

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201923Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # **201923**

SUPPL # **N/A**

Trade Name **Iluvien**

Generic Name **fluocinolone acetonide**

Applicant Name **Alimera Sciences, Inc.**

Approval Date **September 26, 2014**

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)(1)

c) 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:

d) Did the applicant request exclusivity?

YES NO

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

3 years

e) 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).

The following currently approved NDAs containing fluocinolone acetonide were identified from DARRTS:

NDA # 21737	Retisert® (fluocinolone acetonide) Intravitreal Implant, 0.59 mg
NDA # 20001	FS (fluocinolone acetonide) Shampoo, 0.01%
NDA # 16161	Synalar®-HP (fluocinolone acetonide) Cream, 0.2%
NDA # 12787	Synalar® (fluocinolone acetonide) Cream, 0.01%
NDA # 15296	Synalar® (fluocinolone acetonide) Topical Solution, 0.01%
NDA # 13960	Synalar® (fluocinolone acetonide) Ointment, 0.025%
NDA# 21112	Tri-Luma (fluocinolone acetonide, hydroquinone, tretinoin) Cream , 0.01%/4%/0.05%

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.)

N/A YES NO

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

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:

Study C-01-05-001A (FAME A)

Study C-01-05-001B (FAME B)

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 Study C-01-05-001A (FAME A) YES NO

Investigation #2 Study C-01-05-001B (FAME B) 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

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 Study C-01-05-001A (FAME A)

IND # 72056 YES NO
Explain:

Investigation #2 Study C-01-05-001B (FAME B)

IND # 72056 YES NO
Explain:

(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? N/A

Investigation #1

YES NO
Explain: Explain:

Investigation #2

YES

Explain:

NO

Explain:

(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: Diana Willard
Title: Chief, Project Management Staff
Date: August 28, 2014

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Transplant and Ophthalmology Products

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/

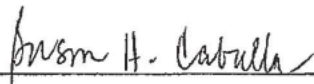
DIANA M WILLARD
09/26/2014

RENATA ALBRECHT
09/26/2014

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Alimera Sciences, 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.



Susan H. Caballa

Senior Vice President

Regulatory and Medical Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 201923	NDA Supplement # N/A	If NDA, Efficacy Supplement Type:
Proprietary Name: Iluvien Established/Proper Name: fluocinolone acetonide Dosage Form: intravitreal insert		Applicant: Alimera Sciences, Inc. Agent for Applicant (if applicable): N/A
RPM: Diana Willard		Division: Division of Transplant and Ophthalmology Products
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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> </div> <div style="width: 50%;"> <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 type="checkbox"/> This application does not rely upon a listed drug. <input 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 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> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is September 26, 2014 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

¹ 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).

<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None CR Letters: December 22, 2010 November 10, 2011 October 17, 2013																				
❖ 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 _____	N/A																				
❖ Application Characteristics ³ Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 3 <table border="0" style="width: 100%;"> <tr> <td><input type="checkbox"/> Fast Track</td> <td><input type="checkbox"/> Rx-to-OTC full switch</td> </tr> <tr> <td><input type="checkbox"/> Rolling Review</td> <td><input type="checkbox"/> Rx-to-OTC partial switch</td> </tr> <tr> <td><input type="checkbox"/> Orphan drug designation</td> <td><input type="checkbox"/> Direct-to-OTC</td> </tr> </table> <table border="0" style="width: 100%;"> <tr> <td style="width: 50%;"> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) </td> <td style="width: 50%;"> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) </td> </tr> <tr> <td> Subpart I <input type="checkbox"/> Approval based on animal studies </td> <td> Subpart H <input type="checkbox"/> Approval based on animal studies </td> </tr> </table> <table border="0" style="width: 100%;"> <tr> <td><input type="checkbox"/> Submitted in response to a PMR</td> <td>REMS: <input type="checkbox"/> MedGuide</td> </tr> <tr> <td><input type="checkbox"/> Submitted in response to a PMC</td> <td><input type="checkbox"/> Communication Plan</td> </tr> <tr> <td><input type="checkbox"/> Submitted in response to a Pediatric Written Request</td> <td><input type="checkbox"/> ETASU</td> </tr> <tr> <td></td> <td><input type="checkbox"/> MedGuide w/o REMS</td> </tr> <tr> <td></td> <td><input type="checkbox"/> REMS not required</td> </tr> </table> Comments:		<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	NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520)	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)	Subpart I <input type="checkbox"/> Approval based on animal studies	Subpart H <input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> Submitted in response to a PMR	REMS: <input type="checkbox"/> MedGuide	<input type="checkbox"/> Submitted in response to a PMC	<input type="checkbox"/> Communication Plan	<input type="checkbox"/> Submitted in response to a Pediatric Written Request	<input type="checkbox"/> ETASU		<input type="checkbox"/> MedGuide w/o REMS		<input type="checkbox"/> REMS not required
<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																				
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<input type="checkbox"/> Submitted in response to a PMC	<input type="checkbox"/> Communication Plan																				
<input type="checkbox"/> Submitted in response to a Pediatric Written Request	<input type="checkbox"/> ETASU																				
	<input type="checkbox"/> MedGuide w/o REMS																				
	<input type="checkbox"/> REMS not required																				
❖ 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)	<input type="checkbox"/> Yes, dates																				
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No																				
❖ Public communications (<i>approvals only</i>)																					
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No																				
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" 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 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 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 type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA 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 type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input 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 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 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>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>Copy of this Action Package Checklist⁴</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Officer/Employee List</p>	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s)</p> <p>CR Letters: December 22, 2010 November 10, 2011 October 17, 2013</p> <p>AP Letter: September 26, 2014</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p><input checked="" type="checkbox"/> Received from Applicant September 18, 2014</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p><input checked="" type="checkbox"/></p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p><input checked="" type="checkbox"/></p>

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

❖ 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 type="checkbox"/> Device Labeling <input checked="" 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. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<input checked="" type="checkbox"/> Included
❖ 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 	<input checked="" type="checkbox"/> Received from Applicant September 18, 2014
❖ 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. 	Two letters: 10/13/10 and 8/6/14 Two reviews: 10/13/10 and 8/1/14
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA – 8/5/14 and 8/28/14 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 8/13/14 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> RPM Filing Review – 10/26/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director September 26, 2014</i>)	<input checked="" type="checkbox"/> Included
❖ 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
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC: October 4, 2010 If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" 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 <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	<input checked="" type="checkbox"/>
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/>
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	N/A – NO MTG
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> 2/2/11
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> 3/4/10
• EOP2 meeting <i>(indicate date of mtg)</i>	
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<u>N/A</u> - NO AC MTG
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	9/26/14 10/17/13 11/10/11 12/22/10
Deputy Director Summary Review <i>(indicate date for each review)</i>	9/16/14 10/17/13 10/19/11
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	9/23/14 9/18/14 10/17/13 10/27/11 12/22/10
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	Team Leader co-signed primary Clinical Reviews 8/22/14 9/9/13 9/19/12 9/13/11 12/20/10
• Clinical review(s) <i>(indicate date for each review)</i>	
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	Not Applicable
❖ 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 <i>(indicate date of review/memo)</i>	Clinical reviewer review of Financial Disclosure on Page 11 of the 12/20/10 Clinical Review

⁶ Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<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>) <u>OSI letters to letters to investigators are included under this tab in the Action Package</u>	Review dated 12/1/10
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	Team Leader co-signed primary Biostatistical Reviews
Statistical Review(s) (<i>indicate date for each review</i>)	9/2/14 9/27/13 4/12/13 6/20/12 8/1/11 3/7/11 12/10/10 8/17/10
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>)	Team Leader co-signed primary Clinical Pharmacology Reviews
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	10/7/13 6/28/11 10/6/10
❖ 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>		7/28/14 - Review of Pharmacology/Toxicology Section of the Labeling
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		11/17/10
❖ 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 Carcinogenicity Studies		
❖ ECAC/CAC report/memo of meeting		
<input checked="" type="checkbox"/> None		
❖ 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) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		8/6/14 10/15/13 9/24/13 9/30/11 7/22/11 12/1/10 10/6/10
❖ Microbiology Reviews		
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		7/25/11 2/9/11 7/30/10
N/A BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
ONDQA Biopharmaceutics Reviews: 9/23/13 6/27/11 7/30/10		
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Categorical Exclusion Review on Page 84 of the 12/1/10 Product Quality Review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <u>NOT</u> include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable – several dates, but last date is 7/28/14 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) <input checked="" type="checkbox"/> Page 84 of the 12/1/10 Product Quality Review states, “The validation package was not submitted to the FDA labs.”

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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



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

COMMUNICATION SHEET

DATE: September 5, 2014

To: Ms. Susan H. Caballa	From: Diana Willard
Company: Alimera Sciences, Inc.	Division of Transplant and Ophthalmology Products
Telephone Number: 678-527-1328	Email: diana.willard@fda.hhs.gov
Cell Phone Number: [REDACTED] (b) (6)	Phone number: 301-796-1600
Subject: NDA 201923 – labeling comments	

Total no. of pages including cover: 3

Comments:

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.

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Dear Ms. Caballa,

Please refer to your NDA 201923 for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

Below are comments regarding the labeling for this product and revisions we would like made:

1. In Section 14 Clinical Studies, please include the following table and provide Baseline BCVA. So the labeling has information to be able to interpret the change from baseline. The table should be located before the tabulated results for “change from baseline.”

Baseline BCVA (Letters)				
	Study 1		Study 2	
	ILUVIEN	Sham	ILUVIEN	Sham
Mean (SD)	53 (13)	54 (11)	53 (12)	55 (11)
Median (Range)	57 (19-75)	58 (25-69)	56 (20-70)	58 (21-68)

The numbers in this table were provided by the biostatistical reviewer for this NDA.

2. In Section 12.3 Pharmacokinetics, please change (b) (4) to “0.19 mcg/day” to be consistent throughout the labeling.

I can be reached at 301-796-1600 should you have any questions.

Sincerely,

Diana M. Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
09/05/2014



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

COMMUNICATION SHEET

DATE: August 15, 2014

To: Ms. Susan H. Caballa	From: Diana Willard
Company: Alimera Sciences, Inc.	Division of Transplant and Ophthalmology Products
Telephone Number: 678-527-1328	Email: diana.willard@fda.hhs.gov
Cell Phone Number: [REDACTED] (b) (6)	Phone number: 301-796-1600
Subject: NDA 201923 – Preliminary label comments	

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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Dear Ms. Caballa,

Please refer to your NDA 201923 for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

Below are our preliminary comments regarding the labels for this product:

Regarding the Tray Labeling:

1. The formatting of the name of the product should be revised to be consistent with the package insert: ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg. We recommend that the font for the proprietary name be of one color (i.e., blue) and of one size. The established name should be a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).
2. We recommend increasing the font size of all of the remaining text on the tray labeling.
3. Consistent with the revised package insert, the statement, [REDACTED] (b) (4) should be revised to read, “For Intravitreal Insertion.”

Regarding the Carton Labeling:

1. The formatting of the name of the product should be revised to be consistent with the package insert: ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg. We recommend that the font for the proprietary name be of one color (i.e. blue) and of one size. The established name should be a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).
2. We recommend increasing the font size of all of the remaining text on the carton labeling.
3. Consistent with the revised package insert, the statement, [REDACTED] (b) (4) should be revised to read, “For Intravitreal Insertion.”
4. You should relocate the National Drug Code (NDC) number to the top panel and the principal display panel. Per 21 CFR 207.35 (b)(3), the NDC number should appear prominently in the top third of the principal display panel.
5. The carton labeling should state what is present in the unit dose intravitreal insert. For example, “Each intravitreal insert contains: fluocinolone acetonide 0.19 mg. Inactive ingredients: etc...”
6. The statement, [REDACTED] (b) (4) should be removed. The statement, [REDACTED] (b) (4) should be removed.

7. If the statement, (b) (4) is important, it should be added to the storage section of the package insert (Section 16). If it is not important, the statement should be removed from the carton, but “Store at 15° - 30° C (59° - 86° F)” should remain.

I can be reached at 301-796-1600 should you have any questions.

Sincerely,

Diana M. Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
08/15/2014

MEMORANDUM

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

DATE: August 12, 2014

TO: NDA 201923

SUBJECT: E-mail from Mr. Dan Meyer, CEO of Alimera Sciences, Inc., regarding discussion topic for December 10, 2013, teleconference with Dr. Cox, Director of the Office of Antimicrobial Products and staff from the Division of Transplant and Ophthalmology Products

APPLICATION/DRUG: NDA 201923/Iluvien/Alimera Sciences, Inc.

Attached is an e-mail from Mr. Dan Meyer, CEO of Alimera Science, Inc., regarding a conference call with Dr. Wiley Chambers that took place on November 27, 2013.

From: Dan Myers [<mailto:dan.myers@alimerasciences.com>]
Sent: Thursday, December 05, 2013 12:51 PM
To: Cox, Edward M
Cc: Milstein, Judit
Subject: phone call

Dear Dr. Cox,

I am copying Judit Milstein on this email as I apologize up front for writing you directly. The reason for my email is to request a 15 minute call with you to address a discussion that my team and I had with Dr. Chambers last week.

The American Academy of Ophthalmology (AAO) recently held its annual conference in New Orleans attended by the world's key opinion leaders in ophthalmology. At that meeting, (b) (4) had the opportunity to talk with Dr. Chambers on the current treatment of diabetic macular edema and in particular, the role that steroids play. (b) (4) discussed ILUVIEN with Dr. Chambers and as a result of that discussion, Alimera had a conference call with Dr. Chambers, which included (b) (4) on November 27, 2013.

The call with Dr. Chambers was very productive, to the point that Dr. Chambers proposed language that might be acceptable to us pending discussion with you and further clarification. Based on that, I informed Dr. Chambers that I was going to follow-up with you. Your position on the content of the discussion would be very helpful for us in preparing for the meeting with FDA on December 13th. As you know, the one hour time slot goes quickly and I would like to make sure we are on the same page in order to maximize our time together. I appreciate your consideration in taking my call and the role you have played in this process.

Sincerely,
Dan

Dan Myers | President/CEO

Alimera Sciences | look forward
6120 windward parkway | suite 290
alpharetta, ga. 30005
t 678 527 1321 | f 678 990 5744
dan.myers@alimerasciences.com
www.alimerasciences.com

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/s/

DIANA M WILLARD
08/12/2014



NDA 201923

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

We acknowledge receipt on March 26, 2014, of your March 26, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We consider this a complete, class 2 response to our October 17, 2013, action letter. Therefore, the user fee goal date is September 26, 2014.

If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana M. Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DIANA M WILLARD
04/11/2014



NDA 201923

MEETING MINUTES

Alimera Sciences, Inc.
Attention: Susan Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) 201923, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2013. The purpose of the meeting was to discuss the path forward for the resubmission of Iluvien in response to the October 17, 2013, Complete Response letter issued by the Agency.

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

If you have any questions, call Diana Willard, Chief, Project Management Staff at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of 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 and Time: December 13, 2013, 9:00-10:00 AM
Location: FDA, White Oak Campus
10903 New Hampshire Ave.
Building 22, Room 1309
Silver Spring, MD 20993

Application Number: NDA 201923
Product Name: Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg

Sponsor/Applicant Name: Alimera Pharmaceuticals, Inc.

Meeting Chair: Renata Albrecht, Director, Division of Transplant and Ophthalmology Products
Meeting Recorder: Judit Milstein, Chief, Project Management Staff

FDA ATTENDEES

Edward M. Cox, Director, Office of Antimicrobial Products (OAP)
David Roeder, Associate Director for Regulatory Affairs, OAP
Renata Albrecht, Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, Deputy Director, DTOP
William M. Boyd, Clinical Team Leader, DTOP
Judit Milstein, Chief, Project Management Staff, DTOP
Dongliang Zhuang, Statistics Reviewer, Division of Biometrics IV
Yan Wang, Statistics Team Leader, Division of Biometrics IV

SPONSOR ATTENDEES

Dan Myers, President, CEO
Susan Caballa, Senior Vice President, Regulatory and Technical Affairs
Ken Green, Senior Vice President, Scientific Affairs and Chief Scientific Officer

(b) (4)

BACKGROUND

NDA 201923 was originally submitted on June 30, 2010, by Alimera Sciences, Inc. (Alimera) for the treatment of diabetic macular edema (DME). A Complete Response letter for this NDA was issued on December 22, 2010. A Class 2 Resubmission in response to this Complete Response letter was submitted by Alimera on May 12, 2011. A second Complete Response letter was issued on November 10, 2011. On April 17, 2013, Alimera submitted a Class 2 Resubmission in response to the second Complete Response letter, and the Division issued a Complete Response letter on October 17, 2013. As a follow up to this action, Alimera requested a meeting with the Division to discuss the path forward for this application, and the

meeting was scheduled for December 13, 2013. This meeting was a follow up to the teleconference held on December 10, 2013.

DISCUSSION

Alimera proposed the following indication: [REDACTED] (b) (4)

[REDACTED] There were discussions about the use of the terms [REDACTED] (b) (4) but the Agency could not provide final agreement on the specific language until the full resubmission was reviewed.

The Division recommended that when Alimera resubmits their application, Alimera provide analyses of the population for the proposed indication, specifically outcomes in patients [REDACTED] (b) (4) or include in the resubmission the location in the application where this information was previously submitted. Alimera agreed with this request. The Division also clarified that safety information needs to be submitted for the overall population as well as the population to be included in labeling.

As a follow up to the discussion during the December 10, 2013, meeting Alimera again acknowledged the progress made on the potential indication for the product and asked whether the Advisory Committee (AC) Meeting was still needed as the original scientific issues were resolved. The Division responded that, upon further consideration, it concluded that an AC Meeting was not necessary at this time.

With regard to the Compliance issues listed in the Complete Response letter, Alimera stated that [REDACTED] (b) (4) sent a response to the District on September 9, 2013, and since then they had not received any answer from the Agency as to the acceptability of their response. Alimera asked if the Division could follow up with Compliance and the Division agreed. Alimera also stated that the validation studies had been repeated and that they expected to have results by the end of December.

