movement study. Avedro stated that the request is a clinical study that does not make sense and study details were not clear. For example, Avedro is not sure what the Agency means by excellent, average, and poor fixators or how to determine whether a subject is a certain type of fixator. The Agency agreed that is a good question, but did not provide a definition of what those categories mean. Avedro stated that these patients cannot fixate as the epithelium is removed and riboflavin is administered to the eye. Based on this conversation, both the Agency and Avedro agreed that additional discussions will be needed to reach agreement on Question #2.

Avedro made it clear that they will not submit any additional data to the Agency until there is clear and definitive agreement from the Agency on the methodology and acceptance criteria. The agency offered to send Avedro a list of the points on which Avedro seeks additional clarity. Avedro will edit that list. After that the Agency will provide additional responses to the protocol.

With reference to Question #6, Avedro asked if answering 2.a.-2.e. would be a complete response to the second CRL. The Agency stated that this relates to the introductory comments

regarding what would be needed to rely on the existing clinical trials. The Agency reiterated that the additional comments in the CRL were in the context of conducting a new clinical trial. However, since Avedro is not going to conduct a new clinical trial, the Agency would ask for additional information as it relates to existing data (reference June 11, 2015 Type A meeting). Avedro stated that the additional comments were not listed as deficiencies in the CRL. Furthermore, the CRL provided the option of a new clinical trial or answering 2.a.-2.e., yet the additional comments in the CRL related only to conducting a new clinical trial. The Agency acknowledged that the CRL was not clear on this matter. The Agency further stated that the information would be essentially what is in the CRL Additional Comments section: e.g., sub-analyses on the existing clinical studies. Avedro stated that they will not be able to answer some of the questions in that section since the data do not exist. Avedro asked if that response would be acceptable to the Agency. The Agency stated that it could not predict how it would consider the response in the context of the review. Avedro pointed out that any sub-analysis does not provide information about the two devices. The Agency clarified that any sub-analysis of existing clinical data would be, for example, for the purposes of labeling.

Avedro asked if the Agency finds that the responses to questions 2.a.-2.e. and the response to the additional information are adequate, whether this will be a bridge to the two devices. The Agency said that this is a review question upon resubmission.

Avedro asked whether it would be easier for the Agency to approve the device if they split the indications for use. An Agency representative replied yes and added that a keratoconus indication is more straightforward, but Avedro would still need additional sub-analysis to show it could be supported. Another Agency representative stated and acknowledged that the application contained two indications that are under consideration by the Agency.

The Agency stated they would provide Avedro with an initial draft of meeting minutes for Avedro's review and comment. Also the Agency stated that if the initial draft does not capture what was discussed in the meeting, Avedro may edit the draft minutes (edits will be tracked) as they understood the discussion during the August 10, 2015 meeting.

ACTION ITEMS:

- Agency will send Avedro the set of items regarding the preliminary agency responses to questions #1-#5 above, for which Avedro seeks more detail. Avedro will provide input on the list. After that representatives from the Agency will hold telephone conferences with Avedro to reach clarification and agreement on the proposed methodology and acceptance criteria.
- The Agency will confirm what is required to address the second CRL.
- The Agency will issue the meeting minutes within 30 days of the August 10, 2015, meeting.

Minutes Preparer: Jacquelyn Smith, MA, Senior Regulatory Project Manager, DTOP

Chair Concurrence: Renata Albrecht, MD, Director, DTOP

Attachments:

Meeting with Avedro

August 19, 2015

Attendees-

CDRH: Bruce Drum, Dexiu Shi, Maryam Mokhtarzadeh, Brad Cunningham, Kesia Alexander, Markham Luke, Damia Jackson

CDER: Jacquelyn Smith, William Boyd, Diana Willard

Avedro: David Muller, Pamela Nelson, Geraldine Riera, Marc Friedman

Question 1 – UV irradiance

Does the agency agree with the proposed methodology, including the addition stated above, setup, sample size, and equivalence acceptance criteria?

CDRH: We agree that what Avedro has proposed looks acceptable.

Does the agency agree with the data presentation as a figure? Does the agency require raw data to be submitted for the figures?

CDRH: We'd like to see-

1. For the XY maps, flat contour maps with either color scales or labeled line contours to indicate irradiance for the isoirradiance planes. If you use color scales, then you can define either discrete color categories or continuous color gradients with sufficient resolution to distinguish irradiance changes of 5-10%.
2. For the profiles, Irradiance vs. X (or Y) position graphs with appropriate axis labels and numerical scales.

Question 2 – Eye movement

Does the agency agree with the proposed method, sample size, and equivalence acceptance criteria as identified in section 4? If not, what is acceptable?

Does the agency agree with the data presentation as a figure? Does the agency require raw data to be submitted for the simulated method?

In addition, based on the meeting discussion, it was agreed that the agency's request for an evaluation in human subjects is not representative of the clinical experience and, therefore, is not a valid request. Avedro requests more details on the following:

- Why Avedro's proposed simulated method is not acceptable?

- If FDA deems utilization of an alternate simulated method necessary, what is the methodology, acceptance criteria and reporting method?

Avedro: What suggestions do you have beyond measuring normal sighted people?

CDRH: We can work with your proposed Gaussian eye movement distribution if you can provide a valid justification for your assumption that the eye movements are the same for both devices.

Avedro: As you saw in the videos we provided, the UV irradiation of the cornea from both devices produces considerable fluorescence that obscures the subject's view of any other fixation target.

CDRH: Are you saying the subjects are mainly just seeing a bright light and they really can't see anything other than that?

Avedro: The brightness from the UV fluorescence is the only thing the patient is seeing. The only thing that resembles a point of fixation is the fact that the fluorescence appears brightest at the center. This statement is applicable to the experience with both devices.

CDRH: Based on that explanation, your argument that the eye movements should be equivalent for both devices is reasonable. However, it is not a trivial matter to convert your proposed smooth Gaussian curve to a sequence of eye movements appropriate for use in your simulations. How will you implement your proposed distribution of eye movements in the simulations?

Avedro: Think of taking a static profile and convolving it within the distribution so we'd be smearing the intensity profile. 68% of the time with one standard deviation, the patient would be fixating within 1mm of the nominal position. 95% of the time the patient would be fixating within 2mm of the nominal position.

CDRH: You also have to integrate over 30 minutes of exposure, so how are you at the same time integrating over X and Y?

Avedro: If you sample the eye every $\frac{1}{2}$ second and monitored the changes in position over 30 minutes then looked at the percentage of time the eye was in each possible position, it would have to correspond to the nominal Gaussian distribution. So over those 30 minutes, 68% of the time the patient would be within 1 mm and 95% of the time they'd be within 2mm. We could write this up and provide more detail.

CDRH: That would be good. When can we expect to receive the document?

Avedro: ~ 10:30 tomorrow.

Question 3 – Focal Plane

Does the agency agree with the proposed method, sample size, and equivalence acceptance criteria as identified in section 4? If not what is acceptable?

Does the agency agree with the data presentation as a figure? Does the agency require raw data to be submitted for the figures?

Regarding the agency recommendation or a calibration procedure, what type of procedure is the agency requesting considering the process described above? How does the agency want this incorporated into the response to deficiency 2e?

CDRH: We would like Avedro to state the distances both according to the manufacturing criteria for the distance from the device to the focal plane the aligned position of the focal plane relative to the patient's cornea. In other words, in the alignment procedure when the patient is under the device, if the physician follows the instructions correctly, where does the focal plane lie relative to the cornea?

Avedro: For both devices, [REDACTED] (b) (4)
[REDACTED]

CDRH: [REDACTED] (b) (4)
[REDACTED]

Avedro: Yes, both devices are designed the same way, [REDACTED] (b) (4)
[REDACTED]

CDRH: In that case you just need to specify [REDACTED] (b) (4)
[REDACTED] for both devices.

Avedro: Unsure about raw data

CDRH: [REDACTED] (b) (4) this should be incorporated in the simulations. Please provide written descriptions of the procedure for determining and calibrating focal length in manufacturing and the procedure for aligning subjects [REDACTED] (b) (4) for both devices.

Question 4 – Optical Simulation Data

Regarding the Avedro proposal in section 5 the method will incorporate elements identified in the agency preliminary response. Avedro agreed to incorporate beam homogeneity, eye movement, focusing data and provide a 3D distribution of energy for each device.

Is the proposed method, including the addition stated above, acceptable? If not what else is needed?

Does the agency agree with the proposed analytical procedures?

Does the agency agree with the data presentation as a figure? Does the Agency require raw data to be submitted for the figures?

CDRH: This approach is acceptable. We suggest providing the XY integrated exposure maps for the results of the simulations, and map of integrated exposure at the corneal surface and at 100, 200, and 300 microns below the surface.

Avedro: We will take slices at 0, 100, 200, 300, 400 microns across the cornea.

CDRH: These maps should include the entire area that's exposed as result of the simulated eye movements. We would also like to see the average exposure within the target area for each of the devices.

Avedro: Are the equivalence criteria proposed acceptable?

CDRH: We believe they are probably acceptable, although it's hard to know what differences are going to be clinically significant. We want to see the comparison; if there aren't any glitches in terms of spatial uniformity, then any other differences can probably be addressed in labeling.

Avedro: [REDACTED] (b) (4) this shouldn't be an issue.

CDRH: [REDACTED] (b) (4)
[REDACTED].

Avedro: [REDACTED] (b) (4)
[REDACTED]

Next steps-

CDRH will type the minutes from today's meeting; send them to CDER who will send them to Avedro.

Avedro will submit the documentation on the proposal for eye movement via email to CDER and CDRH by 10:30 EST tomorrow, August 20, 2015.

CDRH will meet with Avedro tomorrow to discuss the proposal.

Meeting with Avedro

August 20, 2015

Attendees-

CDRH: Bruce Drum, Dexiu Shi, Maryam Mokhtarzadeh, Brad Cunningham, Kesia Alexander, Damia Jackson

CDER: Jacquelyn Smith, William Boyd, Renata Albrecht

Avedro: David Muller, Pamela Nelson, Geraldine Riera, Marc Friedman

CDRH/DOED met with Avedro Wednesday, August 19th to discuss the issues surrounding the device-to-device comparisons and the firm's approach and methodology to addressing this matter (items 2a-2e outlined in the 3/15/15 CRL). While both parties were able to reach an agreement with respect to most of the points; the firm submitted additional documentation as it relates to eye movement. Today's meeting; Thursday, August 20th is a continuation of this discussion.

Question 2 – Eye movement

Avedro: We received the minutes and agree with the information captured. Did the Center receive the document we sent regarding eye movement? If so, do you agree with how we propose to capture the information discussed yesterday?

CDRH: Yes, we did receive the proposal and it looks acceptable. However, we would like clarification on a couple of additional issues:

Beam Shape: We are curious about how Avedro was able to [REDACTED] (b) (4)

Avedro: [REDACTED] (b) (4)

[REDACTED] Drawings of the original [REDACTED] (b) (4) are provided in section 2 of the Briefing Document.

Beam Focal Distance:

CDRH: Do you have any comparative information about precision of the adjustment for both devices with respect to setting the position of the beam focal plane relative to the cornea? Are they similar in precision or is there more variability in one than the other?

Avedro: The specification requirements are [REDACTED] (b) (4)

CDRH: Our question is with regard to alignment precision, not manufacturing specs. Is there a difference in how accurate and repeatable the physician's ability is to set the distance when aligning the subject?

Avedro: In Section 3.2.2 of the document we explain the doctors are trained on how to do the alignment. We're planning to train the people here the same way so we can measure how accurate the physician's alignment is with a side-viewing camera.

CDRH: It would be helpful if you could provide comparison data on the precision between both devices.

Avedro: We can provide that data. We believe these discussions have adequately addressed our approach for questions 2a-2e.

CDRH: We agree with your approach.

Avedro: We're prepared to modify the briefing book to reflect what we've agreed on with the protocols and the acceptance criteria and resubmit it asking if FDA agrees with the approach.

Retinal Exposure [REDACTED] (b) (4):

CDRH: One last point; when we looked at the video you sent it raised a concern [REDACTED] (b) (4)

[REDACTED] Have you done any analysis to confirm the light levels on the retina are safe (i.e., a light hazard analysis)?

Avedro: [REDACTED] (b) (4)

[REDACTED] We can provide the calculation for your review.

CDRH: We would appreciate seeing the calculation. [REDACTED] (b) (4)

Avedro: We will include the calculation in the briefing book.

CDRH: The calculation should include the expected retinal irradiance [REDACTED] (b) (4) and the wavelength.

Avedro: [REDACTED] (b) (4)

[REDACTED] We will provide the information.

CDER: Please use track changes for the edits in the revisions you provide of the briefing book.

Avedro: We will send a clean copy and a track changes copy.

Meeting with Avedro

August 26, 2015

Attendees-

CDRH: Bruce Drum, Dexiu Shi, Maryam Mokhtarzadeh, Brad Cunningham, Kesia Alexander, Damia Jackson

CDER: William Boyd, Renata Albrecht, Diana Willard

Avedro: David Muller, Pamela Nelson, Marc Friedman, Desmond Adler

CDRH met with Avedro on August 19, 2015 and August 20, 2015 to discuss the device-to-device comparisons and obtain agreement on the protocol and acceptance criteria outlined in their briefing book. On Friday, August 21, 2015, Avedro sent clean and redlined versions of the briefing book to ensure it adequately reflected the agreements reached over the course of the two-day discussion. On Monday, August 24, 2015, Avedro requested a meeting to “ensure that we are all on the same page.” CDRH agreed to the meeting and returned the briefing book with the comments/feedback embedded within the document. At the meeting, which occurred on August 26, 2015, both parties provided clarification regarding verbiage and a consensus was reached on the path forward.

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
09/29/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: August 14, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324-- Photrexa Viscous, Photrexa, and the KXL-System

Total no. of pages including cover: 5

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light. We also refer to the discussion, in the August 10, 2015 Type A meeting, regarding the need for additional clinical trial analyses. Below is an outline of the information that we are requesting for the existing clinical trials.

Information Request

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 \geq 22 years of age.
 - b. There is concern that illumination diameter may impact safety and effectiveness. The KXL device only includes a fixed illumination diameter of 9.5 mm. Since the UV-X device was studied with three illumination diameters, 7.5 mm, 9.5 mm, and 11.5 mm, please submit the analysis with only subjects that have specific documentation of receiving the 9.5 mm illumination diameter at the time of treatment.
 - c. There is concern that all subject enrolled in the studies may not have had progressive disease, as intended. Therefore, please remove (b) (4)

Please 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 1.a-c immediately above) and use this cohort in your response to the remaining items 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 Photrexa 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. Indicate whether 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. 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.
 4. For the following endothelial cell count (ECC) analyses, please use observed data only (no LOCF):

For study eyes and all eyes (separately), please provide mean within eye change in ECC at each visit the measurement was performed. Also, please provide the mean change in ECC within eyes from baseline to 12 months for eyes that received crosslinking treatment. In these analyses please provide summary statistics including (but not limited to) range. Please provide distributions of change in ECC in +/-5% interval bins. Please provide a discussion regarding eyes which had a concerning level of change in ECC (eyes which lost >25% ECC and/or in which ECC dropped below 2000). Please provide additional information about these clinical course in these eyes (such as adverse events, etc. which may be related to or resulting from the change in ECC).

Please remember to provide these analyses separately for pediatric eyes separately and for each indication separately.