The Division inquired whether any additional information was available on the new inserter to address the technical difficulties with the use of the inserter. Alimera stated that they have enhanced the training and instructions for use in the product marketed in Europe and that they will include a safety update on the use of the new inserter. The Division requested that Alimera provide evidence that physicians can effectively use the new inserter.

Alimera inquired as to whether the resubmission of their NDA would be considered a Class 1 or Class 2 resubmission. The Division replied that because facility re-inspections may be needed, this would be a Class 2 resubmission.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

The Division will follow up with the Office of Compliance about the status of the (b) (4)
[REDACTED] response.

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/s/

RENATA ALBRECHT
01/30/2014



NDA 201923

MEETING MINUTES

Alimera Sciences, Inc.
Attention: Susan Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) 201923, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also refer to the teleconference between representatives of your firm and the FDA on December 10, 2013. The purpose of the meeting was to discuss the path forward for a submission in response to the October 17, 2013, Complete Response letter issued by the Agency.

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

If you have any questions, call Diana Willard, Chief, Project Management Staff at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of 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 and Time: December 10, 2013
Meeting Format: Teleconference

Application Number: NDA 201923
Product Name: Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg

Sponsor/Applicant Name: Alimera Pharmaceuticals, Inc.

Meeting Chair: Renata Albrecht, Director, Division of Transplant and Ophthalmology Products
Meeting Recorder: Judit Milstein, Chief, Project Management Staff

FDA ATTENDEES

Edward M. Cox, Director, Office of Antimicrobial Products (OAP)
David Roeder, Associate Director for Regulatory Affairs, OAP
Renata Albrecht, Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, Deputy Director, DTOP
William M. Boyd, Clinical Team Leader, DTOP
Judit Milstein, Chief, Project Management Staff, DTOP

SPONSOR ATTENDEES

Dan Myers, President, CEO
Susan Caballa, Senior Vice President, Regulatory and Technical Affairs
Ken Green, Senior Vice President, Scientific Affairs and Chief Scientific Officer

BACKGROUND

NDA 201923 was originally submitted on June 30, 2010, by Alimera Sciences, Inc. (Alimera) for the treatment of diabetic macular edema (DME). A Complete Response letter for this NDA was issued on December 22, 2010. A Class 2 Resubmission in response to this Complete Response letter was submitted by Alimera on May 12, 2011. A second Complete Response letter was issued on November 10, 2011. On April 17, 2013, Alimera submitted a Class 2 Resubmission in response to the second Complete Response letter, and the Division issued a Complete Response letter on October 17, 2013. As a follow up to this action, Alimera requested a meeting with the Division to discuss the path forward for this application, and the meeting was scheduled for December 13, 2013. On December 5, 2013, Dan Myers, President and CEO of Alimera sent an e-mail to Dr. Cox, asking for a teleconference before the December 13, 2013, meeting, to discuss potential alternate indications for this application.

DISCUSSION

Alimera stated that based on a telephone call with Dr. Chambers on November 27, 2013, during which the language for a new indication was discussed, they wanted to propose and discuss with the Division an alternate indication for Iluvien: [REDACTED] (b) (4)

A discussion followed [REDACTED] (b) (4)

The Division stated that in general, the proposed indication might be acceptable, understanding that further discussion on the exact language will be needed. Both the Division and Alimera agreed to continue discussions on this issue at the December 13, 2013, scheduled meeting.

Alimera acknowledged the progress made on the potential indication and asked the Division whether an Advisory Committee (AC) Meeting was still needed. The Division agreed to consider whether a meeting was needed and indicated that a response would be provided at a later date.

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/s/

RENATA ALBRECHT
01/30/2014



NDA 201923

TELECONFERENCE MINUTES

Alimera Sciences, Inc.
Attention: Ms. Susan H. Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) dated June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also refer to the teleconference between representatives of your firm and the FDA on October 23, 2013. The purpose of the meeting was to discuss questions pertaining to the upcoming January 27, 2014, Advisory Committee Meeting for Iluvien.

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

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes


MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Category: Guidance

Meeting Date and Time: October 23, 2013

Application Number: NDA 201923

Product Name: Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg

Indication:  (b) (4)

Applicant Name: Alimera Sciences, Inc.

Meeting Chair: Edward Cox, M.D., M.P.H.

Meeting Recorder: Diana Willard

FDA ATTENDEES

Edward Cox, M.D., M.P. H.	Director, Office of Antimicrobial Products
Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Diana Willard	Chief, Project Management Staff, DTOP

ALIMERA SCIENCES, INC. ATTENDEES

Dan Myers	President, CEO
Susan Caballa	Senior Vice President, Regulatory and Technical Affairs
Ken Green, Ph.D.	Senior Vice President, Scientific Affairs and Chief Scientific Officer

BACKGROUND

NDA 201923 was originally submitted on June 30, 2010, by Alimera Sciences, Inc. (Alimera) for treatment of diabetic macular edema (DME). A Complete Response letter for this NDA was issued on December 22, 2010. A Class 2 Resubmission in response to this Complete Response letter was submitted by Alimera on May 12, 2011. A second Complete Response letter was issued on November 10, 2011. On April 17, 2013, Alimera submitted a Class 2 Resubmission in response to the second Complete Response letter.

During an October 16, 2013, meeting between Alimera and the Agency, issues pertaining to a potential Advisory Committee Meeting for Iluvien were discussed. It was agreed at that time that an Advisory Committee would be convened in late January 2014.

This teleconference was requested by Alimera to discuss questions they had concerning the January 2014 Advisory Committee Meeting. An October 22, 2013, e-mail (attached) was sent by Mr. Meyers to Dr. Cox containing questions for this teleconference.

DISCUSSION

Following introductions, Mr. Meyer thanked the Agency for the October 16, 2013, meeting and the open, collegial dialog that took place during that meeting.

Alimera brought up the following concerns during this teleconference:

1. Alimera stated that the company was struck by the tone of the October 18, 2013, Complete Response (CR) letter that clearly contained Dr. Chambers bias against long term use of Iluvien. Further, the CR letter seems to position Iluvien as a last line therapy and recommended another study. Alimera does not believe another study is warranted.
2. Alimera noted that the October 17, 2013, CR letter stated that there was a lack of evidence consisting of adequate and well-controlled investigations for the indication, (b) (4) and raised concerns regarding this statement.
3. Who oversees the Advisory Committee (AC)? What is the process?
4. What input will Alimera have in writing the questions? Alimera stated that how the Committee is run, what questions are asked, and how the wording of the questions is crafted, are critical to the outcome.

Discussion regarding concerns:

The Agency stated that the team reviewed the data and material submitted for the Iluvien application and identified deficiencies that need to be addressed prior to an approval. The deficiencies identified in the CR letter were the end result of the team review process. Part of the goal of the CR letter was also to identify all the scientific differences in opinion regarding this product for this indication in order to aid in preparations for the AC meeting.

The Agency noted that for the deficiencies outlined in the CR letter, there are recommendations for resolving the deficiencies. The reason for recommending another study in the CR letter was in large part as a possible mechanism to resolve the scientific differences of opinion, as outlined during the October 16, 2013, meeting.

Alimera stated that the wording, (b) (4) was proposed (b) (4)

(b) (4) It was never Alimera's intent to propose an indication that would lead to the recommendation for another study, as outlined in the CR letter. The Agency stated that Alimera could submit a document to the application clearly identifying the indication they propose for Iluvien.

Advisory Committee Meetings are run by the chairman of the Committee. Alimera could contact Advisors and Consultants staff to identify who the chair will be for the January 2014 AC meeting.

Advisory Committee Meetings generally focus on the main issues raised during the review of the application. As we know there are differences of scientific opinion between Alimera and the Agency regarding this product, those differences need to be clear to the AC members and openly discussed at the meeting: the Agency does not censure open discussion.

Both Alimera and the Agency will prepare materials that will be provided to the AC members for their review prior to the meeting as the issues should be known in advance in order to minimize any new issues being identified during the meeting. The materials from the Agency will bring forth for open discussion at this public hearing both the safety and efficacy of Iluvien based on data from the FAME trials as well as current treatments available for this indication, including anti-VEGF products. Although an anti-VEGF product was not approved at the time the FAME trials were initiated, as there is now a currently approved product it is germane to any public discussion of this disease. Further, the Agency will likely ask the AC whether the population that was studied in the FAME trials is reflective of a population that can be identified today. Should Alimera choose not to discuss anti-VEGF treatment options or the population studied in the Iluvien trials in the materials they prepare for the AC, that is their choice.

Along with the AC members, FDA reviewers who conducted reviews of the data will be present at the meeting. Several of the reviewers will provide presentations to the Committee. Part of the content of the presentations will be to outline the differences of opinion between Alimera and the Agency.

Alimera stated that in the October 16, 2013, meeting attended by Dr. Jenkins, Dr. Cox, and Dr. Albrecht, there was a more collegial environment than that experienced in prior meetings for Iluvien attended by Dr. Chambers. Alimera asked for assurance that going forward to the AC, the environment of the dialog and interactions would be the same as for those on October 16, 2014. Alimera asked about the attendance of Dr. Jenkins and Dr. Cox at the January 2014 AC Meeting.

The AC Chairman chairs the meeting and the Agency noted that such meetings are generally run with respect for all opinions. Although there is no guarantee, Dr. Cox routinely attends AC Meetings when products in the Office of Antimicrobial Products are presented. If Dr. Cox could not attend due to competing priorities, he could request that his Deputy Director, Dr. John Farley, attend. Dr. Cox will contact Dr. Jenkins regarding his attendance and Ms. Willard will inform Alimera of Dr. Jenkins' reply.

Alimera noted that how the meeting is run and how the questions are crafted is very important. The order of the questions and what the questions can suggest can be critical to the outcome of the meeting. The Agency stated that in early to mid-December, the Division would meet with Alimera to discuss the focus of the AC and what materials would be sent to the AC members by both Alimera and the Agency. At this meeting, Alimera has the opportunity to share drafts of the documents they plan to provide AC members and the slides they plan to present. Noting that the Agency would draft the final questions for the AC, it was stated that drafts of potential questions could be discussed at the December meeting.

Addendum: In an October 30, 2013, e-mail to Ms. Caballa, Ms. Willard stated that Dr. Cox had contacted Dr. Jenkins regarding his attendance at the January 27, 2014, Advisory Committee (AC) Meeting. Ms. Willard stated that the January 27, 2013, AC meeting is on Dr. Jenkins calendar. His attendance, however, will be dependent on what other issues/meetings are on his calendar for that date/time.

Attachment

From: Dan Myers [<mailto:dan.myers@alimerasciences.com>]

Sent: Tuesday, October 22, 2013 4:45 PM

To: Cox, Edward M; Willard, Diana M

Subject: Conference call questions

Dr. Cox,

Per your request, attached are our thoughts and questions that may help maximize our time in tomorrow's conference call. I look forward to speaking with you.

Dan

Dan Myers | President/CEO

Alimera Sciences | look forward
6120 windward parkway | suite 290
alpharetta, ga. 30005
t 678 527 1321 | f 678 990 5744
dan.myers@alimerasciences.com

www.alimerasciences.com



October 22, 2013

Dr. Cox,

We thank you for your time, attention and participation in this matter. We recognize that this is an unusual process and appreciate your help in better understanding the path forward.

Questions:

1. At our meeting on October 16, 2013, we understood that FDA was going to convene an Advisory Committee Meeting in order to obtain outside, expert advice on the risks and benefits of ILUVIEN as identified during the FAME trials and whether an appropriate indication can be crafted from the FAME trials. Upon reading the CRL response, we want to make sure our understanding of the purpose of the Advisory Committee Meeting is aligned with that of FDA. *Does FDA agree that the focus of the Advisory Committee Meeting will be on assessing the risks and benefits of ILUVIEN as demonstrated in the FAME trials?*

2. In the CRL FDA issued on October 17, 2013, FDA based its decision not to approve ILUVIEN in part on Alimera's proposed indication: (b) (4)

[Redacted]

We proposed this language (b) (4)

[Redacted]

[Redacted] Alimera would welcome a labeling discussion with FDA to determine the most appropriate label for ILUVIEN based on the FAME trials and subgroup analysis. We believe that the Advisory Committee could provide useful input on the most appropriate label for ILUVIEN in the United States based on the results of the FAME trials. *How does FDA intend to request feedback from the Advisory Committee on labeling?*

3. We understand that we will be working with you to develop questions for consideration at the Advisory Committee Meeting.

Do you have a time line and a process that you can propose so we can properly prepare our briefing materials?

4. Assuming the Advisory Committee recognizes the positive risk benefit of ILUVIEN for treatment of DME and the CMC issues are resolved, *what would be the path forward for the review of a resubmission?*

A handwritten signature in black ink that reads "Dan Myers".

Dan Myers
President & CEO
Alimera Sciences, Inc.

6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Phone 678.990.5740 Fax 678.990.5744
www.alimerasciences.com

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/s/

RENATA ALBRECHT
01/23/2014



NDA 201923

MEETING MINUTES

Alimera Sciences, Inc.
Attention: Ms. Susan H. Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) dated June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 16, 2013. The purpose of the meeting was to discuss the following:

1. manufacturing compliance issues,
2. rationale for not extending the PDUFA Goal Date,
3. clinical issues, and
4. plans for a future Advisory Committee Meeting.

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

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Category: Guidance

Meeting Date and Time: October 16, 2013, from 1:00 to 2:00 PM

Meeting Location: White Oak Building 22, Room 1309

Application Number: 201923

Product Name: Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg

Indication: [REDACTED] (b) (4)

Sponsor/Applicant Name: Alimera Sciences, Inc.

Meeting Chair: Edward M. Cox, M.D., M.P.H.

Meeting Recorder: Diana Willard

FDA ATTENDEES

John Jenkins, M.D.	Director, Office of New Drugs
Ed Cox, M.D., M.P. H.	Director, Office of Antimicrobial Products (OAP)
David Roeder, M.S.	Associate Director of Regulatory Affairs, OAP
Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
LCR Tara Goen	Branch Chief (acting), OC/OMPQ/DGMPA/NDMAB
Jaundria Williams, Ph.D.	Compliance Officer, OC/OMPQ/DGMPA/NDMAB
Judit Milstein, M.S.	Chief, Project Management Staff, DTOP
Diana Willard	Chief, Project Management Staff, DTOP

ALIMERA SCIENCES, INC. ATTENDEES

Dan Myers	President, CEO
Susan Caballa	Senior Vice President, Regulatory and Technical Affairs
Ken Green, Ph.D.	Senior Vice President, Scientific Affairs and Chief Scientific Officer

ALIMERA SCIENCES, INC. CONSULTANTS



BACKGROUND

NDA 201923 was originally submitted on June 30, 2010, by Alimera Sciences, Inc. (Alimera) for treatment of diabetic macular edema (DME). A Complete Response letter for this NDA was issued on December 22, 2010. A Class 2 Resubmission in response to this Complete Response letter was submitted by Alimera on May 12, 2011. A second Complete Response letter was issued on November 10, 2011. On April 17, 2013, Alimera submitted a Class 2 Resubmission in response to the second Complete Response letter. The PDUFA Goal Date for the April 17, 2013, resubmission is October 17, 2013.

Pursuant to a letter and e-mail addressed to Dr. Woodcock, Director, Center for Drug Evaluation and Research, and e-mails to Dr. Jenkins, Director, Office of New Drugs, regarding this application, this meeting was scheduled, as stated in an October 11, 2013, e-mail to Ms. Caballa from Ms. Willard, for:

1. Discussion of manufacturing compliance issues
2. Discussion of rationale for not extending the PDUFA Goal Date
3. Discussion of clinical issues
4. Discussion of plans for a future Advisory Committee Meeting

DISCUSSION

Following introductions, Dr. Cox noted that the PDUFA Goal Date for this application was October 17, 2013, and that the Agency planned to move forward with an action by the due date. During this meeting, the Agency discussed the agenda items forwarded to Alimera on October 11, 2013.

1. Discussion of manufacturing compliance issues

Noting that there had been communications between Alimera and the Agency regarding what information could be discussed concerning the compliance issues for this application without representatives from (b) (4) providing authorization, the Agency stated that the (b) (4) manufacturing facility was found to have significant CGMP deficiencies on inspection which have not been resolved. The deficiencies were communicated to (b) (4) on the FDA Form-483, Inspectional Observations. The Agency does not view the compliance issues resolvable in this review cycle.

Alimera noted that Ms. Caballa was present at the (b) (4) manufacturing facility for the portion of the FDA inspection that pertained to Illuvien. Alimera stated that it was their understanding that the deficiencies from the most recent inspection pertain to method transfer protocols and analytical methods. The current method transfer protocols being used were developed in 2008. Noting that new guidances pertaining to method transfer were issued by the WHO in 2011 and 2012, Alimera stated that they are now being held to these new standards. Alimera stated that they have agreed to update the protocols based on the current guidance and that these issues will be resolved by the end of December 2013. Alimera stated that there have been 13 batches successfully manufactured at the (b) (4) facility and that product from these batches have been sold in countries where the product is currently approved, with no adverse events due to manufacturing reported.

Alimera stated that there had been an agreement with the review chemist regarding the in-process controls. Alimera further stated that the investigator, as documented during the July/August 2013 inspection of the (b) (4) facility, was not in agreement with the review chemist regarding the in-process controls. Alimera stated that they would like to discuss with the Agency this difference between what the review chemist agreed to regarding the in-process controls and what the investigator wrote in the report. The Agency noted that for this application, per common practice, inspectional findings were discussed after the inspection closeout using a team-based approach (with the review chemist and compliance). The Agency also stressed the importance of good communication between Alimera and all of its contract manufacturers/suppliers.

2. Discussion of rationale for not extending the PDUFA Goal Date

When assessing whether a submission will be accepted as a major amendment that would extend the PDUFA clock, the Agency makes a determination on such factors as how much new information is in the submission, whether the new information is pertinent to the application, and whether there are other known deficiencies that could be adequately addressed by a 3-month extension.

The Agency noted that examples of submissions that would qualify as major amendments would include clinical study reports of studies not previously submitted or major new re-analyses of already submitted data.

The Agency noted that the September 9, 2013, submission contained minimal new information and, therefore, was not classified as a major amendment. Another consideration is that the guidance for industry regarding Good Review Management Practices states that, in general, when considering whether to extend the review clock for a major amendment, the Agency looks at the application in its entirety. In the case of this application, there is no certainty when the compliance issues will be resolved, and therefore, these issues would also be important considerations in the determination of whether or not to extend the clock, if a qualifying major amendment had been submitted.

3. Discussion of clinical issues

It was stated that any outstanding clinical issues would be delineated in the action letter.

4. Discussion of Plans for a Future Advisory Committee

Alimera's counsel stated that Alimera has been working diligently with the review Division to come to a mutual understanding of this disease, the natural history of the disease, and how best to treat it. To that end, Alimera stated it had brought known experts in the field to meetings with the Agency for open dialog. These experts have come away frustrated over the differences of opinion between themselves and the Agency. Alimera believes a reasonable course would be to take this application to an Advisory Committee.

Alimera provided a brief history regarding their requests dating back two years for an Advisory Committee meeting for this application. The Agency noted that convening an Advisory Committee is not a basis for extending the PDUFA Goal Date. The Agency also noted plans for an Advisory Committee that could take place near the end of January 2014.

Alimera suggested a possible alternative meeting to an Advisory Committee Meeting which would include experts in this disease, but which could be convened sooner. The Agency stated that such a meeting would not be consistent with the Federal Advisory Committee Act, including the need for filing of Conflict of Interest (COI) papers for each Special Government Employee (SGE).

There was discussion regarding fundamental differences in what Alimera and the Agency view as the science for this disease and how it should be treated. Alimera believes that, for this application, the Agency failed to listen to the opinions of the experts Alimera brought to meetings regarding scientific issues and that the process with this application has not been a fair one in Alimera's opinion. The Agency reiterated its belief that the differences are a matter of scientific opinion, and the difference in scientific opinion is a reason to convene an Advisory Committee.

The Agency noted that this Advisory Committee Meeting could take place off the clock, as there would be no pending resubmission for the application. Regarding the process for an Advisory Committee, the Agency stated that Advisors and Consultants staff poll Committee members for available dates, review COI statements for each member and any other consultant SGEs invited, and work with applicants to ensure a productive meeting. The Division routinely offers to meet with applicants prior to the Advisory Committee Meeting to review topics to be discussed at the meeting. At the time the Division meets with the applicant, the specific questions to the Advisory Committee have not, in general, been finalized.

Discussion that takes place during an Advisory Committee Meeting could inform the way Alimera could address deficiencies outlined in an action letter. An Advisory Committee

Meeting in itself does not address any deficiency, but discussion from the Advisory Committee could be used as an aid in addressing deficiencies.

The Agency noted that compliance issues for this application would be resolved between (b) (4) and the district. (b) (4) should then notify Alimera that the compliance issues have been resolved. In order to support resubmission, Alimera should state in a Complete Response submission that the compliance issues have been resolved; the Division would verify this resolution through CDER Office of Compliance.

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

/s/

RENATA ALBRECHT
11/20/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201923

MEETING MINUTES

Alimera Sciences, Inc.
Attention: Ms. Susan H. Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) dated June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2013. The purpose of the meeting was to obtain feedback on the progress of the review and any identified deficiencies in the April 17, 2013, Class 2 resubmission in response to the November 10, 2011, Complete Response letter.

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

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Guidance

Meeting Date and Time: July 26, 2013, from 8:30 to 9:30 AM
Meeting Location: White Oak Building 22, Room 1309

Application Number: 201923
Product Name: Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg
Indication: [REDACTED] (b) (4)

Sponsor/Applicant Name: Alimera Sciences, Inc.

Meeting Chair: Renata Albrecht, M.D.
Meeting Recorder: Diana Willard

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/Division of Biometrics IV (DBIV)
Dongliang Zhuang, Ph.D.	Statistical Reviewer, OB/DBIV
Lin Qi, Ph.D.	Product Quality Reviewer, Office of New Drug Quality Assessment/Branch V
Lois Almoza, M.S.	Regulatory Health Project Manager
Christina Marshall, M.S.	Regulatory Health Project Manager
Diana Willard	Chief, Project Management Staff, DTOP

ALIMERA SCIENCES, INC. ATTENDEES

Susan Caballa	Senior Vice President, Regulatory and Technical Affairs
Ken Green, Ph.D.	Senior Vice President, Scientific Affairs and Chief Scientific Officer

Dan Myers
Barry Kapik

President, CEO
Senior Director, Biostatistics

ALIMERA SCIENCES, INC. CONSULTANTS

(b) (4)

BACKGROUND

NDA 201923 was originally submitted on June 30, 2010 by Alimera Sciences, Inc. (Alimera) for treatment of diabetic macular edema (DME). A Complete Response letter for this NDA issued on December 22, 2010. A Class 2 Resubmission in response to this Complete Response letter was submitted by Alimera on May 12, 2011. A second Complete Response letter issued on November 10, 2011. On April 17, 2013, Alimera submitted a Class 2 Resubmission in response to this second Complete Response letter.

This meeting was requested by Alimera to obtain feedback on the progress of the review and to discuss any identified deficiencies in the April 17, 2013, Class 2 resubmission that submitted in response to the November 10, 2011, Complete Response letter.

DISCUSSION

Following introductions, Alimera stated that they would like to address any concerns the Agency has regarding Iluvien that would prevent approval. During the meeting, Alimera made a presentation; the slides from this presentation are attached.

Alimera stated that based on the clinical trials that have been conducted, they believe a subgroup has been identified that would benefit from the product, patients with duration of DME (b) (4)

Alimera stated that in two separate clinical studies, (b) (4)
(b) (4) the duration of DME was captured on the Case Report

Form [REDACTED] (b) (4) The sponsor noted that based on data from clinical trials of Iluvien (FAME A and B) and ranibizumab (RISE and RIDE), they consider that DME transitions to a state that benefits from continuous use of this product.

The Agency noted that this subset was identified from data collected during conduction of the studies and was not pre-specified in the protocol. Further, there are data from available literature demonstrating that within the first six months from diagnosis, DME may resolve on its own in roughly 30% of cases, making any effect observed during the Iluvien studies difficult to definitively attribute to this product.

Alimera and their consultants briefly summarized their position [REDACTED] (b) (4)

The Agency noted that Alimera did not study the population in whom they now propose to use the product; the usual approach to demonstrate safety and effectiveness is to conduct a study in the population that will use the product. As noted previously, the Agency continues to have concerns about the relative benefit to risk ratio in the population studied in the clinical trials, and this continues to be an issue for this product.

The Agency acknowledged that [REDACTED] (b) (4)

[REDACTED] such information would be important in considering both the efficacy and safety, as well as risk benefit in the target patient population, The Agency added that a single study of one-year duration was being recommended.

Alimera and their consultants stated that not treating patients diagnosed with DME carries a serious risk in terms of potential vision loss. Alimera believes that practicing ophthalmologists need a product that can improve outcome for DME patients and this product is effective for these patients.

Emphasizing that the review is on-going, the Agency noted that based on the data submitted in the application for Iluvien, in the subset of patient with duration of DME [REDACTED] (b) (4)

[REDACTED] the rate of adverse reactions was higher 8 out of 10 have cataract surgery, and 4 out of 10 have elevated intraocular pressure. From the review to date, it appears that the data in the application demonstrate that more subjects have serious side

effects than receive benefit from this product. Alimera stated that the 3-line of improvement in visual acuity is a high standard and that other patients had some degree of benefit. The Agency asked Alimera to provide a discussion of the benefit attained by the remaining patients, and provide a rationale why the degree of toxicity seen was acceptable relative to the benefit in these 80% of non-responding patients. There was a brief question about whether further criteria could be identified to select those patients likely to respond to Iluvien treatment.

Any further information needed or questions that arise as the review of the application continues will be promptly conveyed to Alimera.

ATTACHMENTS

Attached to these minutes are slides sent by Ms. Barbara Bauschka of Alimera via e-mail to Ms. Willard on July 25, 2013.

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immediately following this page

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/s/

RENATA ALBRECHT
08/23/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201923

MEETING PRELIMINARY COMMENTS

Alimera Sciences, Inc.
Attention: Ms. Susan H. Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also refer to your June 25, 2013, correspondence, received June 25, 2013, requesting a meeting to obtain feedback on the progress of the review and any identified deficiencies in the April 17, 2013, Class 2 resubmission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana M. Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Guidance

Meeting Date and Time: July 26, 2013, from 8:30 to 9:30 AM
Meeting Location: White Oak, Building 22, Room 1309

Application Number: NDA 201923
Product Name: Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg
Indication: [REDACTED] (b) (4)

Applicant Name: Alimera Sciences, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 26, 2013, from 8:30 to 9:30 AM, between Alimera Sciences, Inc. and the Division of Transplant and Ophthalmology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

The questions outlined in your June 25, 2013, Meeting Request are presented in **bold font** and our responses are in *italic font*.

- 1. We believe the benefits of ILUVIEN for patients with chronic DME clearly outweigh the well-known and manageable risks of cataract formation and elevated IOP associated with ILUVIEN and corticosteroids as a class. Does FDA agree?**

FDA Response: This is a review issue and can only be determined upon the final review of the submission. The issues and concerns (including, but not limited to, the identification of patient subgroups by history without documented ophthalmic examinations, the documented incidence of cataract development, the documented incidence of elevated intraocular pressure, the effects of persistent elevated IOP which may only be diagnosable five to ten years later, the documented need for some patients with elevated IOP to be treated with surgical procedures introducing lifelong risks of endophthalmitis, the need for chronic therapy in a condition which has a variable time course and includes spontaneous remissions, the ability to distinguish the benefit and risks of cataract surgery from the effects of the drug product, the appropriate statistical adjustments for the multiple endpoints and subgroups evaluated) which have been identified and/or cited during the development of the product and/or described in prior action letters remain under review.

- 2. If FDA does not agree, Alimera believes an Advisory Committee Meeting should be convened so that experts in the field can provide FDA with perspective on the benefits of ILUVIEN as well as the magnitude of the risks associated with the drug which Alimera considers to be anticipated and minimal. Does the Agency agree?**

FDA Response: The decision to take a non-NME product to an advisory committee is an Agency decision based on whether the Agency believes that the application includes sufficient information upon which to make an informed decision and whether additional expertise from an Advisory Committee and the public would be helpful to the Agency in identifying additional areas of review.

- 3. Has FDA identified any issues that would stand in the way of approval of ILUVIEN^{(b) (4)} [REDACTED]?**

FDA Response: This is a review issue and can only be determined upon the final review of the submission. The issues identified in the response to question 1 are important considerations in the review of the application.

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/s/

DIANA M WILLARD
07/19/2013



NDA 201923

MEETING REQUEST GRANTED

Alimera Sciences, Inc.
Attention: Ms. Susan H. Caballa
Senior Vice President, Regulatory and Technical Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Caballa:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also refer to your June 25, 2013, correspondence requesting an End of Ninety-Day Conference to obtain feedback on the progress of the review and any identified deficiencies in the April 17, 2013, Class 2 resubmission. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: July 26, 2013
Time: 8:30 – 9:30 AM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Invited CDER Participants:

Robert Temple, M.D.	Deputy Center Director for Clinical Science
Edward Cox, M.D., Ph.D.	Office Director, Office of Antimicrobial Products (OAP)
Dave Roeder, M.S.	Associate Director of Regulatory Affairs, OAP
Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Rhea Lloyd, M.D.	Clinical Reviewer, DTOP

Sonal Wadhwa, M.D.	Clinical Reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Dongliang Zhuang, Ph.D.	Statistical Reviewer, OB/DBIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Balajee Shanmugan, Ph.D.	Product Quality Team Leader, Office of New Drug Quality Assessment (ONDQA)/Branch V
Qi Lin, Ph.D.	Product Quality Reviewer, ONDQA/Branch V
Diana Willard	Chief, Project Management Staff, DTOP

Please e-mail me any updates to your attendees at diana.willard@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Diana Willard at 6-0833; Ramou Mauer at 6-1600.

Any background information provided for the meeting (three paper copies or one electronic copy to the application and 18 desk copies to me) should be submitted at least two weeks prior to the meeting.

Submit the 18 desk copies to the following address:

Ms. Diana Willard
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6132
10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code **20903** if shipping via United States Postal Service (USPS).

Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

NDA 201923
Page 3

If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana M. Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

DIANA M WILLARD
07/02/2013



NDA 201923

INFORMATION REQUEST

Alimera Sciences Inc.
Attention: Barbara H. Bauschka
Sr. Vice President Regulatory and Technical Affairs
6120 Windward Parkway
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) submitted June 30, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien® (fluocinolone acetonide) intravitreal insert.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 3, 2013, in order to continue our evaluation of your NDA.

1. It is noted that the drug product stability lots were manufactured in March 2009. Please update the NDA with available stability data.
2. The method transfer report-08202 recommends [REDACTED] (b) (4) [REDACTED] Update the analytical procedure (CTM – 200501) to include the (b) (4) direction.
3. Provide any available information on performance tests conducted to establish the slider mechanism of the inserter unit to demonstrate that the inserter unit does not inadvertently disengage during usage and performs reliably.

If you have any questions, call 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/

DOROTA M MATECKA
06/18/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver Spring
MD 20993

NDA 201923

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

We acknowledge receipt on April 17, 2013, of your April 17, 2013, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We consider this a complete, class 2 response to our November 10, 2011, action letter. Therefore, the user fee goal date is October 17, 2013.

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana M. Willard
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DIANA M WILLARD
04/26/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 201923

ACKNOWLEDGE INCOMPLETE RESPONSE

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

We acknowledge receipt on March 27, 2013, of your March 27, 2013, submission to your new drug application (NDA) for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We do not consider this a complete response to our action letter for the following reasons:

The *Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance*¹ defines Good Clinical Practice (GCP) as “A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.” It further defines Audit as “A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).” The Guidance also states that “The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.”

The following deficiency in the content of your application needs to be addressed:

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>

You have data tables based on unaudited data in the Interim Safety Report for Study C-01-11-008.

The Agency's expectation is that clinical data submitted as part of a Complete Response be based on final, audited data. Therefore, we will not start the review clock until we receive a complete response.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{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

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/s/

RENATA ALBRECHT
04/10/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201923

MEETING MINUTES

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert).

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2012. The purpose of the meeting was to discuss what further steps need to be taken in order for NDA 201923 to be approved.

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

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{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

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: NDA

Meeting Date and Time: June 19, 2012, 1:00 PM
Meeting Location: Building 22, Room 1315

Application Number: 201923
Product Name: Iluvien (fluocinolone acetonide intravitreal insert).
Indication: [REDACTED] (b) (4)

Sponsor Name: Alimera Sciences, Inc.

Meeting Chair: Renata Albrecht, M.D.
Meeting Recorder: Diana Willard

FDA ATTENDEES

Center for Drug Evaluation and Research (CDER)

Office of the Center Director

Robert Temple, M.D. Deputy Center Director for Clinical Science

Division of Transplant and Ophthalmology Products (DTOP)

Renata Albrecht, M.D.	Division Director
Wiley A. Chambers, M.D.	Deputy Director
Ozlem Belen, M.D. MPH	Deputy Director for Safety
William Boyd, M.D.	Clinical Team Leader
Martin Nevitt, M.D.	Clinical Reviewer
Jennifer Harris, M.D.	Clinical Reviewer
Lucious Lim, M.D.	Clinical Reviewer
Rhea Lloyd, M.D.	Clinical Reviewer
Diana Willard	Chief, Project Management Staff

Office of Biostatistics (OB), Division of Biometrics IV (DBIV)

Yan Wang, Ph.D.	Biostatistical Team Leader
Mushfiqur Rashid, Ph.D.	Biostatistical Reviewer

APPLICANT ATTENDEES

Alimera Sciences, Inc.

Barbara Bauschka	Director, Regulatory Affairs
Kathleen Billman	Director, Scientific Affairs
Susan Caballa	Senior Vice-President, Medical and Regulatory Affairs
Ken Green, Ph.D.	Chief Scientific Officer, Senior Vice-President, Scientific Affairs
Barry Kapik	Director, Biostatistics and Data Management, Scientific Affairs
Yvonne Johnson, O.D.	Executive Director, Medical Affairs
Dan Myers	Chief Executive Officer

Consultants

(b) (4)

1.0 BACKGROUND

Alimera Sciences, Inc. (Alimera) submitted a request for an end-of-review meeting on April 12, 2012, to discuss what further steps need to be taken in order for NDA 201923 to be approved. The meeting was scheduled for June 19, 2012. A briefing package was received on May 21, 2012. The Division provided Alimera with responses to the questions outlined in the briefing package, via email, on June 14, 2012. The questions are captured below in bold font, followed by the preliminary FDA responses (*italics*) and meeting comments (regular font).

Sponsor Questions

For the purposes of this response, your questions are in **bold** font and our responses are in *italics* font.

- 1. The Sponsor conducted two adequate and well-controlled studies (FAME A and FAME B). Each study demonstrated a statistically significant difference from sham in the proportion of patients gaining 15 or more letters from baseline in BCVA at the pre-**

specified primary timepoint (Month 24) based on the Full Analysis population (defined as all randomized subjects with LOCF for missing data).

Does the Agency agree that ILUVIEN was statistically superior to sham at 24 months in the primary analysis of ≥ 15 -letter improvement in BCVA in both phase 3 trials?

FDA Response:

Yes; however your question does not address the issues needed to consider the totality of the data in a clinical risk versus benefit assessment. In addition, the visual acuity endpoint at Month 24 is confounded by the development of cataracts in many patients, cataract surgery in some patients, and previous demonstrations by other products designed to treat diabetic ocular complications that results at month 24 are not necessarily predictive of future visual results.