5. Please provide a comprehensive literature review to support the use of the to-be-marketed combination product with the KXL System as described in the March 2015 Complete Response Letter, Additional Comment #4.
6. Data were collected from two questionnaires in your trial, (1) the Refractive Status and Vision Profile (RSVP) Questionnaire and (2) the Subjective Complaint (SC) Questionnaire. In addition, your submission identified adverse events (AEs) which included, but were not limited to reports of eye pain, glare and halos. However, the source of the reported AEs is not clear. Please indicate whether the AE information was obtained from a clinician's report (i.e., a clinician-reported outcome), questionnaire (SC or RSVP), or other source. Furthermore, it is unclear whether the subjective complaint questionnaire (SC) was a patient-reported outcome or a clinician-reported outcome. If more than one source was used to identify the same AE, identify how the information

NDA 203324
Information Request

was pooled and the rationale for that selection. For each of the two questionnaires used in these trials, please provide results and analyses including the following: response frequency for each item, cumulative distribution function, and evidence that each questionnaire is an appropriate tool to measure the selected concept in this intended use population.

7. 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 post-refractive 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).

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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
08/14/2015



NDA 203324

MEETING MINUTES

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light.

The purpose of the June 11, 2015, Type A, meeting was to discuss the complete response letter, dated March 29, 2015.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager at 301 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 11, 2015

Meeting Location: CDER WO22 1313

Meeting Type: Type A

Application Number: NDA 203324

Product Name: Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light

Indication: Corneal Collagen Cross-linking

Applicant Name: Avedro, Inc.

Meeting Chair: Renata Albrecht, M.D.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Renata Albrecht, MD	Director, Division of Transplant and Ophthalmology (DTOP)
Lori Kotch, PhD	Pharmacology/Toxicology Supervisor, DTOP
Aaron Ruhland, PhD.	Pharmacology/Toxicology Reviewer, DTOP
William Boyd, MD.	Medical Leader, DTOP
Rhea Lloyd, MD	Medical Officer, DTOP
Martin Nevitt, MD	Medical Officer, DTOP
Diana Willard	Chief Project management Staff, DTOP
Judit Milstein	Chief Project management Staff, DTOP
Yan Wang, PhD	Statistics Team Leader, DTOP
Dongliang Zhuang, PhD	Statistics Reviewer, DTOP
Daphne Lin, PhD	Deputy Director, OTS/OB/DBIV
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Bradley Cunningham, MS	Chief, CDRH/ODE/DOED/DSDB
Jeffrey Silberberg, PhD	Senior Electronics Engineer, CDRH/OSEL/DBP
Thinh Nguyen, MS	Director, OC/OSMP/OCP
Patricia Love, MD	Deputy Director, OC/OSMP/OCP
John Weiner, JD	Associate Director, OC/OSMP/OCP

Katherine Schumann, MS
Xin Fang, PhD
Bruce Drum, PhD

James Reese, PhD

Acting ADRA/OAP
Statistics Reviewer, CDRH/OSB/DBS/CODB
Physicist/Vision Science Reviewer,
CDRH/ODE/DOED/DSDB
Health Science Administrator, OSMP/OOPD

AVEDRO, INC ATTENDEES

David Muller, PhD
Pamela Nelson, MBA
Geraldine Riera

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

President and Chief Executive Officer
Vice President, Regulatory Affairs
Director, Regulatory Affairs
Regulatory Consultant
Founder and President (b) (4)
Senior Counsel, (b) (4)
Special Counsel, (b) (4)
Consultant, (b) (4)

BACKGROUND

The purpose of the meeting was to discuss FDA's, June 10, 2015, preliminary comments, in response to Avedro's questions, contained in the May 27, 2015 meeting package. The meeting began with opening remarks and introduction of the attendees. Avedro thanked FDA for scheduling the meeting, reviewing the briefing package, and providing preliminary comments. A complete list of the preliminary comments is attached.

Questions

1. CDRH determined that "the information submitted to establish similarity of the two device constituent parts is not sufficient", and asserted that a new clinical study should be conducted using the KXL System.
 - a. What is the scientific basis for rejecting the comparative information submitted on the two device constituent parts?

Agency Response:

As stated in the Agency Complete Response Letter of March 29, 2015, we recommend that you conduct a clinical study (or studies) showing that Photrexa Viscous and Photrexa with the KXL-System when used in the corneal collagen cross-linking procedure is safe and effective for the Indication(s) proposed or alternatively, provide sufficient information to bridge the combination product device constituent, KXL System, to the IROC UV-X device used in the clinical studies submitted. If you choose the latter alternative, we cannot make an assessment that the two devices are interchangeable until you provide the additional comparative information identified at Item 2a – 2e beginning on Page 2 of the Complete Response Letter of March 29, 2015. If you select this option then also consider the FDA Additional Comments in the context of the existing data.

b. What is the regulatory authority for applying a drug review standard to the device constituent part?

Agency Response:

Avedro's combination product was submitted under the NDA and as such is subject to the NDA requirements in addition to those requirements that apply because it includes a device constituent part.

2. What is FDA's justification for failing to provide these CDRH comments in the first complete response letter, when 21 CFR 314.110(a)(1) requires FDA to identify "all of the specific deficiencies that the agency has identified in the application"?

Agency Response:

Under the Prescription Drug and User Fee Act (PDUFA) a Complete Response letter should contain all the deficiencies identified in the application during the review of the application. The deficiencies identified for the device constituent part during the first cycle were included in the first Complete Response letter dated March 14, 2014. Additional deficiencies were included in the second Complete Response letter dated March 29, 2015 because they were identified based on the information provided in the Complete Response submitted September 29, 2014, and during the course of the review of that response.

3. The Advisory Committee voted to approve the product for the proposed orphan indications for use, and that vote included the KXL System constituent part. What is FDA's rationale for not adopting the vote of the Advisory Committee, and why was the rationale not provided in the Second CRL?

Agency Response:

Although the Agency considers and often follows the Advisory Committee's recommendations, in this case, the application could not be approved because of remaining deficiencies; see response to Question 1b. These deficiencies are listed in CRL.

4. Does the Agency agree with Avedro's response to Second CRL #1? Specifically, does the Agency agree that no further information is required in order to establish similarity between the two device constituent parts?

Agency Response:

See response to Question 1a.

MEETING DISCUSSION

Avedro opened the discussion by noting the clinical importance of corneal cross-linking in patients with keratoconus or post refractive corneal ectasia. Avedro asked to focus the meeting on the topic of their Question 1a and stated that they plan to address the request about comparability of the KXL System to the IROC UV-X device by providing sufficient information

to bridge the combination product device constituent, KXL System, to the IROC UV-X device used in the clinical studies submitted.

The Agency stated that the Complete Response Letter (CRL) of March 29, 2015, provided the options for a new clinical trial(s) with the KXL System or submission of additional comprehensive analyses on the KXL System and the IROC UV-X device to demonstrate that the two devices are interchangeable (Items 2a - 2e). The CRL also requested that in the design of new clinical trial(s) Avedro consider the Agency's Additional Comments. It was noted by the Agency that clinical trial design issues were raised at the Advisory Committee meeting.

Avedro stated that they are still committed to doing a post-approval study, but that they are not in a position to do another clinical study before approval.

Avedro asked the Agency to be specific regarding what bridging would be adequate between the IROC UV-X device used in the clinical study, and the KXL System. Avedro stated they have responses to 2a – 2e, and Avedro believes their data show the IROC UV-X device to be clinically interchangeable with the KXL System. Since the Agency stated the devices have not been demonstrated to be interchangeable, Avedro stated they would request another Type A meeting and submit their 2a – 2e responses in the briefing material. The Agency agreed to a Type A meeting and discussion. The Agency recommended that Avedro's responses should include information on the clinical implications of any identified differences (e.g., for each indication, to effectiveness, and to safety) as well as provide what they consider to be an acceptable range of similarity or difference between the devices (e.g., error bars where applicable), and discuss and justify why the differences are or are not of clinical importance.