Specifically, in our efficacy evaluation at Month 24, we consider the efficacy rates to be low (approximately 26-31%) and the difference between groups (26-31% versus 14-18%) to be minimal. The majority of the beneficial effect appears to occur during first 6 months, and the product appears to cause clinically significant decreases in visual acuity by month 24. These clinical trials showed that there was a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. This development of cataracts in eyes which were phakic at baseline created difficulty in interpreting visual acuity during months 12 to 24. The timing of the development of the cataracts and the time needed for postoperative recovery, suggested to us that the 36-month clinical trial data would be a more appropriate representation of potential long term benefit.

Table 3: Number (%) of Subjects with a ≥ 15 -Letter Increase from Baseline in BCVA in the Study Eye (FAME A and FAME B, Full Analysis Population)

Time Point	FAME Study A			FAME Study B		
	Treatment Group			Treatment Group		
	Sham N=95	0.2 µg/day FA N=190	0.5 µg/day FA N=196	Sham N=90	0.2 µg/day FA N=186	0.5 µg/day FA N=199
Month 18, n (%)	(b) (4)					
Difference ¹						
P-value ²						
Month 24, n (%)	14 (14.7)	51 (26.8)	51 (26.0)	16 (17.8)	57 (30.6)	62 (31.2)
Difference ¹		-12.1	-11.3		-12.9	-13.4
P-value ²		0.029	0.034		0.030	0.027
Month 30, n (%)	(b) (4)					
Difference ¹						
P-value ²						
Month 36, n (%)	(b) (4)					
Difference ¹						
P-value ²						

Reference: Refer to Module 5.3.5.1, C-01-05-001A Synopsis Table 14.2.1.4 and Module 5.3.5.1, C-01-05-001B Synopsis Table 14.2.1.4

¹ Difference is sham minus active. A negative value denotes a higher percentage of subjects in the active group who showed improvement in BCVA.

² P-value based on a CMH chi-square test stratified by baseline VA.

In our safety evaluation of the same trials, 70-80% of phakic patients developed cataracts during trial with the associated impairment of vision that is caused by cataract development.

In addition to the risk of cataract development, the risk of increased intraocular pressure elevation (IOP) is nearly three times higher in the Iluvien treatment arm than the control arm. A significant number of patients developed elevations in intraocular pressure (35-45%). Of the patients who developed ocular hypertension, the elevation in pressure was large (>12 mmHg) in most of them and required surgical intervention in an unacceptably high number of patients (5-8%). Surgical intervention for elevated IOP carries with it a continuing increased risk of serious ocular infections.

Table 42: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects (36-Month Integrated FAME Studies, Safety Population)

Category	Treatment Group		
	Sham (N = 121) n (%)	0.2 µg/day FA (N = 235) n (%)	0.5 µg/day FA (N = 265) n (%)
Any cataract-related AE	61 (50.4)	192 (81.7)	235 (88.7)
Cataract NOS	51 (42.1)	168 (71.5)	212 (80.0)
Cortical cataract	1 (0.8)	1 (0.4)	2 (0.8)
Diabetic cataract	0 (0.0)	1 (0.4)	0 (0.0)
Nuclear cataract	5 (4.1)	8 (3.4)	9 (3.4)
Subcapsular cataract	8 (6.6)	27 (11.5)	24 (9.1)
Cataract operation	33 (27.3)	188 (80.0)	231 (87.2)

Reference: Refer to Module 5.3.5.3, ISS-36 Month Table 5.15

Table 41: Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye (36-Month Integrated FAME Studies, Safety Population)

Category	Treatment Group		
	Sham (N = 185) n (%)	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)
IOP elevation considered an AE ¹	22 (11.9)	139 (37.1)	179 (45.5)
IOP elevation increase ≥12 mmHg	15 (8.1)	108 (28.8)	135 (34.4)
IOP elevation to over >25 mmHg	18 (9.7)	123 (32.8)	166 (42.2)
IOP elevation to over >30 mmHg	8 (4.3)	69 (18.4)	90 (22.9)
Trabeculectomy surgery performed	0 (0.0)	5 (1.3)	10 (2.5)
Trabeculectomy surgery performed	0 (0.0)	10 (2.7)	22 (5.6)
Glaucoma surgery performed ²	1 (0.5)	8 (2.1)	13 (3.3)
Vitrectomy performed for elevated IOP	0 (0.0)	1 (0.3)	2 (0.5)
Any surgical intervention ³	1 (0.5)	18 (4.8)	32 (8.1)

Reference: Refer to Module 5.3.5.3, ISS-36 Month Table 5.11

¹ Includes adverse event reports of ocular hypertension and intraocular pressure increased

² Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocycloablation, and laser peripheral iridotomy.

³ Includes trabeculectomy, glaucoma surgery, and vitrectomy for elevated IOP.

The risks of cataract development and IOP elevation are significant and are not offset by the potential benefits demonstrated by Iluvien in these clinical trials.

- FDA's review of the 24-month clinical study data identified issues associated with the overall benefit/risk profile of ILUVIEN in the original patient population. FDA requested additional information, including 36-month data from the FAME studies, and provided guidance regarding potential subgroup analyses.**

The Sponsor reviewed results from the existing and pre-planned analyses and identified a baseline patient variable (duration of DME ^{(b)(4)}) that was associated with a significantly improved ILUVIEN benefit/risk profile for patients. The Sponsor submitted analyses by duration of DME in its NDA resubmission (May 12, 2011). As described in its CRL (November 10, 2011), FDA considered these post-hoc analyses.

However, although the Sponsor did not describe its duration of DME subgroup analysis in either its protocols or the SAP (and apologizes for this oversight), this analysis was nevertheless prospectively planned. The Sponsor provides evidence to support this statement in Appendix B of this briefing package.

Does the Agency concur that the Sponsor's analysis of the duration of DME subgroups was prospectively planned?

FDA Response:

We cannot confirm that your analysis of the duration of DME subgroups was prospectively planned. The duration of DME subgroup analysis was not provided in either the protocol or in the SAP. We would normally consider this type of analysis to be a post-hoc analysis.

Regardless of the prospective or non-prospective nature of your duration of DME subgroup analysis, the risks of the cataract and IOP adverse reactions previously noted are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

- When the primary efficacy analysis (Full Analysis Population, LOCF for missing data, T = 24 months) of the Duration of DME ^{(b)(4)} subgroup is adjusted for multiple comparisons, the results remain statistically significant (see Section 5.3).**

Does the Agency concur that statistical significance is maintained in the primary efficacy analyses of both phase 3 trials after adjusting for multiple comparisons?

FDA Response:

No. We do not agree that there is an appropriate post-hoc multiplicity adjustment for the primary efficacy analyses on the DME subgroup.

In addition, we have questions about the clinical interpretation of "duration of DME." DME can wax and wane over time. Did clinicians interpret duration of DME to mean the time when

the first episode of DME occurred in a patient's life, the most recent episode of DME excluding the current episode, or the current episode of DME? The clinicians do not appear to have been required to document any previous clinical findings of DME. The proposed subgroup "Duration of DME [REDACTED] (b) (4)" is therefore not well defined or documented a priori.

It is also unclear how you determined the clinical relevance of "Duration of DME [REDACTED] (b) (4),"

Regardless of the clinical relevance or adjustment for multiplicity, the risks of cataract development and IOP elevation remain in this subgroup. These risks are considered significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

4. **The analysis based on duration of DME at baseline is based on a subgroup that was identified prior to administration of drug, namely duration of DME [REDACTED] (b) (4). In addition, results from the individual phase 3 trials demonstrated that ILUVIEN was [REDACTED] (b) (4)**

The Sponsor therefore believes that this satisfies FDA's criteria for subgroup selection (see Section 5).

Does the Agency concur that the baseline characteristic of "duration of diabetic macular edema" satisfies the Agency's criteria for subgroup selection?

FDA Response:

No, for the reasons listed in our response to Questions 2 and 3. Regardless of the clinical relevance, prospective or non-prospective analysis or any adjustment for multiplicity, the risks of cataract development and IOP elevation remain in this subgroup. These risks are considered significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

Table 16: Number (%) of Subjects with a ≥ 15 -Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) (FAME A and FAME B, with LOCF)

(b) (4)



Table 16: Number (%) of Subjects with a > 15 -Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) (FAME A and FAME B, with LOCF (Continued)

(b) (4)



5. The Sponsor presents the benefit/risk profile and additional analyses for ILUVIEN in the duration of DME (b)(4) subgroup in this briefing package. The Sponsor believes that the benefits outweigh the risks in this subgroup (see Section 5.7).

Does the Agency concur that the improved benefit observed in the subgroup of subjects with duration of DME (b)(4) outweighs the risks?

FDA Response:

No. The subgroup of subjects with duration of DME (b)(4) continue to demonstrate the risks associated with the drug. See tables below. These risks include an increased risk of cataract formation and an increased risk of IOP elevation. Cataract formation and elevated IOP can lead to decreased vision and a subset of these patients will require additional surgery which introduces additional risks to the patient.

Table 46: Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye for Subjects with a DME Duration (b)(4) (36-Month Integrated FAME Studies, Safety Population)

(b)(4)



Table 47: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)

(b) (4)



6. In the meeting minutes of February 2, 2011 and in the CRL of November 10, 2011, FDA indicated that because the injector system proposed for marketing is different from the injector system used in the clinical studies, Alimera should provide data on 100 eyes using the new injector. Alimera has initiated a physician utilization study (FAME Extension Study, Protocol C-01-11-008) (b) (4)

Does the Agency agree to accept as part of the CRL response the physician utilization results from this trial based on (b) (4)

FDA Response:

No. Applications are expected to be complete at the time of submission. We continue to recommend that you submit a comparative study with at least 100 eyes enrolled into the trial using the (b) (4) inserter versus at least 50 eyes enrolled using the inserter configuration utilized in the prior clinical trials. We note however, this will not address the potential safety risks identified in our responses to Questions 1-5.

7. If incorporating additional post-marketing oversight would allow the Agency to approve ILUVIEN for the proposed indication, based on the current dataset, Alimera proposes strategies to mitigate risk. The primary safety concerns associated with the use of ILUVIEN for the treatment of DME are the risks of elevated IOP and the

formation or progression of cataracts. Alimera proposes to mitigate those risks

(b) (4)

Alimera would appreciate the opportunity to partner with the Agency to develop a plan that is practical and meets the objectives.

(b) (4)

Does the Agency concur that these mitigation strategies for ILUVIEN are appropriate?

FDA Response:

While you may voluntarily submit a proposed [redacted] the FDA must make a determination

(b) (4)

(b) (4)

would not be accepted

(b) (4) *Your proposal*

(b) (4)

Iluvien has demonstrated a propensity to cause cataracts and elevations in IOP. These risks are serious, occur with significant frequency, and cannot be prevented [redacted]

(b) (4)

(b) (4)

is not appropriate for this product at this time.

2.0 MEETING DISCUSSION

Following introductions, the Agency turned the meeting over to Alimera to allow them the time to address any issues or comments they wanted to bring forward for discussion.

Alimera chose not to follow the questions outlined in the May 21, 2012, meeting package and began by having three of their attendees summarize the history of the NDA, the disease and their interpretation of the data currently submitted to the NDA. This presentation included a number of detailed testimonials on the subgroup of patients they routinely see in practice and the improvement these patients have experienced after implantation of the Iluvien intravitreal insert. It was stated that treatment of chronic macular edema is an unmet medical need and that the FAME trial identified patients who would benefit the most from the Iluvien intravitreal insert. Further, Alimera stated that although some patients had an increase in intraocular pressure (IOP) and others developed cataracts with the use of Iluvien intravitreal insert, Alimera expressed their belief that the benefits for patients outweigh the risks in patients who are at “the end of their rope.” Alimera noted that the “brittle” patients enrolled in the FAME trial can develop neovascular inflammation over a matter of days and having the Iluvien intravitreal insert as an approved option for treatment would benefit the patient.

Acknowledging the comments from Alimera and their consultants, the Agency noted that (b) (4)

(b) (4)
80% of eyes in phakic patients developed cataracts, up to 40% of patients developed elevated IOP and 5% to 8% had to have surgery to lower their IOP. It was noted that the subgroup of patients reported to have DME (b) (4) have approximately equal numbers of cataracts and increases in IOP as those with shorter duration of disease. While agreeing that since the initiation of the FAME trial there have been changes in filtering surgery, if a patient does undergo surgery for IOP, that patient still has an increased risk of infection or other complications. The development of, and surgery for, cataracts is also a significant risk that has to be considered in any risk/benefit analysis for this product. While the Agency agrees that patients with an Iluvien intravitreal insert show a modest improvement in vision, the Agency concluded that the benefits do not outweigh the risks for this product. If the majority of enrolled patients had shown a large clinical benefit and a minority of patients had minor adverse events, the Agency might have interpreted the data differently. Fundamentally, the Agency concluded that the benefit of Iluvien does not outweigh the risks associated with the use of Iluvien. It was also noted that the concern about the risks associated with long term corticosteroid use were mentioned early during development and that the hypothesis offered by the sponsor was that the amount of drug (fluocinolone) was sufficiently low that cataract development and elevated intraocular pressure would be unlikely to occur. However, the results of the trials show that these significant adverse reactions occur while the

rate of improvement in vision is low. Alimera commented that while the increase in 15 letters was seen in a smaller portion of the population, other patients also achieved a clinical benefit. Alimera also commented that the various adverse reactions could be managed.

The Agency suggested that if Alimera chooses to provide further analyses based on the data already submitted, it may be beneficial to perform analyses that address qualitative benefits. The applicant could provide a qualitative evaluation of what constituted significant benefit, and include an explanation of why the adverse reactions are not considered to be of particular concern. Any qualitative evaluation should include a discussion of the risks associated with cataract surgery, the risks associated with IOP elevation and the risks associated with surgical procedures performed for elevated IOP.

In summary, the Agency emphasized that based on our interpretations of the results, the risks of cataract development, IOP elevation, and surgery remain a concern for this subgroup of patients. Alimera will need to explain convincingly why these risks, and the management of them, do not outweigh the observed benefits.

ADDENDUM

Following the meeting with Alimera, the Agency had the following additional comments for consideration:

1. Regarding surgery for IOP, explain why the surgery used in the treatment of patients enrolled in the clinical trial and its associated risk does not outweigh the benefit shown.
2. Regarding cataract formation and management, explain why the high frequency of development of cataracts and associated surgery is acceptable.
3. Regarding vision, examine the distribution of benefit (15 letters, 20 letters, 25 letters, etc) in the population. If you examine distribution of less than 15 letters, discuss how that represents a clinical benefit.
4. Does removal of the Iluvien insert promptly reverse the adverse events, such as elevated IOP? If so, are there data to support the reversal?

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

/s/

RENATA ALBRECHT
07/18/2012



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

**Food and Drug
Administration Silver
Spring MD 20993**

NDA 201923

MEETING PRELIMINARY COMMENTS

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert).

We also refer to your April 12, 2012, correspondence, received April 12, 2012, requesting a meeting to discuss what further steps need to be taken for NDA 201923 to be approved. We further refer to your May 21, 2012, correspondence, containing meeting materials for the June 19, 2012 meeting scheduled between the FDA and Alimera Sciences, Inc.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

Meeting Preliminary Comments
Division of Transplant and Ophthalmology Products

Meeting Date/Time: June 19, 2012 at 1:00 PM
Meeting Location: White Oak Building 22
10903 New Hampshire Avenue
Silver Spring, Maryland 20903
Room 1315

Meeting Type: Type B meeting

Application: NDA 201923
Drug: fluocinolone acetonide intravitreal implant
Sponsor: Alimera Sciences

The following are the Division's preliminary responses to the questions posted in your briefing package dated May 21, 2012, for Iluvien (fluocinolone acetonide intravitreal implant), 0.19 mg, for the treatment of diabetic macular edema.

If these answers and comments to your questions are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. You can also request that the face-to-face meeting be converted to a teleconference.

Please note that if there are any major changes to your development plan, or the purpose of the meeting, or new questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting to be held on June 19, 2012. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

The applicant is requesting a face-to-face type B NDA meeting to discuss what further steps need to be taken in order for NDA 201923 to be approved.

For the purposes of this response, your questions are in **bold** font and our responses are in *italics* font.

3.1. Sponsor Questions

- 1. The Sponsor conducted two adequate and well-controlled studies (FAME A and FAME B). Each study demonstrated a statistically significant difference from sham in the proportion of patients gaining 15 or more letters from baseline in BCVA at the pre-specified primary timepoint (Month 24) based on the Full Analysis population (defined as all randomized subjects with LOCF for missing data).**

Does the Agency agree that ILUVIEN was statistically superior to sham at 24 months in the primary analysis of ≥ 15 -letter improvement in BCVA in both phase 3 trials.

FDA Response:

Yes; however your question does not address the issues needed to consider the totality of the data in a clinical risk versus benefit assessment. In addition, the visual acuity endpoint at Month 24 is confounded by the development of cataracts in many patients, cataract surgery in some patients, and previous demonstrations by other products designed to treat diabetic ocular complications that results at month 24 are not necessarily predictive of future visual results.

Specifically, in our efficacy evaluation at Month 24, we consider the efficacy rates to be low (approximately 26-31%) and the difference between groups (26-31% versus 14-18%) to be minimal. The majority of the beneficial effect appears to occur during first 6 months, and the product appears to cause clinically significant decreases in visual acuity by month 24. These clinical trials showed that there was a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. This development of cataracts in eyes which were phakic at baseline created difficulty in interpreting visual acuity during months 12 to 24. The timing of the development of the cataracts and the time needed for postoperative recovery, suggested to us that the 36-month clinical trial data would be a more appropriate representation of potential long term benefit.