(b) (4)
The Agency stated that its comments were in the context of the submitted NDA for KXL System. (b) (4)

ACTION ITEMS:

- Avedro will submit a request for a Type A meeting to their NDA, and include the comparative information on the two devices, identified at Item 2a-2e, in the Complete Response Letter of March 29, 2015 (pages 2-3), as the briefing material within a week of the June 11, 2015 meeting. During this Type A meeting or shortly thereafter, the Agency will provide feedback on Avedro's responses to 2a - 2e, and any additional clinical trial subset analyses that are submitted.
- The Agency will issue the meeting minutes within 30 days of the June 11, 2015, meeting.

Minutes Preparer: Jacquelyn Smith, MA, Senior Regulatory Project Manager, DTOP
Chair Concurrence: Renata Albrecht, MD, Director, DTOP

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/s/

RENATA ALBRECHT
07/10/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: March 18, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 9

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013 and your resubmission dated September 29, 2014, submitted for your riboflavin ophthalmic solution and the KXL System.

We have provided some comments for the carton/container labeling. Please address these comments and submit your revised labeling no later than Wednesday, March 25, 2015.

We are providing the information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

Carton Box

(b) (4)

Reviewer's Comments:

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

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

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

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

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

(b) (4) should be revised to read, "Storage: Store at 15° – 25° C (xx° – xx° F).

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

The statements, (b) (4) are inadequate. The statements should be revised to include all ingredients, active and inactive.

Container Label – Syringe

(b) (4)



Reviewer's Comments:

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

[redacted]

[redacted] (b) (4) *should be revised to read,* [redacted] (b) (4)

Pouch Label – Light Block Pouch (foil)



(b) (4)

Reviewer's Comments:

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

[redacted]

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

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

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

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

The statements, (b) (4) are inadequate. The statements should be revised to include all ingredients, active and inactive.

Pouch Label – Tyvek Pouch

(b) (4)

Reviewer’s Comments:

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

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

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

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

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

[redacted] (b) (4) *should be revised to read, “Storage: Store at 15° – 25° C (xx° – xx° F)*

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

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/s/

JACQUELYN E SMITH
03/18/2015

Smith, Jacquelyn

From: Pamela Nelson <PNelson@avedro.com>
Sent: Monday, March 16, 2015 10:11 AM
To: Smith, Jacquelyn
Subject: RE: NDA 203324- Avedro KXL device

Hi Jacquelyn,

Below please find our response to the question:

Avedro Response:

We confirm [REDACTED] (b) (4) The presentation slide is a not to scale depiction of the imaging system. There is no focusing mechanism. We apologize for any confusion.

From: Smith, Jacquelyn [<mailto:Jacquelyn.Smith@fda.hhs.gov>]
Sent: Thursday, March 12, 2015 6:12 AM
To: Pamela Nelson
Subject: NDA 203324- Avedro KXL device

Hi Pam,

We have the following information request regarding the KXL and UVX devices.

During the Advisory Committee meeting, you presented information comparing UV-Focal Plane between the UV-X and the KXL systems (“Device Comparison – UV Focal Plane”; Slide CC-33). From your panel presentation, it appears [REDACTED] (b) (4)

Please confirm [REDACTED] (b) (4) please confirm whether the presentation slide is an accurate depiction of the focusing mechanism.

Regards,
Jacquelyn

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/s/

JACQUELYN E SMITH

03/16/2015

Email sent to applicant on March 12, 2015

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Monday, March 09, 2015 12:50 PM
To: 'Pamela Nelson'
Subject: NDA 203324

Hi Pam,

Thanks for the March 4, 2015 email containing responses to the EMC deficiencies. After review, we still have the following outstanding deficiencies. Please address by Friday, March 13, 2015.

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)".

Secondly, please provide me with a WORD version of the updated Operator's Manual. The Operator's manual is updated to coincide with Photrexa/ Photrexa Viscous proprietary name, correct? The previous spoke of Photrexa

(b)
(4)

Finally, in Section 17, Patient Counseling Information, of your package insert (PI), the statement " Please Distribute the Enclosed Patient Information Sheet" was included. Did you plan to provide a patient information sheet or was this inadvertently included in the PI?

Thank you for addressing the above items.

Regards,
Jacquelyn

From: Pamela Nelson [<mailto:PNelson@avedro.com>]
Sent: Wednesday, March 04, 2015 11:19 AM
To: Smith, Jacquelyn
Subject: NDA 203324

Hi Jacquelyn,

The following is Avedro's response to the Agency's March 2nd information request.

The requested materials were submitted to the NDA previously and are provided in this email as pdf attachments for ease of review. Below is a list of the reports and when those documents were originally submitted.

- SN 0027(14 JUL 2014) Section 3.8 - IEC60601-1-6 Ed 2 KXL Report
- SN 0027(14 JUL 2014) Section 3.8 - VAL-00091-RPT
- SN 0027(14 JUL 2014) Section 3.8 - VAL-00095-RPT
- SN 0031(12 FEB 2015) - Current KXL manual

Best,
Pam

From: Smith, Jacquelyn [<mailto:Jacquelyn.Smith@fda.hhs.gov>]
Sent: Monday, March 02, 2015 2:07 PM
To: Pamela Nelson
Subject: NDA 203324

Hi Pam,

On February 23, CDRH evaluated responses from Avedro regarding EMC deficiencies. Some were acceptable and some were acceptable pending examination of the Operator's Manual and EMC test reports (Agency request 7, 8, 9 and 10). Please provided a copy of the updated Operator's Manual and a copy of the EMC test reports by the Friday, March 6th.

PS: Sorry, I missed your call, but I was out sick on Friday and working from home today due to bad weather.

Regards,
Jacquelyn

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/s/

JACQUELYN E SMITH
03/09/2015

CDER SEALD Endpoints

From: CDER SEALD Endpoints
Sent: Friday, February 20, 2015 6:38 PM
To: Smith, Jacquelyn; Boyd, William M
Cc: 'Papadopoulos, Elektra'
Subject: RE: Finalized - NDA-203324 SEALD Consult Request (FRM-CONSULT-13)

Dear William and Jacquelyn,

This email is in response to a SEALD Study Endpoints Team consult request made by the Division of Transplant and Ophthalmology Products (DTOP) for NDA 203324, which is being developed for the treatment of progressive keratoconus and corneal ectasia after refractive surgery. The sponsor has included the Refractive Status and Vision Profile Questionnaire (RSVP) in phase 3 studies within this NDA for exploratory purposes. The Division requested that the Study Endpoints Team review and comment on the quality and validity of the questionnaire, fitness for purpose, and interpretation of the results.

The sponsor has not provided any information or documentation of critical elements needed for our review. For example, we do not have information on the conceptual framework, scoring algorithm or development history of the instrument. Therefore, we are unable to determine whether the RSVP is a well-defined and reliable assessment in the targeted patient population and a consult review cannot be completed.

We also note that the sponsor decided not to summarize the data for the RSVP results based on the following statement (Clinical Study Report for UVX-001): "The rationale for this decision was that the randomized eye in the case of subjects assigned to the sham group could later have received the CXL treatment; in addition, the fellow eye could also have been treated later. These circumstances would have made interpreting the results inappropriate as the questionnaire doesn't allow for analysis by eye."

The SEALD Study Endpoints Team does not generally review exploratory assessments. Given that the RSVP was used for exploratory/descriptive purposes, and the sponsor does not seek labeling claims, a SEALD consult review is not needed and we will close out this consult request with this email.

Please let us know if you have any additional questions.