Table 3: Number (%) of Subjects with a ≥ 15 -Letter Increase from Baseline in BCVA in the Study Eye (FAME A and FAME B, Full Analysis Population)

Time Point	FAME Study A			FAME Study B		
	Treatment Group			Treatment Group		
	Sham N=95	0.2 µg/day FA N=190	0.5 µg/day FA N=196	Sham N=90	0.2 µg/day FA N=186	0.5 µg/day FA N=199
Month 18, n (%)	(b) (4)					
Difference ¹						
P-value ²						
Month 24, n (%)	14 (14.7)	51 (26.8)	51 (26.0)	16 (17.8)	57 (30.6)	62 (31.2)
Difference ¹		-12.1	-11.3		-12.9	-13.4
P-value ²		0.029	0.034		0.030	0.027
Month 30, n (%)	(b) (4)					
Difference ¹						
P-value ²						
Month 36, n (%)	(b) (4)					
Difference ¹						
P-value ²						

Reference: Refer to Module 5.3.5.1, C-01-05-001A Synopsis Table 14.2.1.4 and Module 5.3.5.1, C-01-05-001B Synopsis Table 14.2.1.4

¹ Difference is sham minus active. A negative value denotes a higher percentage of subjects in the active group who showed improvement in BCVA.

² P-value based on a CMH chi-square test stratified by baseline VA.

In our safety evaluation of the same trials, 70-80% of phakic patients developed cataracts during trial with the associated impairment of vision that is caused by cataract development.

In addition to the risk of cataract development, the risk of increased intraocular pressure elevation (IOP) is nearly three times higher in the Iluvien treatment arm than the control arm. A significant number of patients developed elevations in intraocular pressure (35-45%). Of the patients who developed ocular hypertension, the elevation in pressure was large (>12 mmHg) in

most of them and required surgical intervention in an unacceptably high number of patients (5-8%). Surgical intervention for elevated IOP carries with it a continuing increased risk of serious ocular infections.

Table 42: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects (36-Month Integrated FAME Studies, Safety Population)

Category	Treatment Group		
	Sham (N = 121) n (%)	0.2 µg/day FA (N = 235) n (%)	0.5 µg/day FA (N = 265) n (%)
Any cataract-related AE	61 (50.4)	192 (81.7)	235 (88.7)
Cataract NOS	51 (42.1)	168 (71.5)	212 (80.0)
Cortical cataract	1 (0.8)	1 (0.4)	2 (0.8)
Diabetic cataract	0 (0.0)	1 (0.4)	0 (0.0)
Nuclear cataract	5 (4.1)	8 (3.4)	9 (3.4)
Subcapsular cataract	8 (6.6)	27 (11.5)	24 (9.1)
Cataract operation	33 (27.3)	188 (80.0)	231 (87.2)

Reference: Refer to [Module 5.3.5.3, ISS-36 Month Table 5.15](#)

Table 41: Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye (36-Month Integrated FAME Studies, Safety Population)

Category	Treatment Group		
	Sham (N = 185) n (%)	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)
IOP elevation considered an AE ¹	22 (11.9)	139 (37.1)	179 (45.5)
IOP elevation increase ≥12 mmHg	15 (8.1)	108 (28.8)	135 (34.4)
IOP elevation to over >25 mmHg	18 (9.7)	123 (32.8)	166 (42.2)
IOP elevation to over >30 mmHg	8 (4.3)	69 (18.4)	90 (22.9)
Trabeculoplasty surgery performed	0 (0.0)	5 (1.3)	10 (2.5)
Trabeculectomy surgery performed	0 (0.0)	10 (2.7)	22 (5.6)
Glaucoma surgery performed ²	1 (0.5)	8 (2.1)	13 (3.3)
Vitrectomy performed for elevated IOP	0 (0.0)	1 (0.3)	2 (0.5)
Any surgical intervention ³	1 (0.5)	18 (4.8)	32 (8.1)

Reference: Refer to [Module 5.3.5.3, ISS-36 Month Table 5.11](#)

¹ Includes adverse event reports of ocular hypertension and intraocular pressure increased

² Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocycloablation, and laser peripheral iridotomy.

³ Includes trabeculectomy, glaucoma surgery, and vitrectomy for elevated IOP.

The risks of cataract development and IOP elevation are significant and are not offset by the potential benefits demonstrated by Iluvien in these clinical trials.

- FDA's review of the 24-month clinical study data identified issues associated with the overall benefit/risk profile of ILUVIEN in the original patient population. FDA**

requested additional information, including 36-month data from the FAME studies, and provided guidance regarding potential subgroup analyses.

The Sponsor reviewed results from the existing and pre-planned analyses and identified a baseline patient variable (duration of DME (b) (4)) that was associated with a significantly improved ILUVIEN benefit/risk profile for patients. The Sponsor submitted analyses by duration of DME in its NDA resubmission (May 12, 2011). As described in its CRL (November 10, 2011), FDA considered these post-hoc analyses.

However, although the Sponsor did not describe its duration of DME subgroup analysis in either its protocols or the SAP (and apologizes for this oversight), this analysis was nevertheless prospectively planned. The Sponsor provides evidence to support this statement in Appendix B of this briefing package.

Does the Agency concur that the Sponsor’s analysis of the duration of DME subgroups was prospectively planned?

FDA Response: We cannot confirm that your analysis of the duration of DME subgroups was prospectively planned. The duration of DME subgroup analysis was not provided in either the protocol or in the SAP. We would normally consider this type of analysis to be a post-hoc analysis.

Regardless of the prospective or non-prospective nature of your duration of DME subgroup analysis, the risks of the cataract and IOP adverse reactions previously noted are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

- 3. When the primary efficacy analysis (Full Analysis Population, LOCF for missing data, T = 24 months) of the Duration of DME (b) (4) subgroup is adjusted for multiple comparisons, the results remain statistically significant (see Section 5.3).**

Does the Agency concur that statistical significance is maintained in the primary efficacy analyses of both phase 3 trials after adjusting for multiple comparisons?

FDA Response: No. We do not agree that there is an appropriate post-hoc multiplicity adjustment for the primary efficacy analyses on the DME subgroup.

In addition, we have questions about the clinical interpretation of “duration of DME.” DME can wax and wane over time. Did clinicians interpret duration of DME to mean the time when the first episode of DME occurred in a patient’s life, the most recent episode of DME excluding the current episode, or the current episode of DME? The clinicians do not appear to have been required to document any previous clinical findings of DME. The proposed subgroup “Duration of DME (b) (4)” is therefore not well defined or documented a priori.

It is also unclear how you determined the clinical relevance of “Duration of DME (b) (4)”

[Redacted] (b) (4)

Regardless of the clinical relevance or adjustment for multiplicity, the risks of cataract development and IOP elevation remain in this subgroup. These risks are considered significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

4. **The analysis based on duration of DME at baseline is based on a subgroup that was identified prior to administration of drug, namely duration of DME [Redacted] (b) (4). In addition, results from the individual phase 3 trials demonstrated that ILUVIEN was [Redacted] (b) (4).**

The Sponsor therefore believes that this satisfies FDA’s criteria for subgroup selection (see Section 5).

Does the Agency concur that the baseline characteristic of “duration of diabetic macular edema” satisfies the Agency’s criteria for subgroup selection?

FDA Response: No, for the reasons listed in our response to Questions 2 and 3. Regardless of the clinical relevance, prospective or non-prospective analysis or any adjustment for multiplicity, the risks of cataract development and IOP elevation remain in this subgroup. These risks are considered significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

Table 16: Number (%) of Subjects with a >15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME [Redacted] (b) (4) FAME A and FAME B, with LOCF

[Redacted Table Content] (b) (4)

Table 16: Number (%) of Subjects with a \geq 15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) (FAME A and FAME B, with LOCF (Continued)

(b) (4)

5. **The Sponsor presents the benefit/risk profile and additional analyses for ILUVIEN in the duration of DME (b) (4) subgroup in this briefing package. The Sponsor believes that the benefits outweigh the risks in this subgroup (see Section 5.7).**

Does the Agency concur that the improved benefit observed in the subgroup of subjects with duration of DME (b) (4) outweighs the risks?

FDA Response: No. The subgroup of subjects with duration of DME (b) (4) continue to demonstrate the risks associated with the drug. See tables below. These risks include an increased risk of cataract formation and an increased risk of IOP elevation. Cataract formation and elevated IOP can lead to decreased vision and a subset of these patients will require additional surgery which introduces additional risks to the patient.

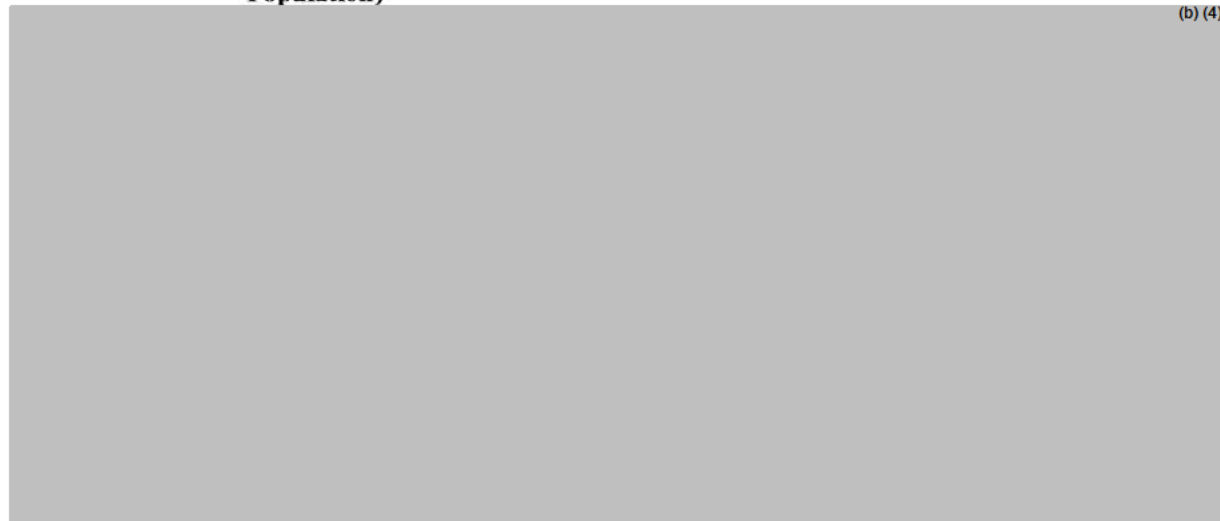
Table 46: Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye for Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)

(b) (4)



Table 47: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)

(b) (4)



The risks of these cataract and IOP adverse reactions are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

6. In the meeting minutes of February 2, 2011 and in the CRL of November 10, 2011, FDA indicated that because the injector system proposed for marketing is different from the injector system used in the clinical studies, Alimera should provide data on 100 eyes using the new injector. Alimera has initiated a physician utilization study (FAME Extension Study, Protocol C-01-11-008) [REDACTED] (b) (4)

Does the Agency agree to accept as part of the CRL response the physician utilization results from this trial based on [REDACTED] (b) (4)

?

FDA Response: No. Applications are expected to be complete at the time of submission. We continue to recommend that you submit a comparative study with at least 100 eyes enrolled into the trial using the [REDACTED] (b) (4) inserter versus at least 50 eyes enrolled using the inserter configuration utilized in the prior clinical trials. We note however, this will not address the potential safety risks identified in our responses to Questions 1-5.

6. If incorporating additional post-marketing oversight would allow the Agency to approve ILUVIEN for the proposed indication, based on the current dataset, Alimera proposes strategies to mitigate risk. The primary safety concerns associated with the use of ILUVIEN for the treatment of DME are the risks of elevated IOP and the formation or progression of cataracts. Alimera proposes to mitigate those risks [REDACTED] (b) (4)

Alimera would appreciate the opportunity to partner with the Agency to develop a plan that is practical and meets the objectives.

(b) (4)

(b) (4)

Does the Agency concur that these mitigation strategies for ILUVIEN are appropriate?

FDA Response:

*While you may voluntarily submit a proposed
the FDA must make a determination*

(b) (4)

(b) (4)

would not be accepted

Your proposal

(b) (4)

*Iluvien has demonstrated a propensity to cause cataracts and elevations in IOP. These risks are
serious, occur with significant frequency, and cannot be prevented*

(b) (4)

is not appropriate for this product at this time.

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

/s/

DIANA M WILLARD
06/14/2012



NDA 201923

MEETING REQUEST GRANTED

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert).

We also refer to your April 12, 2012, correspondence requesting a meeting to discuss what further steps need to be taken in order for NDA 201923 to be approved. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: June 19, 2012
Time: 1:00 – 2:00 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

Probable CDER participants:

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/Division of Biometrics IV (DBIV)

Rima Izem, Ph.D.	Statistical Reviewer, OB/DBIV
Lori Kotch, Ph.D.	Acting Pharmacology/Toxicology Team Leader, DTOP
Balajee Shanmugam, Ph.D.	Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)/Division of New Drug Quality Assessment II (DNDQAI)
Lin Qi, Ph.D.	Chemistry, Manufacturing and Controls Reviewer, ONDQA/DNDQAI
Diana Willard	Chief, Project Management Staff, DTOP

Please e-mail me any updates to your attendees at Diana.Willard@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Diana Willard at 301-796-0833; Ramou Mauer at 301-796-1600.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 18 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by May 22, 2012, we may cancel or reschedule the meeting.

Submit the 18 desk copies to the following address:

Ms. Diana Willard
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 6114
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

DIANA M WILLARD
05/07/2012



NDA 201923

MEETING REQUEST CANCELLATION

Alimera Sciences, Inc.
Attention: Ms. Barbara Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 250
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien[®] (fluocinolone acetonide intravitreal inserts), 0.19 mg.

We also refer to your March 8, 2012 communication requesting cancellation of the meeting we scheduled on February 3, 2012 in response to your January 23, 2012, meeting request due to a redeployment of your resources and personnel. The April 12, 2012, meeting has been cancelled.

If you have any questions, please call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DIANA M WILLARD
04/09/2012



NDA 201923

MEETING REQUEST GRANTED

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert).

We also refer to your January 23, 2012, correspondence requesting an End-of-Review meeting to discuss "... what further steps Alimera needs to take for application approval" in response to the information outlined in the November 10, 2011 Complete Response letter from the Division. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: April 12, 2012
Time: 9:00 AM to 10:00 AM
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

Probable CDER participants:

Renata Albrecht, M.D.	Director/Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, M.D.	Deputy Director/DTOP
William Boyd, M.D.	Clinical Team Leader/DTOP
Martin Nevitt, M.D.	Clinical Reviewer/DTOP
Yan Wang, Ph.D.	Statistical Team Leader/Office of Biostatistics ()B)/Division of Biometrics IV (DBIV)
Rima Izem, Ph.D.	Statistical Reviewer/OB/DBIV

Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader/Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCP IV)
Yongheng Zhang, Ph.D. Balajee Shanmugam, Ph.D.	Clinical Pharmacology Reviewer/OCP/DCP IV Chemistry, Manufacturing and Controls (CMC) Team Leader/Office of New Drug Quality Assessment (ONDQA)/Division of New Drug Quality Assessment II (DNDQA II)
Lin Qi, Ph.D. Terry Miller, Ph.D.	CMC Reviewer/ONDQA/DNDQA II Acting Pharmacology/Toxicology Team Leader/ DTOP

Please e-mail me any updates to your attendees at diana.willard@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Diana Willard at 301-796-0833; Ramou Mauer at 301-796-1600.

Submit background information for the meeting (three paper copies or one electronic copy to the application and thirteen desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by March 15, 2012, we may cancel or reschedule the meeting.

Submit the thirteen desk copies to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
Attn: Diana Willard
White Oak Building 22, Room: 6114
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology
Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
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VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
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/s/

DIANA M WILLARD
02/03/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72,056

MEETING MINUTES

Alimera Sciences, Inc.
Attn: Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway
Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to the Type B meeting between representatives of your firm and FDA on March 4, 2010. The purpose of the meeting was to discuss the NDA filing of Fluocinolone Acetonide Intravitreal Implant for treatment of diabetic macular edema.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B (Teleconference)
Meeting Category: PreNDA meeting

Meeting Date and Time: March 4, 2010, (10:00 – 11:00 EST)
Meeting Location: White Oak, BLDG #22, RM #1315

Application Number: IND 72056
Product Name: Fluocinolone Acetonide Intravitreal Implant
Indication: Treatment of diabetic macular edema.
Sponsor/Applicant Name: Alimera Sciences, Inc.

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Raphael R. Rodriguez

FDA ATTENDEES: Wiley Chambers, William Boyd, Marin Nevitt, Jennifer Harris, Kimberly Bergman, Mushfiqur Rashid, Sonal Wadhwa, Wendy Schmidt, Conrad Chen, Linda Ng, Raphael Rodriguez

SPONSOR ATTENDEES: Susan Caballa, Yvonne Johnson, Barbara Bauschka

Questions:

1. Pediatric Waiver

Alimera Sciences will be requesting a Pediatric Waiver for ages birth to 18 years, in accordance with section 505B(a)(4)(A)(i) of the Act.

Does the Agency agree that Iluvien will qualify for a Pediatric Waiver?

FDA response: If Alimera intends to make any statements implying that Iluvien is potentially effective in pediatric patients such as those above, then the Iluvien should be studied in pediatric patients. If Alimera limits all use of Iluvien to diabetic macular edema, then a study of the effects of Iluvien in pediatric patients with diabetic macular edema is impractical because the number of patients with clinically relevant diabetic macular edema is very small.

2. Carcinogenicity Test Waiver

Alimera Sciences will be requesting a Carcinogenicity Test Waiver for Iluvien.

Does the Agency agree that Iluvien is eligible for a Carcinogenicity Test Waiver?

Agency Response:

FDA response: Based on the systemic exposure of FA in the 24-month ocular toxicity study in rabbits, which is below the LOQ (100-200 pg/mL), the waiver of carcinogenicity study may be granted. However, as stated in the previous comments during the September 2, 2008 Meeting, the final decision regarding the waiver request for the carcinogenicity study will depend on the human PK data. Please submit the human PK data for evaluation.

Additional Comment:

It is not clear whether there are any differences in formulation of CTM (Clinical Trial Materials) made by two different suppliers/manufacturers. Since the previous non-clinical ocular studies were conducted with different inserts made earlier, the pivotal 24-month rabbit ocular study should be conducted with the insert targeted for development and marketing. Please document any differences in the composition of the tested vs. the proposed clinical formulations. A similar comment was made during the September 2, 2008 Meeting.