Best regards,
Jessica

Jessica Voqui, PharmD, MS
Lieutenant Commander - USPHS
Regulatory Review Officer
Study Endpoints (SEALD)
FDA | CDER | Office of New Drugs
SEALD.Endpoints@fda.hhs.gov

From: Smith, Jacquelyn
Sent: Thursday, February 12, 2015 4:02 PM
To: CDER SEALD Endpoints
Subject: FW: Finalized - NDA-203324 SEALD Consult Request (FRM-CONSULT-13)

Jessica,

Documents are attached. We would need a preliminary response before the February 24, 2015 AC meeting.

Thanks,
Jacquelyn

From: Smith, Jacquelyn
Sent: Thursday, February 12, 2015 3:03 PM
To: Papadopoulos, Elektra
Subject: FW: Finalized - NDA-203324 SEALD Consult Request (FRM-CONSULT-13)

Dr. Papadopoulos,

Just following up with an email of the information provided in the attached consult request. I'm also providing the information documents.

Regards,
Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
White Oak, Room 6114
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Telephone: (301) 796-1002
Fax: (301) 796-9881
Email: jacquelyn.smith@fda.hhs.gov

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/s/

JESSICA VOQUI
02/23/2015

ELEKTRA J PAPADOPOULOS
02/23/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: February 20, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 4

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013 and your resubmission dated September 29, 2014, submitted for your riboflavin ophthalmic solution and the KXL System.

This is regarding the statistical information request dated Feb. 12. This analysis is to evaluate the treatment effect regardless of adherence to the randomized arm. This analysis uses the last observed Kmax value at or prior to 12 month from baseline for all subjects, including sham subjects regardless of whether their study eyes received CXL treatment at Month 3 or 6. This analysis uses the same baseline value as the one used in your primary analysis at Month 12. The FDA statistical reviewer has conducted this analysis and the results are attached. Please submit your analysis results by the end of next week.

FDA Exploratory Analysis Results of Mean Change from Baseline in Kmax at Month 12 (ITT, LOCF)

Study	CXL Mean (SD)	Sham Mean (SD)	Difference (95%)	P-value
Progressive Keratoconus				
UVX-001	-1.4 (2.8)	-0.3 (4.1)	-1.1 (-2.9, 0.8)	0.2534
UVX-002	-1.7 (4.7)	-0.1 (2.7)	-1.5 (-2.8, -0.3)	0.0159
Corneal Ectasia				
UVX-001	-1.0 (1.7)	0.8 (3.4)	-1.8 (-3.4, -0.2)	0.0243
UVX-003	-0.5 (2.2)	-0.2 (2.7)	-0.4 (-1.3, 0.5)	0.3791

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
02/20/2015



**Food and Drug Administration
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COMMUNICATION TRANSMITTAL SHEET

DATE: February 18, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 6

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013 and your resubmission dated September 29, 2014, submitted for your riboflavin ophthalmic solution and the KXL System.

We also refer to the following information request. Please provide a response as soon as possible, prior to the AC meeting, if possible.

Information Request

By study design, the study eyes in the sham group could receive CXL treatment at Month 3 or later. We also note that in Study UVX-002, there were two sham subjects whose study eye received CXL treatment prior to Month 3. Our summary of the number of sham subjects whose study eye received CXL is provided in Table 1. Please produce and submit your summary table if there are errors in this table. Additionally, to help us understand when and how many CXL-treated sham study eyes had Kmax values, please produce summary results for the number of sham subjects whose study eye received CXL treatment and had Kmax value over time (preferably using the format provided in Tables 2-5). In Tables 2-5, we propose to use the following definition for the time windows:

- 1-month: $0 < K < 28 \pm 15$
- 2-month: $28 \pm 15 \leq K < 2 * 28 \pm 15$
- 3-month: $2 * 28 \pm 15 \leq K < 3 * 28 \pm 15$
- 4-month: $3 * 28 \pm 15 \leq K < 4 * 28 \pm 15$
- i-month: $(i-1) * 28 \pm 15 \leq K < i * 28 \pm 15$

Table 1: Number of Sham Subjects Whose Study Eye Received CXL				
	Progressive Keratoconus		Corneal Ectasia	
Visit	UVX-001 (N=29)	UVX-002 (N=74)	UVX-001 (N=25)	UVX-003 (N=63)
Month 1?		2		
Month 3	9	47	11	42
Month 6	16	18	10	16

Table 2: Number of Sham Subjects Whose Study Eyes Received CXL prior to Month 3 and had Kmax Values				
	Progressive Keratoconus		Corneal Ectasia	
Time* from Day 0 (randomization)	UVX-001 (N=25?)	UVX-002 (N=67?)	UVX-001 (N=21)	UVX-003 (N=58)
1 month				
2 month				
3 month				
.....				
13 month?				

Table 3: Number of Sham Subjects Whose Study Eyes Received CXL at Month 3 and had Kmax Values				
	Progressive Keratoconus		Corneal Ectasia	
Time from Day 0 (randomization)	UVX-001 (N=25?)	UVX-002 (N=67?)	UVX-001 (N=21)	UVX-003 (N=58)
4 month				
5 month				
6 month				
.....				
15 month				

Table 4: Number of Sham Subjects Whose Study Eyes Received CXL at Month 6 and had Kmax Values				
	Progressive Keratoconus		Corneal Ectasia	
Time from Day 0 (randomization)	UVX-001 (N=25?)	UVX-002 (N=67?)	UVX-001 (N=21)	UVX-003 (N=58)
4 month				
5 month				
6 month				
.....				
18 month				

Table 5: Number of Sham Subjects Whose Study Eyes Received CXL and had Kmax Values				
	Progressive Keratoconus		Corneal Ectasia	
Time from Day 0 (randomization)	UVX-001 (N=25?)	UVX-002 (N=67?)	UVX-001 (N=21)	UVX-003 (N=58)
1 month				
2 month				
3 month				
.....				
12 month				
.....				

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
 Senior Regulatory Health Project Manager
 Division of Transplant and Ophthalmology Products
 FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
02/18/2015



NDA 203324

INFORMATION REQUEST

Avedro, Inc.
Attention: Pamela Nelson, Vice President, Regulatory Affairs
230 Third Avenue
Fifth Floor
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photrexa and Photrexa (b) (4)

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have identified several areas that require further information. As we continue with our review it is likely that we will have more questions. Please provide a prompt written response to the following information requests by February 26, 2015, in order to continue our evaluation of your NDA.

1. Please commit to placing the first 3 batches of the drug product without dextran and the first 3 batches of the drug product with dextran that are manufactured using drug substance (b) (4) on long term stability. These batches should be packaged with the syringes in the Tyvek pouches inside the light-blocking foil pouches.
2. Please commit to establishing the linearity of response for the specified impurities (b) (4) over at least the range from the Limit of Quantitation to the drug product specification limit. Provide the report to the Annual Report.
3. Please note that at this stage we only feel that the stability data support an 18 month expiration dating period. (b) (4)

If you have any questions, please contact Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

Dorota Matecka, Ph.D.
Acting Branch Chief, Branch III
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research

Dorota M.
Matecka -S

Digitally signed by Dorota M. Matecka -S
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ou=FDA, ou=People,
0.9.2342.1.9200300.100.1.1=1300123291,
cn=Dorota M. Matecka -S
Date: 2015.02.16 17:54:42 -0500



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: February 12, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 3

Document to be mailed: YES NO

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NDA 203324
Information Request

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013 and your resubmission dated September 29, 2014, submitted for your riboflavin ophthalmic solution and the KXL System.

We also refer to the following information request. Please address and respond back to us as soon as possible.

Information Request

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.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
02/12/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: February 11, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
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NDA 203324
Information Request

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013 and your resubmission dated September 29, 2014, submitted for your riboflavin ophthalmic solution and the KXL System.

We also refer to the following information request. Please address and respond back to us as soon as possible.

Information Request

Please conduct an analysis of the mean change in Kmax from baseline to Month 12 according to the intent-to-treat principle. For subjects in the sham group, their last Kmax 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 at which the subject crossed over from sham to CXL. You can present the analysis results in the same format as for your current primary efficacy analysis.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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JACQUELYN E SMITH
02/11/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: February 4, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 5

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013 and your amendment dated September 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Photrexa (Riboflavin) Ophthalmic Solution, 0.12% and Photrexa Viscous (Riboflavin with 20% Dextran), Ophthalmic Solution, 0.12%.

Please respond to the following information request. We request that these analyses and discussions be available no later than February 13, 2015.

Information 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"

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.

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.”

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.”

2. Evaluation of data collected

a. **MANUAL KERATOMETRY**

- i. Evaluation similar in methodology to the primary efficacy criteria except using manual keratometry readings.

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%; > or = 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.).

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)

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

3. Pediatric Subjects

Reorganize the pediatric information (separate tables) for the primary efficacy variable and for endothelial cell counts to describe subjects ≤ 16 years of age and ≤ 21 years of age.

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.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
02/04/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: January 12, 2015

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 6

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013, your Type A meeting package dated June 30, 2014, and your resubmission dated September 29, 2014, submitted for your riboflavin ophthalmic solution and the KXL System.

We are in the reviewing process of your NDA and have the following information request:

Information Request

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 (b) (4)

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 (b) (4) % of the user-selected value) and user-selected time (within (b) (4)

Information Request

(b) (4) %, whichever is larger) to deliver the total fluence (J/cm^2 , (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 (b) (4) tests. Please affirm that all of these modifications will be included in all production units.

Modifications Required for Compliance

Modifications were required for the following tests:

[Redacted] (b) (4)

In order to be compliant [Redacted] (b) (4) the following modifications were implemented.

[Redacted] (b) (4)

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.

[Redacted] (b) (4)

Information Request

(b) (4)

3. In the Operator's Manual, the Symbol Table, the text shown for the non-ionizing symbol (#17) is confusing and misleading. Please change (b) (4) to something like "this device includes RF transmitters". This information is needed to help assure the safety and effectiveness of the KXL System.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
01/12/2015



NDA 203324

INFORMATION REQUEST

Avedro, Inc.
Attention: Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue, 5th Floor
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photrexa Viscous, Photrexa, KXL Device.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. Please provide a written response to the following information requests by November 20, 2014, in order to continue our evaluation of your NDA.

Your determination of the drug product assay value is not adequate and lacks precision. Judging from the stability data provided in P.8 of the submission dated September 29, 2014, you measure the assay to a precision (b) (4).

[Redacted]

[Redacted] (b) (4)

Please submit revised batch analysis and stability data.

If these requests are not clear to you or if you have additional questions please ask for further guidance.

If you have any questions, please contact Navdeep Bhandari, Regulatory Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, PhD
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

**Balajee
Shanmugam -S**

Digitally signed by Balajee Shanmugam -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300217143,
cn=Balajee Shanmugam -S
Date: 2014.10.20 14:43:31 -04'00'

Smith, Jacquelyn

From: ees_admin@fda.gov
Sent: Wednesday, March 05, 2014 10:10 AM
To: Cuff, Althea; Shanmugam, Balajee; Godwin, Francis; Smith, Jacquelyn; Zhou, Maotang; Salganik, Maria*; Spain, Nancy *; Bhandari, Navdeep; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 203324/000 Decision: WITHHOLD, Decision Date: 03/05/2014, Re-evaluation Date:

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cderr.fda.gov). To contact the EES technical staff, send an email to CDER EES Help (EESHHELP@fda.hhs.gov). Thank you.

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Thursday, February 20, 2014 9:01 AM
To: Pamela Nelson (PNelson@avedro.com)
Subject: Information Request for NDA 203324

Hi Pam,

Please see the below information request. A response is needed as soon as possible.

Information Request

In the Clinical Overview (Module 2.5), you state on page 14, Section 4.1.3, "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 protocols for UVX-001, -002, and -003, submitted on 9/16/13 as part of their respective clinical study reports, do not have amendments extending the primary endpoint to Month 12. Please provide that date the protocols were revised to extend the primary endpoint to Month 12 for UVX-001, -002 and -003. Please provide copies of the revised protocols.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
02/20/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: February 11, 2014

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for riboflavin ophthalmic solution and the KXL System.

We have the following information request:

Information Request

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.

Please discuss whether any of 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 on are:

Induction Period: (b) (4) 30 minutes
 Irradiance: 3 mW/cm²
 Total Energy: 5.4 J/ cm²
 Exposure Time: 30 minutes

However, (b) (4) 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.

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 (b) (4) %.
 6.2.6.8. Power uniformity over the illuminated area shall be (b) (4) % RMS.

Please address the following concerns:

- a. A tolerance range ((b) (4) %) is given for UV-A output. Please provide your rationale for why this tolerance range is selected and/or the justification that the (b) (4) % illumination fluctuation will be safe for proposed treatment.
- b. Please provide the test result to demonstrate power uniformity over the illuminated area is (b) (4) % RMS for KXL system.
4. You state that “UVA radiation is generated by (b) (4) UV LED (365nm). (b) (4)

(b) (4) 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 (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 (b) (4) VAC (b) (4) 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:



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".

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

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
02/11/2014



NDA 203324

**METHODS VALIDATION
MATERIALS RECEIVED**

Avedro, Inc.
Attention: Pamela Nelson
VP Regulatory Affairs
230 Third Avenue
5th floor
Waltham, MA 02451

Dear Pamela Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Photrexa (riboflavin ophthalmic solution) 0.12% and to our November 18, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 19, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/20/2013



NDA 203324

INFORMATION REQUEST

Avedro, Inc.
Attention: Pamela Nelson, Vice President, Regulatory Affairs
230 Third Avenue
Fifth Floor
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photrexa and Photrexa (b)(4)

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have identified several areas that require further information. As we continue with our review it is likely that we will have more questions. Please provide a prompt written response to the following information requests by January 15, 2014, in order to continue our evaluation of your NDA.

1. In Section S.4, Table 2 you present batch analyses for 3 batches of drug substance manufactured (b)(4) and one batch (UEB1006078) manufactured (b)(4). However, in Table 4 you compare one of the (b)(4) batches with an apparently different (b)(4) batch, 6147952. Please indicate which batch(es) of (b)(4) drug substance were used for clinical trial material and to manufacture the validation batches described in the NDA. For each of the clinical and validation batches of drug substance please provide analytical data such as that in Table 2 and tabulated HPLC data such as that in Tables 3 and 4, if not already supplied.
2. As you state in Section 2.6 (page 11) "the absorption of UVA by riboflavin generates radical riboflavin and singlet oxygen to form cross-links". It is unclear if the various riboflavin-related substances contribute equally to forming singlet oxygen. Please provide information (or literature citations) on whether riboflavin itself, riboflavin 5'-phosphate, and other riboflavin phosphates and diphosphates produce these reactive intermediates and/or accomplish cross linking in roughly similar amounts when irradiated by the laser.
3. Please provide the specification that you use for sterile water for injection and some sample Certificates of Analysis.
4. It is unclear how you determine the assay value for the label claim (b)(4). Please confirm if this is so and describe how the assay value is determined.
5. Indicate if the amount of riboflavin in the 10% dextran solutions used for supporting stability data and in the solutions used for the pivotal clinical trials is within (b)(4)% of the labeled claim (b)(4).

6. You state in Amendment of 11/27/13, page 7, “ [REDACTED] (b) (4) [REDACTED] To justify this proposal, provide stability data and/or stress data to show that these compounds are not degradants.
7. In the Amendment of 11/27/13 you state that incoming dextran 500 is tested for specific optical rotation (pages 2-3). Please indicate how optical rotation would distinguish dextran 500 from other grades of dextran, or indeed other products with a similar rotation, and ensure that the material had not become damaged in transit. We recommend adding a test for average molecular weight for incoming dextran 500.
8. Please indicate the average drop size (with standard deviation) for each formulation.