3. 120-day Safety Update

120-day Safety Update Cut-off Date

Does the Agency agree that the data cut-off date for the 120-day Safety Update can be a date in July, 2010?

FDA response: We would expect the cutoff date to be no more than 2 months prior to the 120-day update.

4. Risk Evaluation and Mitigation Strategies (REMS) Plan

Alimera Sciences is not planning to submit a Risk Evaluation and Mitigation Strategies (REMS) Plan as part of the NDA.

Does the agency agree that a Risk Evaluation and Mitigation Strategies (REMS) Plan is not required?

FDA response: We are not able to comment until the NDA has been submitted and reviewed.

5. Table of Contents

Expected Table of Contents

The NDA submission will be an eCTD submitted through the Agency's Electronic Submissions Gateway (ESG). The submission is expected to contain the items detailed in this Table of Contents.

Does the Agency have any comments, concerns, additions or subtractions to this Table of Contents?

FDA response: Please submit the Case Report Forms for all discontinued patients, regardless of the reason for their discontinuation.

Please add a folder named 'datasets' in Module 5. This folder should include the following subfolders for each study:

Raw datasets along with the defined document, blank and annotated CRFs.

Derived datasets along with the defined document

SAS programs used to produce the derived datasets

SAS programs used to produce the summary tables, figures and listings for the study report.

Furthermore, we highly recommend that the format of the dataset be complied with the CDISC SDTM requirements.

6. Inserter Documentation in the CTD submission structure

(b) (4) a one-time use inserter, which is placed inside a (b) (4) tray, sealed with a (b) (4) lid and then placed in an appropriately labeled carton. The inserter was designed and tested according to device guidances and directives.

What documentation in regards to the inserter should be included in the NDA?

FDA response: The documentation should include its specification and tolerances and a hazards analysis.

Where in the CTD should the documentation about the inserter be placed?

FDA response: Include in Module 3, Section 3.2.P.7, as requested in the next question.

Should Alimera Sciences place the inserter drawings with the rest of the packaging information in Module 3, Section 3.2.P.7?

FDA response: Acceptable.

7. Priority Review

Alimera Sciences is requesting Priority Review for this submission.

Does the Agency agree that Iluvien qualifies for Priority Review?

FDA response: At the time of the NDA submission, the agency will determine if Iluvien qualifies for Priority Review.

8. Submission of images outside the eCTD

What is the procedure to submit these images outside of the eCTD?

FDA response: The submission can contain both electronic and paper data. The film and paper components would be labeled with the appropriate Module designation as if the entire submission were paper.

The images should be ordered by trial, investigator, and patient number and in sequential order from pre-treatment, to post-treatment follow-up visits.

9. Electronic Submission

Alimera will be submitting the NDA as an electronic CTD utilizing the Agency's Electronic Submissions Gateway.

Procedural Questions:

Does the Division request notification of the submission or any other communication regarding the submission?

FDA response: It is recommended that the project manager at the FDA be called a few weeks prior to the NDA's submission.

Does the Division prefer hyperlinks and bookmarks done in any specific manner?

FDA response: Hyperlinks and bookmarks are preferred but no specific manner is recommended.

Are there requirements for the hyperlinking and bookmarking of specific documents, i.e. batch records, Case Report Forms, narratives?

FDA response: There are no specific requirements for hyperlinking and bookmarking of specific documents. Refer to the FDA website on submitting eCTD documents:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM085361>

For documents which are greater than 100 MB, does the Division want the documents to be split or submitted as a whole?

FDA response: Submit as a whole.

Are there any other comments the Agency would like to make in regards to our electronic submission?

FDA response: No additional comments.

10. Manufacturing/Quality

a. Proposal for Sub-lot manufacturing

Does the Agency agree with this proposal?

FDA response: Yes, it appears reasonable. Clarification will be needed on how release or expiry dates will be set for the batch/sublots.

b. Proposal to use [REDACTED] (b) (4)

Does the Agency agree with this proposal?

FDA response: Yes, we concur [REDACTED] (b) (4)

c. Proposal for Release Rate testing [REDACTED] (b) (4)

Does the Agency agree with this proposal?

FDA response: Yes, it appears reasonable. Justification should be provided [REDACTED] (b) (4)
[REDACTED] and a final decision will be made in the NDA. In addition, supporting data [REDACTED] (b) (4)

(b) (4) should be submitted to the NDA, The values obtained (b) (4) for release.

d. Proposal for Packaging Validation Batches

Does the Agency agree with this proposal?

FDA response: With the re-opening of the carton, it is not clear if the sterility of the drug product will be affected.

It is our understanding that at some PAIs the Investigator evaluates data from developmental batches and the protocol for validation of the commercial process. In that situation, a plan is devised for evaluating the executed protocol at a later date (e.g., post-approval but before marketing). This plan may be applicable to this intravitreal insert since the proprietary name has not yet been agreed-upon, and may need to be marked on some of the sterile parts of the product. It is recommended that the District Office be consulted for such proposal.

e. Stability Data

Does the Agency agree with this proposal?

FDA response: Yes, it is acceptable. However, please note that expiry dating period is granted based on the quality and quantity of stability data.

Additional Comment.

The inserter should be marked with the product name.

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/s/

WILEY A CHAMBERS
09/30/2011



NDA 201923

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Alimera Sciences, Inc.
Attention: Barbara Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

We acknowledge receipt on May 12, 2011, your May 12, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

We consider this a complete, class 2 response to our December 22, 2010, action letter. Therefore, the user fee goal date is November 12, 2011.

If you have any questions, call Lori Gorski, Regulatory Health Project Manager, at (301) 796-0722.

Sincerely,

{See appended electronic signature page}

Lori M. Gorski
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Drug
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LORI M GORSKI

05/26/2011

Acknowledgement of resubmission

From: Dean, Jane
Sent: Wednesday, March 16, 2011 12:02 PM
To: 'Barbara Bauschka'
Subject: RE: Statistical Plan - Follow-up

Hi, Barbara – I have responses to your questions from the review team. Please see them embedded within your email in **bold blue** below.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov



consider the environment before printing this e-mail

From: Barbara Bauschka [<mailto:barbara.bauschka@alimerasciences.com>]
Sent: Thursday, February 10, 2011 1:49 PM
To: Dean, Jane
Subject: Statistical Plan - Follow-up

Jane:

After reviewing the statistical reviewers' response to the Statistical Plan we submitted and the information contained in the Complete Response Letter (CRL) our team has these comments and questions. We can be available for further discussions via teleconference if the reviewers would like to do so. As always thanks for your help, and let me know if you have any questions.

Barbara
Follow-up:

In the complete response letter (CRL) from the FDA regarding the Iluvien submission, the agency requested several sensitivity analyses of the primary efficacy endpoint, i.e., the proportion of subjects with a ≥ 15 -letter improvement from baseline in BCVA at month 24. Two of the three sensitivity analyses require the use of multiple imputation. A telephone call with the FDA's statisticians was held on January 14, 2011 to discuss the specifics regarding the use of multiple imputation. During this discussion, the agency did not provide any specific methods, but did request that Alimera prepare a statistical analysis plan that would describe an approach for performing the sensitivity analyses

involving multiple imputation. Alimera agreed and submitted the plan to the NDA on January 21, 2011.

During the Type A meeting with the FDA on February 2, 2011, the agency provided written comments to Alimera's statistical analysis plan for these sensitivity analyses involving multiple imputation. The comments included using new software and more complex statistical methods than originally proposed. These analyses were not identified at the time the original FAME Statistical Analysis Plan was submitted and agreed to by the Agency in 2009. It is Alimera's plan to re-submit a revised statistical analysis plan for performing these sensitivity analyses after incorporating the agency's feedback.

Alimera is planning to submit a formal response to the CRL by March 31, 2011 without the results of the sensitivity analyses involving multiple imputation.

- Does the agency agree that the results of these post-hoc sensitivity analyses will have no impact on the approvability of Iluvien? **No.**
- Will the agency agree to another telephone call to discuss the revised statistical analysis plan prior to its resubmission? **Yes, however, the timing will have to be based on available schedules.**
- Will the agency agree to accepting the results of these post-hoc sensitivity analyses within 6 weeks of FDA's approval of the revised statistical analysis plan? **No. We recommend that the results be submitted at the time of any resubmission of the NDA or before.**
- Or, would the Agency consider performing the analyses themselves as the Agency has the experience in these analyses and the entire database will be included in the resubmission? **We would prefer that you do the analysis but it is not a requirement.**

Barbara Bauschka 
Director, Regulatory Affairs
Alimera Sciences, Inc.
o: 678-527-1330
f: 678-990-5743
c: (b) (6)
Skype: (b) (6)

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/s/

JANE A DEAN
03/16/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201923

MEETING MINUTES

Alimera Sciences, Inc.
Attention: Barbara Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

We also refer to the meeting between representatives of your firm and the FDA on February 2, 2011. The purpose of the meeting was to discuss the steps necessary for the application to be approved.

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 Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

Reference ID: 2906656

Reference ID: 3645984



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance

Meeting Date and Time: February 2, 2011, 3:00 pm – 4:00 pm
Meeting Location: Building 22, Conference Room 1309
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Application Number: NDA 201923
Product Name: Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Indication: Treatment of diabetic macular edema
Applicant Name: Alimera Sciences, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Jane A. Dean, RN, MSN

FDA ATTENDEES

Division of Anti-Infective and Ophthalmology Products (DAIOP):

William Boyd, MD	Clinical Team Leader
Wiley A. Chambers, MD	Acting Director
Jane A. Dean, RN, MSN	Project Manager
Steven Fong, PhD	Product Quality Microbiology Reviewer
Tapash Ghosh, PhD	Biopharmaceutics Reviewer
Jennifer Harris, MD	Clinical Reviewer
Rima Izem, PhD	Statistics Reviewer
Dorota Matecka, PhD	Product Quality Reviewer
Linda Ng, PhD	Product Quality Team Leader
Martin Nevitt, MD	Clinical Reviewer
Yan Wang, PhD	Statistics Team Leader

SPONSOR ATTENDEES

Alimera Sciences, Inc.:

Barbara Bauschka	Director, Regulatory Affairs
Kathleen Billman	Director, Scientific Affairs
Susan Caballa	Senior Vice-President, Regulatory and Medical Affairs
Ken Green, PhD	Senior Vice-President, Chief Scientific Officer
Barry Kapik	Director, Biostatistics and Data Management,
Dan Myers	Chief Executive Officer

1.0 BACKGROUND

Alimera Sciences, Inc. (hereafter referred to as Alimera) submitted a New Drug Application (NDA) June 30, 2010, which was filed August 28, 2010. Review issues were identified and were sent to Alimera in a letter dated September 10, 2010. The NDA was assigned as a Priority Review because there are no currently approved drug therapies for the treatment of diabetic macular edema (DME). DME is a serious, chronic, debilitating disease that is the primary cause of vision loss associated with diabetic retinopathy. Based on this determination, the Prescription Drug User Fee Act (PDUFA) goal date was December 30, 2010.

Alimera received a Complete Response letter from the Division of Anti-Infective and Ophthalmology Products (hereafter referred to as the Division) December 22, 2010. A Type A meeting request was received from Alimera December 23, 2010, to discuss the action and the meeting was scheduled for February 2, 2011.

2.0 MEETING OBJECTIVE

The purpose of the meeting was to discuss with the Division the steps necessary for the application to be approved.

3.0 DISCUSSION

The Division received the briefing document for the meeting on January 18, 2011. The specific questions in this document are identified in **Bold**. Division responses to each question were sent to Alimera via email on January 28, 2011. The responses are labeled **FDA Response to Question XX**. Discussion of specific questions are captured under **Discussion**. For the sake of clarity, the numbering of each question corresponds to the numbering used by Alimera in the briefing document.

4.0 QUESTIONS

4. WAIVER REQUEST FOR PEDIATRIC STUDIES

Is the Waiver Request for Pediatric Studies granted?

FDA Response to Question 4:

A waiver request would only be granted in this case after a drug has been found to be otherwise approvable.

5. EFFICACY AND SAFETY

5.1. Cataract Development and the Request for 36 Month Data

5.1.1. Impact of Cataract on Phakic Eyes

Will submission of the 36 month clinical trial data in these formats meet the Agency's needs for review?

FDA Response to Question 5.1.1:

Your Full Analysis population is the same as the FDA definition of Intent-to-Treat with Last Observation Carried Forward (ITT with LOCF).

Unless you have correlated center point thickness to visual acuity (or another acceptable endpoint) in validated clinical trials, the results for center point thickness are not necessarily clinically relevant.

Results should be provided for separate analysis by study (Fame A and Fame B) in addition to the ISE at 36 months. The efficacy results should demonstrate a "win" in each trial separately, not just in the combined ISE data set.

Discussion: The Division stated that graphs Alimera intends to do should be done on each individual study. Refer to **5.1.1. Impact of Cataract on Phakic Eyes** in the briefing document. Alimera must demonstrate a "win" where the benefits outweigh the risks of using the drug product. Carving out a subset requires that subsets be able to be identified prior to administering the drug product. The information would be considered as part of the indication for the label. Alimera must present the supporting data if there is a subpopulation where the benefits outweigh the risks.

Regarding the Division's definition of "win":

Demonstration of safety and efficacy to support approval of an NDA will require that at least two adequate and well-controlled, multi-center trials show that the benefits of the drug product outweigh its risks. Statistically significant differences in visual function (e.g., visual acuity, visual field, etc.) is recommended to be at least 36 months after the initiation of therapy.

5.1.2. Exploratory Analyses

5.1.2.1. Risk-Benefit at the Study Eye Level

Is Alimera's approach to the construction of the two-way tables consistent with your proposal?

FDA Response to Question 5.1.2.1:

Acceptable, although it may be the case that the benefit of the drug product does not outweigh the risks. Additionally, the BCVA should also be presented at the following specific time points: 6, 12, 24, 30 and 36 months, and not just at "any time through M 36.

5.1.2.2. Exploration of Association of Cataract Surgery with Decline in Vision

Are Alimera's proposed analyses adequate to explore this association for the Agency's purposes?

FDA Response to Question 5.1.2.2:

Acceptable.

5.1.2.3. Sensitivity Analysis

Does the Agency have any other suggestions for sensitivity analyses?

FDA Response to Question 5.1.2.3:

No additional suggestions at this time.

We will have additional comments regarding your Statistical Analysis Plan when we have completed our review of your most recent submission. We will arrange a teleconference to discuss our comments with you. (See **5.0 Attachments and Handouts** appended to the minutes.)

5.2. Intraocular Pressure and the Request for 36 Month Data

5.2.1. Impact of IOP Increases

5.2.1.1. IOP Increases due to Iluvien Plateau Over Time

5.2.1.2. Assessment of Ocular Safety Associated with Elevated IOP

5.2.1.3. Subjects with lower IOP at Baseline have less Risk of Safety Issues due to Elevated IOP while on Iluvien

5.2.1.4. Effect of Multiple Iluvien Inserts on IOP Safety

5.2.1.5. Effect of Elevated IOP due to Iluvien on Optic Nerve Based on Assessments by the Reading Center

5.2.1.6. Effect of IOP Elevation on Vision at Month 36

5.2.1.7. Benefit to Risk Discussion regarding IOP elevation due to Iluvien

Does the Agency have any other suggestions to aid Alimera in better fulfilling this request?

FDA Response to Question 5.2.1:

For 5.2.1.5 Effects of Elevated IOP on Optic Nerve; 36 month follow up may be too early to recognize potential optic nerve damage, especially if the IOP is elevated below 10 mm Hg.

For 5.2.1.6 Effects of IOP Elevation on Vision; it would be unlikely for BCVA to change due to elevated IOP unless the entire nerve fiber layer is extinguished.

5.0 New Inserter Use in Study C-01-08-006 and Request for Clinical Study Report

Does this Interim Safety Report satisfy the Agency's request?

FDA Response to Question 5.3:

It is expected that at least 100 eyes would have been treated with the New Inserter prior to NDA approval (assuming there are no additional safety issues with the new inserter). From Section 5.3.2.3 in this submission, it appears study C-01-08-006 has used the new inserter to treat only 8 eyes.

Discussion: The Division stated that the final configuration of the inserter should not have differed from that utilized in the clinical trials supporting safety and efficacy. When those trials utilizing the New Inserter are completed, Alimera can submit the results to the NDA.

Safety updates are required for all ongoing trials that use the drug product.

Testing of the instructions for use by physicians is expected as part of the evaluation of the New Inserter.

5.4. Safety Database Update

5.4.1. Safety Update on C-01-05-001A (FAME A) and C-01-05-001B (FAME B) Studies

5.4.2. Safety Data for Other Clinical Trials

5.4.2.1. Safety Update for C-01-06-002 (FAMOUS Study)

5.4.2.2. Safety Update for Tables for C-01-08-004 (MAP-GA Study)

5.4.2.3. Safety Update for C-01-08-006 (FAVOR Study)

5.4.2.4. Safety Update for Investigator-Sponsored MAP Study

Will this safety update fulfill this requirement?

FDA Response to Question 5.4.2: Acceptable for review.

5.5. Discussion of Efficacy Rates

5.5.1. Magnitude of Efficacy

FDA Comment for 5.5.1:

Comparing Month 24- Month 36 results may be confounded by when cataract surgery was performed; the timing of cataract surgery would need to be identified.

5.5.2. Assessment of Robustness of Efficacy Data

Will the draft statistical analysis plan provide the requested analysis information?

FDA Response to Question 5.5.2: Acceptable.

5.5.3. Duration of Efficacy

Does the Agency have any other suggestions to aid Alimera in fulfilling the Agency's request?

FDA Response to Question 5.5.3:

It is unclear how *in vivo* vitreous samples were obtained to calculate *in vivo* kinetics. Please clarify.

Unless you have correlated retinal thickness to visual acuity (or another acceptable endpoint) in validated clinical trials, the results for retinal thickness are not necessarily clinically relevant.