If you have any questions, please contact Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
12/20/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: December 17, 2013

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A., Sr. Project Manager
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 3

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for riboflavin ophthalmic solution and the KXL System.

We have the following information request:

Information Request

Please conduct sensitivity analysis using multiple imputation method to handle missing data for the Kmax parameter for each post-baseline visit. We recommend that you update relevant analysis results to include the estimate of the treatment difference and its 95% CI at each study visit based on the following analysis methods: (1) your primary analysis method, (2) the ANCOVA with baseline as covariate, and (3) the multiple imputation method. We recommend that you add these analysis results to your CSR Table 14.2.1.1.1-14.2.1.1.3: one additional column for the estimate of the treatment difference and its 95%CI and one additional row for multiple imputation analysis results, as these tables will help us review and compare these analysis results in one place.

When addressing the issue of missing data using multiple imputation method, we recommend you consult “The prevention and treatment of missing data in clinical trials” by the Panel on Handling Missing Data in Clinical Trials (https://download.nap.edu/catalog.php?record_id=12955)

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
12/17/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: December 17, 2013

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 3

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for riboflavin ophthalmic solution and the KXL System.

We have the following information request:

Information Request

Please conduct sensitivity analysis using multiple imputation method to handle missing data for the Kmax parameter for each post-baseline visit. We recommend that you update relevant analysis results to include the estimate of the treatment difference and its 95% CI at each study visit based on the following analysis methods: (1) your primary analysis method, (2) the ANCOVA with baseline as covariate, and (3) the multiple imputation method. We recommend that you add these analysis results to your CSR Table 14.2.1.1.1-14.2.1.1.3: one additional column for the estimate of the treatment difference and its 95% CI for the results of the three analysis methods and one additional row for the p-value based on the multiple imputation analysis method, as these tables will help us review and compare these analysis results in one place.

When addressing the issue of missing data using multiple imputation method, we recommend you consult “The prevention and treatment of missing data in clinical trials” by the Panel on Handling Missing Data in Clinical Trials

(https://download.nap.edu/catalog.php?record_id=12955)

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
12/17/2013



NDA 203324

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Avedro, Inc.
Attention: Pamela Nelson
Vice President Regulatory Affairs
230 Third Avenue
5th Floor
Waltham MA 02451

Dear Pamela Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Photrexa (riboflavin ophthalmic solution) 0.12%.

We will be performing methods validation studies on Photrexa (riboflavin ophthalmic solution) 0.12%, as described in NDA 203324.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

HPLC Method for Photrexa and Photrexa (b) (4)

Samples and Reference Standards

(b) (4) Riboflavin 5'-phosphate sodium (b) (4)
Vials of Photrexa ophthalmic solution
Vials of Photrexa (b) (4) ophthalmic solution
(b) (4) if available
(b) (4) if available
dextran

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/18/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: October 15, 2013

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, for riboflavin ophthalmic solution and the KXL System.

We have the following information request:

Information Request

1. *Please provide all available data that were collected for untreated fellow eyes. We noted that, for example, among 179 ectasia subjects, a total of 65 fellow eyes in the CXL group and 66 fellow eyes in the sham group didn't receive any treatment. We could not find data collected during the follow-up procedure and examination for these untreated fellow eyes. If data were collected for these untreated fellow eyes, please provide all data including their key efficacy data, you stated that "All available data that were collected for the untreated fellow eyes have been included in the CSRs for UVX-001, UVX-002 and UVX-003." Please provide the location of these data.*

It doesn't seem that you have included the data for the untreated fellow eyes in the pooled dataset *adefx.xpt*. If this is the case, please include the data for the untreated fellow eyes.

2. *Please provide analyses for the proportion of subjects who experienced ≥ 1 D decrease in Kmax from baseline, you stated that "The requested analyses of the proportion of subjects who experienced ≥ 1 D decrease in Kmax from baseline is presented in Section 11.4 of the amended CSRs for UVX-001, UVX-002 and UVX-003." We noted that you only presented the distribution of change in Kmax from baseline in randomized CXL eyes. We recommend you also provide the distribution of change in Kmax from baseline in randomized sham eyes, and the treatment comparison between the two groups at Month 3 and Month 12 for the proportion of subjects who experienced ≥ 1 D decrease in Kmax from baseline.*

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
10/15/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: October 8, 2013

To: Ms. Pamela Nelson, VP, Regulatory Affairs	From: Jacquelyn Smith, M.A
Company: Avedro, Inc	Division of Transplant and Ophthalmology Products
Fax Number: 781-768-3435	Fax Number: 301-796-9881
Phone Number: 781-768-3430	Phone Number: 301-796-1600
Email: pnelson@avedro.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 203324--riboflavin ophthalmic solution

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16 2013, received September 16, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for riboflavin ophthalmic solution and the KXL System.

We have the following information request:

Information Request

Per 21 CFR 314.50(c)(1)(iii), the application is required to contain either a claim for categorical exclusion under 21 CFR 25.31 or an environmental assessment under 21 CFR 25.40. Submit the above documentation as soon as possible. The environmental impact should take into account if approval of the NDA will increase the use of the active moiety and if the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
10/08/2013



NDA 203324

NDA ACKNOWLEDGMENT

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) for the following:

Name of Drug Product: riboflavin ophthalmic solution and KXL System

Date of Application: September 16, 2013

Date of Receipt: September 16, 2013

Our Reference Number: NDA 203324

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 15 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 203324** submitted on September 16, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
09/23/2013

16 September 2013

Mutahar Shamsi, Director
New England District Office
One Montvale Ave, 4th Floor
Stoneham, MA 02180

**Re: NDA No. 203324 (Sequence 0007)
Corneal Collagen Cross-linking
Field Copy Certification**

Dear Mr. Shamsi:

The NDA re-submission to Avedro's New Drug Application No. 203324 was submitted on 16 September 2013 (Sequence 0007) and the electronic archival copy can be accessed through the FDA network for the field copy technical sections described in 21 CFR 314.50 (1)(3).

Please do not hesitate to contact me for additional information or assistance. I can be reached at (781) 768-3430 or at pnelson@avedro.com.

Sincerely,



Pamela Nelson
Vice President, Regulatory Affairs

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET
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A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

1. APPLICANT'S NAME AND ADDRESS AVEDRO INC Pamela Nelson 230 3RD AVE STE 27 WALTHAM MA 024517552 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 203-324
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 781-768-3430	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME riboflavin ophthalmic solution / KXL System	6. USER FEE I.D. NUMBER PD3013525
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7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? YES NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT

ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [] YES [X] NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Pamela Nelson 	Vice President, Regulatory Affairs	7/23/13

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$0.00

Form FDA 3397 (01/10)



NDA 203324

REFUSAL TO FILE

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your, March 8, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (riboflavin ophthalmic solution)/KXL™ System.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. None of the submitted trials, UVX-001, UVX-002 or UVX-003, utilized the commercial formulation proposed in the NDA. There is no safety or efficacy data in this application for the commercial formulation proposed in this NDA. The proposed commercial formulation should be revised to be consistent with the formulations utilized in the clinical trials or adequate and well controlled clinical trials for the two indications should be performed with the currently proposed commercial formulation.
2. Chemistry, manufacturing and controls (CMC) information provided in the NDA for the drug substance is insufficient for us to perform a substantial review. Please provide the drug substance CMC information either in the NDA or by reference to a DMF with a letter of authorization (LOA) from the DMF holder.
3. Data from the following one-time studies for the proposed commercial drug product were not included in the NDA. Please provide this information.
 - a. Freeze-thaw cycling studies (3 cycles)
 - b. Weight loss through expiry on primary stability batches
 - c. Leachables/extractables on container/closure by using screening analytical methods (such as HPLC, GC etc) and studies on at least one stability batch through expiry.
4. The NDA does not provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. Stability data submitted for the historical batches are inadequate. They were only tested for limited quality attributes at only a few time points. Furthermore, per the Code of Federal Regulations (CFR), 21 CFR

211.166(a)(4), evaluation of stability shall be based on the same container-closure system in which the drug product is proposed to be marketed. Please provide 12-months long-term and 6-months accelerated stability data for three batches of the commercial formulation in the commercial container-closure system (including, as appropriate, any secondary packaging and container label) as recommended in International Conference on Harmonisation (ICH) Q1A(R2) to evaluate the stability of the commercial drug product over the proposed shelf-life.

5. In addition to the change in formulation, the container closure system used in clinical trials (b)(4) is different from the proposed marketing packaging configuration (3 mL pre-filled syringes). Please provide a complete comparison of the clinical trial material (including container-closure system) and the proposed commercial drug product, including all similarities and differences.
6. The NDA should include product specific information for sterility assurance: container closure integrity tests, (b)(4) validation information, method suitability studies for endotoxin and sterility tests, and any hold time studies for the product. Please provide this information.
7. An accurate and complete English translation of any part of the application that is not in English is required. Publications by Kohlhaas M, Spoerl E, Speck A, et al., Schnitzler E, Spoerl E, Seiler T., Spoerl E, Schreiber J, Hellmund K, et al., were submitted in German without translation. Please provide English translations of these articles.

Additional potential review issues

1. In your resubmission, please list all manufacturing and testing facilities and assurance that all the listed facilities are ready for inspection.
2. The Clinical Study Reports (CSRs) for UVX-002 and UVX-003 do not contain unpooled demographic or adverse event data. The CSRs should be revised to contain both pooled and unpooled demographic and adverse event data. These CSRs should be separate, independent documents which adequately describe each individual trial without pooling. It is acceptable to include pooled efficacy data as secondary, supportive analyses in the CSRs.
3. The submitted twelve month data are not true observed values; they are "carried forward" observations. Twelve month data and analyses should be submitted which utilize the true observed values at 12 months, not "carried forward" observations.
4. The proposed labeling discusses (b)(4) the pre-filled syringe. Please provide a description (b)(4) and its use. If (b)(4) a previously cleared device, please provide verification of the 510(k). If it is not a cleared device, please provide the (b)(4) method and validation studies or a letter of authorization to a Drug Master File in which this information can be found.

5. The manufacturing process uses (b) (4) Please provide the (b) (4) method and validation for it or a letter of authorization to a Drug Master in which this information can be found.
6. As requested in the pre-NDA meeting on September 12, 2011, please provide a rationale for (b) (4) the finished drug product.
7. To support the proposed dosing regimen of (b) (4)/KXL, please provide a summary report that tabulates the descriptive statistics (e.g., mean, median, min, max) of the actual number of riboflavin drops per instillation, the total number of riboflavin drops administered during each of the treatment phases (i.e., after corneal debridement, anterior chamber penetration, corneal thickening, UVA irradiation) and the cumulative number of drops received during the entire corneal crosslinking treatment process for each Phase 3 clinical trial. Please provide these tables for analysis of both individual and pooled studies. Please include an analysis dataset in .xpt format providing the requested information for each patient enrolled in the Phase 3 trials. Please include in the dataset a data column to indicate the type of riboflavin formulation (e.g., 0% dextran; 20% dextran; etc.) administered.
8. When submitting riboflavin dosing datasets (e.g., RIB1D.xpt, RIBACD.xpt, HYPRIBD.xpt, RIB2D.xpt), please associate each dosing-time profile provided with the particular treatment received by including a data column similar to the TXRANDTX column of the TX.xpt dataset where 1=CXL study eye, 2=sham study eye, 3=CXL fellow eye, 4=crossover of control eye.
9. The study design allowed subjects in the control group to cross over to receive CXL treatment after Month 3. Please provide information on the timing of the crossover (You could use tabulation or graph as you see appropriate.), and for each visit, tabulate the number of subjects remaining in the study, staying with the randomized treatment, and the number of subjects who had Kmax measurements. This should be provided for each individual study and the pooled studies. You could use a table as follows.

Visit	CXL		Control		
	Stayed with randomized treatment	# of subjects with Kmax	Stayed with randomized treatment	Crossed over	# of subjects with Kmax
Month 1					
Month 3					
Month 6					
Month 12					

10. Please provide a pooled dataset including the following variables for all ITT subjects from Studies UVX-001, UVX-002, and UVX-003. You may want to change some of the variable names to be consistent with the names used in your raw datasets.

Variable	Label	Type	Codes	Comment
PROJ_ID	Study Identifier	Char	001, 002, 003	
SITE_ID	Site Identifier	Char		
Age	Age (years)	Num		
Race	Race	Char	Include all possible codes	
Ethnicity	Ethnicity	Char	Include all possible codes	
Sex	Sex	Char	Female, Male	
TRT	Randomized Treatment	Char	Sham, CXL	
Severity	Baseline disease severity	Char	mild, moderate, severe	
Completed	Did the subject complete the study?	Char	Yes, No	
Discont	Reason for discontinuing from the study	Char	Include all possible codes	
EYE_TYPE	Type of EYE	Char	Keratoconus, Corneal Ectasia	
VISIT_C	Visit identifier	Char	Baseline, Month 1, Month 3, Month 6, Month 12	
Visit	Visit identifier	Num	0, 1, 3, 6, 12	
Visit_dtn	Visit date	Num		
Eye	Eye	Char	Left, right	
Study_eye	Study eye	Char	Left, right	
TRT_SE	Treatment received at each visit for study eye	Char	Sham, CXL	
TRT_DT_SE	Treatment date for study eye	Num		
TRT_FE	Treatment received at each visit for fellow eye	Char	Sham, CXL	
TRT_DT_FE	Treatment date for fellow eye	Num		
Kmax_SB	Baseline Kmax for study eye	Num		
Kmax_SO	Observed Kmax for study eye at each visit (measurement should be provided regardless of subject's treatment status)	Num		
Kmax_SL	LOCF Kmax for study eye at	Num		

	each visit			
CKmax_SO	Change in observed Kmax from baseline for study eye	Num		
CKmax_SL	Change in LOCF Kmax from baseline for study eye	Num		
LOCF	LOCF flag for Kmax SL	Char	Yes, No	
Kmax_FB	Baseline Kmax for follow eye	Num		
Kmax_FO	Observed Kmax for follow eye at each visit	Num		
CKmax_FO	Change in observed Kmax from baseline for follow eye	Num		

11. Please provide all available data that were collected for untreated fellow eyes. We noted that, for example, among 179 ectasia subjects, a total of 65 fellow eyes in the CXL group and 66 fellow eyes in the sham group didn't receive any treatment. We could not find data collected during the follow-up procedure and examination for these untreated fellow eyes. If data were collected for these untreated fellow eyes, please provide all data including their key efficacy data.
12. Please examine the distribution of Kmax and conduct additional analyses (for example, nonparametric analysis) to examine the robustness of the primary efficacy analysis results.
13. Please conduct analyses of Kmax adjusting for baseline Kmax.
14. Please provide analyses for the proportion of subjects who experienced ≥ 1 D decrease in Kmax from baseline.

We also note that, while you identified your application in your 356h form as being a 505(b)(2) NDA, your patent certification states that the provisions of 21 U.S.C. 355(b)(2) do not apply to your NDA. If you do not intend for this application to be a 505(b)(2) NDA, please amend your 356h form accordingly. If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which we consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act (in other words, an application approved under section 505(j) of the Act (i.e., ANDA, generic drug) may not be cited as a listed drug relied upon). The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Jacquelyn Smith, M.A., Senior Regulatory Project Manager, at 301-796-1600.

Sincerely yours,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

WILEY A CHAMBERS
05/04/2012
For Renata Albrecht