To use "no interruption in functional vision" would require "functional vision" to be validated to an acceptable endpoint (such as to visual acuity). The study was not designed to determine differences in the amount of laser and intravitreal injections.

5.6. Discussion of Steroid Class

Does the Agency have any other suggestions to aid Alimera in better fulfilling this request?

FDA Response to Question 5.6:

No additional suggestions.

6. MANUFACTURING AND CONTROLS

6.1. Development and Validation Reports for the *in-vitro* Release Rate Test Method

Does the Agency have any comments on the draft protocol for demonstrating the validity of the release rate test method?

In what manner should Alimera submit electronic *in-vitro* release rate datasets and profiles?

FDA Response to Question 6.1:

While the draft protocol for demonstrating the validity of the release rate test method appears acceptable, final decision on the adequacy of the protocol can not be made without official review. You may submit the full protocol to the IND for the Agency to review before embarking on the study.

Some suggestions are as follows:

- Please concentrate on a particular pH and molarity based on the in-vivo target medium (e.g., aqueous humor) instead on trying different pHs and molarities. That target condition should be in line with the IVIVC you have developed.
- Make sure that you have a way to monitor that your device remains submerged during the entire study period.
- Demonstrate accuracy and precision of your release method. This is different from accuracy and precision you need to show in your analytical (HPLC) method.
- Also include the IVIVC report in your IND submission for the Agency's comment.
- Clearly define what you want to achieve with your IVIVC.

Discussion: Alimera should submit the *in vitro* release rate datasets and profiles so that the Division can also analyze the results.

Additional information is needed on the justification for selection of dissolution method parameters as part of the dissolution method development. See ICH Q2R1. The report should be robust and discriminating justifying the selection of medium, pH, molarity, temperature and the variations in formulation and process for the finished product. Also, information on IVIVC must be submitted if not submitted previously.

6.2. Endotoxin Analytical Test Procedure and Specification

Will this analytical procedure, specific to the unit, address the Agency's comments

FDA Response to Question 6.2:

A unit specific analytic procedure is acceptable. The method should provide the specific procedures and acceptance criteria to be used for Iluvien drug product, and conform to the requirements of USP <85>.

7. SUMMARY DISCUSSION

Are there any other steps that Alimera needs to take before the application may be approved?

FDA Response to Question 7:

None currently identified.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Alimera summarized their understanding of the meeting of what steps need to be taken before their product can be approved. The steps are:

1. Separate analyses should show that the benefit outweighs the risk of using the drug product.
2. The Division wants to see the 36 month data. Statistical significance is not necessarily a requirement for the 36 month data but the benefits must outweigh the risks at a defined timepoint.
3. Once the Division has information that it believes is interpretable, it expects to proceed to an Advisory Committee.
4. The Division would like to see the results from the drug product being used in the configuration that is intended to be marketed in at least 100 eyes.
5. Physicians must be observed actually using the drug product to ensure that the instructions for use are adequate. The information must be available before marketing the drug product.
6. The release method Alimera uses needs to be tested using different technicians, different laboratories, and on different dates. A description of how the insert stays submerged during the testing is required.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Division will distribute meeting minutes within 30 days.	FDA	March 4, 2011
Alimera will consider the Division's responses and suggestions and resubmit the NDA once all issues have been resolved.	Alimera	TBD

5.0 ATTACHMENTS AND HANDOUTS

A copy of the Division's response to **5.1.2.3 Sensitivity Analysis** is appended to the minutes. The comments were distributed before the start of the meeting and subsequently sent to Alimera by email on February 3, 2011, after the meeting ended.

Statistical comments on Sensitivity Analyses

Please consider the following comments and resubmit your statistical analysis plan for review. Our comments regarding sensitivity analyses 2 and 3 are separated into three parts, corresponding to the three steps in multiple imputations:

1. Comments on proposed imputation step which generates m complete datasets
2. Comments on proposed analysis step which fits an analysis model to each of the m complete data sets
3. Comments on proposed combination step which combines the estimates from all complete data sets' fits

We also provide comments on data to submit regarding the sensitivity analyses as well as documentation to provide with the results.

Comments on proposed imputation step generating m complete datasets:

- 1 We agree with the following:
 - a Total number of complete dataset m to be 25. This is a reasonable number of complete datasets to be generated from multiple imputations method considering the amount of missing values at month 24. If the percent of missing values exceeds 30% at month 36, you should consider increasing m accordingly.
 - b Strategy of imputing the continuous BCVA first and deriving the binary primary variable from that BCVA imputations and the baseline BCVA.
- 2- We recommend that you consider the following changes to your proposal:
 - a Use a different procedure than PROC MI for the imputation step. PROC MI assumes multivariate normality of the data. Since in our next comment we propose that you consider a larger model with both continuous and categorical variables, the assumption of multivariate normality is unlikely to hold. The paper by Horton and Kleinman (2007) provides a good review of statistical methods and statistical packages handling the mix of continuous and categorical variables (for example using the chained equations method with IVEware in SAS or MICE library in R and Splus). The more recent MI library in R also handles this type of models.
 - b- Include additional variables in the imputation model. Multiple imputations methods assume that the data is missing at random (MAR), so it is important that the imputation model includes any variable which may either be associated to BCVA or to missingness. For instance, in addition to BCVA over time, the model could include all baseline characteristics and cataract timing information. Experts

in MI methods recommend that the imputation models include variables to be used in the analysis step, so including the treatment assignment in the imputation models is recommended. Interaction terms between these variables may be included if they improve the models' fit. Transformation of some variables (such as box-cox) may be necessary to insure convergence of fitting algorithms.

- c- Do not replace BCVA measurements of subjects who dropped out (resp. who died) by their baseline BCVA before the imputation step in sensitivity analysis 2 (resp. sensitivity analysis 3). Instead, impute all missing BCVA first in the imputation step. Then, derive the binary primary outcome and replace the binary outcome for all dropouts (resp. deaths) by failure before the analysis step in sensitivity analysis 2 (resp. sensitivity analysis 3).
- d- There is no need to round off the BCVA continuous measurement from the imputation step.

Comments on proposed analysis step:

In the analysis step, tests and confidence intervals are derived for the binary primary endpoint based on each complete dataset. In Subsection 7.3, you propose (b) (4)

However, in Subsection 7.4, you propose (b) (4)

Since the derived p-value in your primary analysis adjusts for stratification (CMH method), we recommend that your confidence intervals in the analysis step (for all sensitivity analyses) also correct for stratification. To correct for stratification using the same assumptions as CMH, you can use the method proposed by Mehrotra and Railkar (2000).

Comments on combination step:

Note that in your formulas in Subsection 7.4, (b) (4)

In the combined 95% confidence interval, we would prefer that you use the t statistic with degrees of freedom v (b) (4) where v is given by the formula:

(b) (4)

What to submit to FDA regarding the sensitivity analyses:

Please submit the following:

- The derived variable for sensitivity analysis 1
- All complete imputed datasets for sensitivity analysis 2 and sensitivity analysis 3
- Code performing the imputation for sensitivity analysis 2 and sensitivity analysis 3

What to describe in the results section of sensitivity analyses:

We recommend that you provide the following (see Box 3 of Sterne et al 2009):

- Report the number of missing values for each variable of interest, or the number of cases with complete data for each important component of the analysis. Give reasons for missing values if possible.
- For analyses based on multiple imputation:
 - Provide details of the imputation modeling: Report details of the software used and of key settings for the imputation modeling. Report the number of imputed datasets that were created.
 - What variables were included in the imputation procedure? How were non-normally distributed and binary/categorical variables dealt with
 - If a large fraction of the data is imputed, compare observed and imputed values. Where possible, provide results from analyses restricted to complete cases, for comparison with results based on multiple imputation. If there are important differences between the results, suggest explanations, bearing in mind that analyses of complete cases may suffer more chance variation, and that under the missing at random assumption multiple imputation should correct biases that may arise in complete cases analyses
 - Discuss whether the variables included in the imputation model make the missing at random assumption plausible
- Exploratory figures (1) checking for convergence of MCMC algorithm or Gibbs sampler (2) comparing imputed values to observed values.

References:

Horton, Nicholas J. and Ken P. Kleinman. (2007) Much Ado About Nothing: A Comparison of Missing Data Methods and Software to Fit Incomplete Data Regression Models. *The American Statistician* 61(1, February):79–90.

Mehrotra DV, Raikar R. (2000) Minimum risk weights for comparing treatments in stratified binomial trials. *Statistics in Medicine* 2000; 19:811– 825.

Sterne JA, White IR, Carlin JB, et al Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338. b2393. (doi: 10.1136/bmj.b2393).

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/s/

WILEY A CHAMBERS
02/28/2011

From: Dean, Jane
Sent: Wednesday, February 02, 2011 6:36 PM
To: 'Barbara Bauschka'
Subject: NDA 201923 (Iluvien) - statistical comments

Hi, Barbara – I'm including in this email the comments we provided at today's meeting that dealt with the sensitivity analyses. They will also be included in the official meeting minutes.

Statistical comments on Sensitivity Analyses

Please consider the following comments and resubmit your statistical analysis plan for review. Our comments regarding sensitivity analyses 2 and 3 are separated into three parts, corresponding to the three steps in multiple imputations:

- 1 Comments on proposed imputation step which generates m complete datasets
- 2 Comments on proposed analysis step which fits an analysis model to each of the m complete data sets
- 3 Comments on proposed combination step which combines the estimates from all complete data sets' fits

We also provide comments on data to submit regarding the sensitivity analyses as well as documentation to provide with the results.

Comments on proposed imputation step generating m complete datasets:

- 1 We agree with the following:
 - a Total number of complete dataset m to be 25. This is a reasonable number of complete datasets to be generated from multiple imputations method considering the amount of missing values at month 24. If the percent of missing values exceeds 30% at month 36, you should consider increasing m accordingly.
 - b Strategy of imputing the continuous BCVA first and deriving the binary primary variable from that BCVA imputations and the baseline BCVA.
- 2- We recommend that you consider the following changes to your proposal:
 - a Use a different procedure than PROC MI for the imputation step. PROC MI assumes multivariate normality of the data. Since in our next comment we propose that you consider a larger model with both continuous and categorical variables, the assumption of multivariate normality is unlikely to hold. The paper by Horton and Kleinman (2007) provides a good review of statistical methods and statistical packages handling the mix of continuous and categorical variables (for example using the chained equations method with IVEware in SAS or MICE library in R and Splus). The more recent MI library in R also handles this type of models.
 - b- Include additional variables in the imputation model. Multiple imputations methods assume that the data is missing at random (MAR), so it is important that

Reference ID: 2900147

Reference ID: 3645984

the imputation model includes any variable which may either be associated to BCVA or to missingness. For instance, in addition to BCVA over time, the model could include all baseline characteristics and cataract timing information. Experts in MI methods recommend that the imputation models include variables to be used in the analysis step, so including the treatment assignment in the imputation models is recommended. Interaction terms between these variables may be included if they improve the models' fit. Transformation of some variables (such as box-cox) may be necessary to insure convergence of fitting algorithms.

- c- Do not replace BCVA measurements of subjects who dropped out (resp. who died) by their baseline BCVA before the imputation step in sensitivity analysis 2 (resp. sensitivity analysis 3). Instead, impute all missing BCVA first in the imputation step. Then, derive the binary primary outcome and replace the binary outcome for all dropouts (resp. deaths) by failure before the analysis step in sensitivity analysis 2 (resp. sensitivity analysis 3).
- d- There is no need to round off the BCVA continuous measurement from the imputation step.

Comments on proposed analysis step:

In the analysis step, tests and confidence intervals are derived for the binary primary endpoint based on each complete dataset. In Subsection 7.3, you propose to derive confidence intervals for the difference in proportion between treatment groups adjusting for stratifying variable using logistic regression. However, in Subsection 7.4, you propose to derive confidence intervals for the difference in proportion between the two treatment groups without adjusting for stratification (i.e. using PROC FREQ).

Since the derived p-value in your primary analysis adjusts for stratification (CMH method), we recommend that your confidence intervals in the analysis step (for all sensitivity analyses) also correct for stratification. To correct for stratification using the same assumptions as CMH, you can use the method proposed by Mehrotra and Railkar (2000).

Comments on combination step:

Note that in your formulas in Subsection 7.4, (b) (4)

In the combined 95% confidence interval, we would prefer that you use the t statistic with degrees of freedom v (b) (4) where v is given by the formula:

(b) (4)

What to submit to FDA regarding the sensitivity analyses:

Please submit the following:

- The derived variable for sensitivity analysis 1

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- Code performing the imputation for sensitivity analysis 2 and sensitivity analysis 3

What to describe in the results section of sensitivity analyses:

We recommend that you provide the following (see Box 3 of Sterne et al 2009):

- Report the number of missing values for each variable of interest, or the number of cases with complete data for each important component of the analysis. Give reasons for missing values if possible.
- For analyses based on multiple imputation:
 - Provide details of the imputation modeling: Report details of the software used and of key settings for the imputation modeling. Report the number of imputed datasets that were created.
 - What variables were included in the imputation procedure? How were non-normally distributed and binary/categorical variables dealt with
 - If a large fraction of the data is imputed, compare observed and imputed values. Where possible, provide results from analyses restricted to complete cases, for comparison with results based on multiple imputation. If there are important differences between the results, suggest explanations, bearing in mind that analyses of complete cases may suffer more chance variation, and that under the missing at random assumption multiple imputation should correct biases that may arise in complete cases analyses
 - Discuss whether the variables included in the imputation model make the missing at random assumption plausible
- Exploratory figures (1) checking for convergence of MCMC algorithm or Gibbs sampler (2) comparing imputed values to observed values.

References:

Horton, Nicholas J. and Ken P. Kleinman. (2007) Much Ado About Nothing: A Comparison of Missing Data Methods and Software to Fit Incomplete Data Regression Models. *The American Statistician* 61(1, February):79–90.

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Sterne JA, White IR, Carlin JB, et al Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338. b2393. (doi: 10.1136/bmj.b2393).

Jane

 Jane A. Dean, RN, MSN
 Regulatory Health Project Manager
 Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov



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/s/

JANE A DEAN
02/02/2011



NDA 201923

MEETING REQUEST GRANTED

Alimera Sciences, Inc.
Attention: Barbara Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

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

We also refer to your December 23, 2010, correspondence requesting a meeting to discuss the steps necessary for Alimera to take for application approval. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting.

The meeting is scheduled as follows:

Date: February 2, 2011
Time: 3:00 pm – 4:00 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

CDER participants:

Division of Anti-Infective and Ophthalmology Products

Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
William Boyd, MD	Clinical Team Leader
Wiley A. Chambers, MD	Acting Director
Steven Fong, PhD	Product Quality Microbiology Reviewer
Rima Izem, PhD	Statistics Reviewer
Dorota Matecka, PhD	Product Quality Reviewer
Stephen Miller, PhD	Product Quality Team Leader
Martin Nevitt, MD	Clinical Reviewer
Yan Wang, PhD	Statistics Team Leader

Please e-mail me any updates to your attendees at jane.dean@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least three weeks prior to the meeting. A foreign visitor is defined

Reference ID: 2885072

Reference ID: 3645984

as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Jane Dean, x61202.

Submit background information for the meeting (one paper copy or one electronic copy to the application and 15 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 19, 2011, we may cancel or reschedule the meeting.

Submit the 20 desk copies to the following address:

If sending via USPS, please send to:

Jane A. Dean, RN, MSN
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6397
10903 New Hampshire Avenue
Silver Spring, Maryland **20993**

If sending via any carrier **other than** USPS
(e.g., UPS, DHL), please send to:

Jane A. Dean, RN, MSN
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6397
10903 New Hampshire Avenue
Silver Spring, Maryland **20903**

If you have any questions, call me at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Jane A. Dean, RN, MSN
Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	February 2, 2011, 3:00 pm
MEETING ENDING DATE AND TIME	February 2, 2011, 4:00 pm
PURPOSE OF MEETING	Type A Guidance
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22, Conference Room 1309 10903 New Hampshire Avenue Silver Spring, MD 20903
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Jane A. Dean, RN, MSN Project Manager Building 22, Room 6397 301-796-1202
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

JANE A DEAN
12/30/2010

Reference ID: 2885072

Reference ID: 3645984

MEMORANDUM

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

DATE: December 14, 2010
TO: NDA 201923 file
FROM: Jane A. Dean, RN, MSN, Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products (DAIOP)
SUBJECT: Telecon with Alimera Science, Inc.

APPLICATION/DRUG: NDA 201923 (Iluvien)

A telecon took place between Alimera Science, Inc., and DAIOP at their request. The Sponsor wanted to know what issues were preventing a discussion of labeling. Attendees from DAIOP were William Boyd, MD, Clinical Team Leader, Wiley Chambers, MD, Acting Director, Tapash Ghosh, PhD, Biopharmaceutics Reviewer, Rhea Lloyd, MD, Clinica Reviewer, Dorata Matecka, PhD, CMC Reviewer, Martin Nevitt, MD, Clinical Reviewer and Linda Ng, PhD, CMC Team Leader. The following issues were identified by the Division:

1. Efficacy rates are low. [REDACTED] (b)(4) Results are not robust. For example, the per protocol analysis does not demonstrate a statistically significant difference in one study. To the extent that this is due to the visual acuity results being carried forward in the ITT analysis, it raises questions about the need for extended treatment.
2. Product has safety problems.
 - a. The product causes cataracts.
 - b. The product causes elevations in IOP.
 - c. If the product causes these class events, it is also likely to impair healing and reduce the eyes ability to recover from infections. This is potentially problematic for a diabetic population.
 - d. The product causes clinically significant decreases in visual acuity, which may or may not be related to the development of cataracts.
3. Primary effect is in the first 6 months. It is not clear that there is any additional benefit beyond the first six months.

Reference ID: 2879097

Reference ID: 3645984

NDA 201923 (Iluvien)
Memorandum of Telecon
December 14, 2010

4. Measurement of visual acuity from months 12 to 24 is confounded by the development of cataracts.
5. Difference between groups with respect to mean visual acuity is minimal.
6. Number of patients “withdrawing consent” is relatively high.

The Sponsor understood the review of the NDA was still pending and that more information would be available once an action has been taken.

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/s/

JANE A DEAN
12/16/2010

From: Dean, Jane
Sent: Friday, January 28, 2011 2:17 PM
To: 'Barbara Bauschka'
Subject: NDA 201923 (Iluvien) - preliminary responses to meeting questions

Barbara, below are the preliminary responses to the meeting questions. Please be advised that any new information or data not contained in your meeting package and presented in response to these comments will not be considered for official comment at the scheduled meeting. The information may be very briefly presented, but must be provided as a submission to the application subsequent to this meeting to allow an opportunity for appropriate review and comment.

In preparation for our upcoming meeting, please be advised that the official advice and recommendations of this division will be communicated during the formal dialogue of our upcoming meeting. Any conversations before or after the official meeting will not reflect the decisions or agreements of the division and thus will not be reflected in the official meeting minutes. If follow-up or clarification on a particular issue is required, those issues should be discussed during the meeting or can be pursued through the formal meetings process in a subsequent meeting or teleconference.

If you wish to change this meeting to a telecon, please contact your Project Manager. If you wish to cancel this meeting, the following responses will become part of the administrative record. Submit your cancellation by letter to your application and contact your Project Manager.

If you wish to discuss another application, the official meeting process should be followed as outlined in the May 2009 "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants".

4. WAIVER REQUEST FOR PEDIATRIC STUDIES

Is the Waiver Request for Pediatric Studies granted?

FDA Response to Question 4:

A waiver request can only be granted after a drug has been approved.

5. EFFICACY AND SAFETY

5.1. Cataract Development and the Request for 36 Month Data

5.1.1. Impact of Cataract on Phakic Eyes

Complete Response Letter:

- a. The development of cataracts in eyes which were phakic at baseline creates difficulty in interpreting visual acuity during months 12 to 24. Due to the timing of the development of the cataracts and the time needed for postoperative recovery, 36-month clinical trial data will need to be evaluated to assess the potential benefits and risks associated with this drug product. Thirty-six month clinical trial data should be submitted to the application*

To address this comment, Alimera plans to submit the following and discuss the impact of cataract on efficacy in phakic eyes:

1. Clinical Study Report synopses for each phase III study (Study C-01-005-01A and C-01-005-01B), based on the 36 month clinical trial data. These synopses

will include tables for all of the planned analyses in the SAP for each study and all datasets for the template of the planned synopses.

2. Updated ISE tables and datasets based on the 36 month clinical trial data
3. Updated ISS tables and datasets based on the 36 month clinical trial data
4. The following to address the temporal profile of cataract formation and correction in the clinical study population:
 - a. Kaplan Meir graphs of time to cataract AE, and time to cataract surgery
 - b. Graphs of ≥ 15 letter increase, ≥ 15 letter decrease, center point thickness for the following populations (based on the ISE full analyses dataset):
 - Total population
 - Pseudophakic at baseline
 - Phakic at baseline, but pseudophakic at month 36
 - Phakic at baseline and phakic at month 36
 - c. 2 – way table, by visit of 15 letter or greater loss and cataract surgery (at anytime), for each treatment group (all randomized, observed cases, ISE).
5. Safety impact of cataract surgery to be addressed:
 - a. Tabulate ocular AE's for each study arm in the 36 month ISS dataset, separating subjects undergoing cataract surgery (post surgery) versus no cataract surgery.
 - b. Graphically present post-cataract surgery BCVA score for insert treated patients versus control patients to assess and compare functional outcome after cataract surgery.
6. Benefit to Risk assessment regarding cataract formation due to Iluvien
Note of clarification: full analysis dataset = classically defined ITT populations

Will submission of the 36 month clinical trial data in these formats meet the Agency's needs for review?

FDA Response to Question 5.1.1:

Your Full Analysis population is the same as the FDA definition of Intent-to-Treat with Last Observation Carried Forward (ITT with LOCF).

Unless you have correlated center point thickness to visual acuity (or another acceptable endpoint) in validated clinical trials, the results for centerpoint thickness are not necessarily clinically relevant.

Results should be provided for separate analysis by study (Fame A and Fame B) in addition to the ISE at 36 months. The efficacy results should demonstrate a "win" in each trial separately, not just in the combined ISE data set.

5.1.2. Exploratory Analyses

5.1.2.1. Risk-Benefit at the Study Eye Level

Complete Response Letter:

In addition to the predetermined analyses in the protocol for the three year data we recommend that you include the following exploratory analyses:

- i. Risk-benefit analyses at the study eye level. This could be explored using two way tables of major adverse event (such as cataract surgery) versus improvement of BCVA by 15 letters or more.*

To address this comment, Alimera plans to submit and discuss the following:

7. Two Way Tables by Treatment Group for AEs for Integrated FAME A and B Studies in Subjects with and without each AE [REDACTED] (b) (4) and with and without 15 letter Improvement [REDACTED] (b) (4) for:
 - c. Cataract Surgery
 - d. IOP Increased + Ocular Hypertension
 - e. Glaucoma + Open Angle Glaucoma
 - f. Any Glaucoma Surgery
 - g. Any use of IOP lowering meds
 - h. Vitrectomy

Is Alimera's approach to the construction of the two-way tables consistent with your proposal?

FDA Response to Question 5.1.2.1:

Acceptable, although it may be the case that the benefit does not outweigh the risk. Additionally, the BCVA should also be presented at the following specific time points: 6, 12, 24, 30 and 36 months [REDACTED] (b) (4)

5.1.2.2. Exploration of Association of Cataract Surgery with Decline in Vision

Complete Response Letter:

ii. Association of decline of BCVA by 15 letters or more to cataract at the study eye level. This could be explored by checking association of cataract surgery to decline in BCVA by 15 letters or more by visit.

To address this comment, Alimera plans to submit and discuss the following:

8. Two way table by treatment group of cataract surgery versus loss of 15 letters at each visit and statistical testing at each visit to show significance of association, and when the association decouples
9. VA outcome in pseudophakes over 36 months, to demonstrate improved vision early, and no lowering in vision between M9-M24
10. Post – cataract surgery vision outcome between treated and control groups.
11. Relevant AE's in the control versus treated groups to show that having cataract surgery with Iluvien is associated with relatively few complications.
12. Compare percent returning to best BCVA score prior to surgery using a frequency distribution.

Are Alimera's proposed analyses adequate to explore this association for the Agency's purposes?

FDA Response to Question 5.1.2.2: *Acceptable.*

5.1.2.3. Sensitivity Analysis

Complete Response Letter:

iii. Sensitivity analyses to address missing values:

5.1.2.3.1. All Missing Observations as Failures

Complete Response Letter:

1. Treating all missing observations as failures in primary endpoint.

To address this comment Alimera plans to submit the following:

13. Summarized results of this analysis using month 36 clinical trial data

5.1.2.3.2. All Dropouts as Failures

Complete Response Letter:

2. Treating all dropouts as failures in primary endpoint, and imputing the other missing values using multiple imputation methods.

To address this comment Alimera plans to submit the following:

14. Summarized results of this analysis using month 36 clinical trial data

5.1.2.3.3. All Deaths as Failures

Complete Response Letter:

3. Treating all deaths as failures in primary endpoint, imputing other missing values using multiple imputation methods, and imputing observed values for subjects with disallowed medication using multiple imputation methods.

To address this comment Alimera plans to submit the following:

15. Summarized results of this analysis using month 36 clinical trial data

Does the Agency have any other suggestions for sensitivity analyses?

FDA Response to Question 5.1.2.3: *No additional suggestions at this time.*

We will have additional comments regarding your Statistical Analysis Plan when we have completed our review of your most recent submission. We will arrange a teleconference to discuss our comments with you.

5.2. Intraocular Pressure and the Request for 36 Month Data

5.2.1. Impact of IOP Increases

Complete Response Letter:

b. The risk of increased intraocular pressure (IOP) is nearly three times higher in the drug treatment groups compared to the Sham (control) group. The 36-month data will need to demonstrate that the drug's benefits will be able to overcome this significant risk identified during the first 24 months of the clinical trials. Thirty-six month clinical trial data should be submitted to the application.

To address this comment, Alimera plans to submit and discuss the following:

5.2.1.1. IOP Increases due to Iluvien Plateau Over Time

16. Using ISS Tables based on month 36 clinical trial data, we will provide cumulative graphs, of the variables below, over time, to demonstrate that IOP changes plateau:

- i. Mean change from baseline IOP
- j. IOP increased AE
- k. IOP medications
- l. IOP >25 mmHg
- m. IOP surgery

5.2.1.2. Assessment of Ocular Safety Associated with Elevated IOP

17. Compare IOP-related AEs for population with IOP lowering meds vs no IOP lowering meds by treatment group

18. Compare all IOP related ocular AE's in the population undergoing IOP lowering surgery versus no IOP lowering surgery, by treatment group

5.2.1.3. Subjects with lower IOP at Baseline have less Risk of Safety Issues due to Elevated IOP while on Iluvien

19. Graph of mean IOP over time as a function of BL IOP (above or below the median).
20. Tabulate ocular AE's, including use of IOP lowering meds, surgery and IOP related events, by BL IOP (above and below the median)
- 5.2.1.4. Effect of Multiple Iluvien Inserts on IOP Safety**
 21. Tabulation of IOP related events by number of inserts
- 5.2.1.5. Effect of Elevated IOP due to Iluvien on Optic Nerve Based on Assessments by the Reading Center**
 22. Present Reading Center assessment based on month 36 clinical trial data
- 5.2.1.6. Effect of IOP Elevation on Vision at Month 36**
 23. Present percent (%) of patients with VA improving by ≥ 15 letters vs Baseline and Mean Change in BCVA in subjects with and without IOP surgery, IOP meds, or IOP increase to >25 mmHg
 24. Two – way tables assessing the association between ≥ 15 letter VA improvement and adverse event of IOP elevation/ocular hypertension or use of IOP lowering medications
- 5.2.1.7. Benefit to Risk Discussion regarding IOP elevation due to Iluvien**

Does the Agency have any other suggestions to aid Alimera in better fulfilling this request?

FDA Response to Question 5.2.1:

For 5.2.1.5 Effects of Elevated IOP on Optic Nerve; 36 month follow up may be too early to demonstrate optic nerve damage, especially if the IOP is only slightly elevated (< 10 mm Hg).

For 5.2.1.6 Effects of IOP Elevation on Vision; it would be unlikely for BCVA to change due to elevated IOP unless the entire nerve fiber layer is extinguished.

New Inserter Use in Study C-01-08-006 and Request for Clinical Study Report

Complete Response Letter:

c. The inserter used in the preclinical and clinical trials was modified; use of the proposed (b) (4) inserter is not supported by clinical data in the application. Clinical data supporting the use of the (b) (4) inserter, including the clinical study report for Study C-01-08-006, should be submitted to the application.

To address this comment, Alimera plans to submit the following:

25. Interim Safety Report for Study C-01-08-006, which will present non – efficacy tables and data listings; including AEs, SAEs, Deaths, IOP and cataract-related events and will include a summary of the questionnaire on use of the inserter .
26. No efficacy analysis will be included due to this being an interim report with few subjects; as well as this being a different indication, namely retinal vein occlusion.

Does this Interim Safety Report satisfy the Agency's request?

FDA Response to Question :

It is expected that at least 100 eyes would have been treated with the New Inserter prior to NDA approval (assuming there are no additional safety issues with the new inserter). From Section 5.3.2.3 in this submission, it appears study C-01-08-006 has used the new inserter to treat only 8 eyes. (MN)

5.3. Safety Database Update

Complete Response Letter:

d. The safety database for the drug product is incomplete. The 120-day Safety Update and Module 5, Section 5.2, do not include data for all clinical trials utilizing the drug product. This information should be submitted to the application.

To address this comment, Alimera plans to submit the following:

5.3.1. Safety Update on C-01-05-001A (FAME A) and C-01-05-001B (FAME B) Studies

Present month 36 findings for Integrated FAME studies summarizing AEs, SAEs, Deaths, IOP and cataract-related events.

5.3.2. Safety Data for Other Clinical Trials

Aside from C-01-05-001A and C-01-05-001B and C-01-06-002, no other clinical studies have been reported at the time of the 120 day safety update. Interim data was provided for these three studies in the 120 day safety update. For this response, final data for C-01-05-001A and C-01-05-001B and updated interim data from C-01-06-002 will be provided. New interim data for other small studies listed below will be provided as part of this response. Data from smaller studies has not been integrated with FAME studies because the larger, longer term FAME data would overwhelm new results.

5.3.2.1. Safety Update for C-01-06-002 (FAMOUS Study)

Alimera will discuss and present AE's, SAE, Deaths including all data in the database through 2010.

5.3.2.2. Safety Update for Tables for C-01-08-004 (MAP-GA Study)

Alimera will discuss and present AE's, SAE, Deaths including all data through 2010 (n=15).

5.3.2.3. Safety Update for C-01-08-006 (FAVOR Study)

Alimera will discuss and present AE's, SAE, Deaths including all data through 2010, (n=8)

5.3.2.4. Safety Update for Investigator-Sponsored MAP Study

Alimera will discuss and present SAE's including all data through, current enrollment (n=6).

Will this safety update fulfill this requirement?

FDA Response to Question 5.3.: *Acceptable.*

5.4. Discussion of Efficacy Rates

Complete Response Letter:

e. Efficacy rates are low. (26-^(b)₍₄₎% vs 14-18%). Results are not robust. Difference between groups with respect to mean visual acuity is minimal. The majority of the beneficial effect appears to occur during first 6 months and the product appears to cause clinically significant decreases in visual acuity at month 24. The need for extended treatment should to be justified in the application.

To address this comment, Alimera plans to submit the following response:

5.4.1. Magnitude of Efficacy

Demonstrate that the magnitude of efficacy is clinically relevant by:

27. Describe sham group to show that this represents the current standard of care

28. Assess treatment effect in year 3 versus control

n. Establish that year 3 is not confounded by cataract using a 2 – way table, by visit, looking at 15 letter or greater loss and cataract surgery (at anytime), for

- o. Compare significant vision loss between treated and controls in year 3
 - p. Present observed cases response
 - q. Compare efficacy for subgroups
 - r. 1 treatment only, with no laser, with no unapproved treatments
 - s. Compare efficacy rates of Iluvien versus anti-VEGF pulse therapy in published studies.
29. Based on those subjects with month 24-Month 36 data, look at magnitude of VA response over the third year of the study.

FDA Response to Question 5.4:

Comparing Month 24- Month 36 results may be confounded by when cataract surgery was performed; the timing of cataract surgery would need to be identified.

5.4.2. Assessment of Robustness of Efficacy Data

5.4.2.1. To demonstrate that the results of the FAME studies are robust based on sensitivity analyses, Alimera will present and summarize the following sensitivity analyses:

30. The following exploratory analyses requested by the Agency:
- t. Sensitivity analyses to missing values:
 - o. Treating all missing observations as failures in primary endpoint.
 - o. Treating all dropouts as failures in primary endpoint, and imputing the other missing values using multiple imputation methods.
 - o. Treating all deaths as failures in primary analysis, imputing other missing values using multiple imputation methods, and imputing observed values for subjects with disallowed medication using multiple imputation methods.
 - u. An analysis plan for implementing the multiple imputation methods is being submitted to the NDA as a separate document for review by the agency.
 - v. Multiple imputation inference involves three separate steps:
 - o. The missing data are filled in m times to generate m complete datasets.
 - o. The m complete datasets are analyzed using standard statistical analyses.
 - o. The results from the m complete datasets are combined to produce inferential results.

The analysis plan provides details regarding the method for creating the multiply imputed datasets (step 1), the standard statistical analyses methods (step 2), and the techniques for generating the valid statistical inferences (step 3).

Will the draft statistical analysis plan provide the requested analysis information?

FDA Response to Question 5.4.2.: *Acceptable.*

5.4.3. Duration of Efficacy

For sham, low dose and high dose patients – Alimera will present and compare change in BCVA over 36 months, % improving by ≥ 15 letters over 36 months and change in retinal thickness over 36 months

- 1. Present and discuss treatment effect in year 3

2. Present and discuss continuous improvement from month 6 forward
 - a. Present efficacy data for month 24 completers over the month 24 – month 36 period
 - b. Present efficacy data for subjects receiving only 1 treatment
3. Present and discuss predicted duration of release of drug from in vitro and in vivo kinetics
4. Present and discuss data for pseudophakes, showing no interruption in functional benefit
5. Present and discuss differences in amount of laser and intravitreal injections administered between the treated and control groups

Does the Agency have any other suggestions to aid Alimera in fulfilling the Agency's request?

FDA Response to Question 5.5.3:

It is unclear how in vivo vitreous samples were obtained to calculate in vivo kinetics. Please clarify.

Unless you have correlated retinal thickness to visual acuity (or another acceptable endpoint) in validated clinical trials, the results for retinal thickness are not necessarily clinically relevant.

To use "no interruption in functional vision" would require "functional vision" to be validated to an acceptable endpoint (such as to visual acuity). The study was not designed to determine differences in the amount of laser and intravitreal injections.

5.5. Discussion of Steroid Class

Complete Response Letter:

f. The product causes steroid class events, it is also likely to impair healing and reduce the eyes ability to recover from infections. This is potentially problematic for a diabetic population. The benefit over these risks needs to be demonstrated.

To address this comment, Alimera plans to submit the following response:

1. Iluvien causes cataract and IOP-related events, but significant differences in impaired healing or impact on recovery from infections *were not observed* in the FAME studies. (AE tables)
 - w. Compare common ocular AE's for control population subjects NOT receiving IVTA to insert subjects
 - Review specific steroid class AEs by treatment group
 - Discuss ocular infections

Does the Agency have any other suggestions to aid Alimera in better fulfilling this request?

FDA Response to Question 5.6: *No additional suggestions.*

6. MANUFACTURING AND CONTROLS

6.1. Development and Validation Reports for the *in-vitro* Release Rate Test Method

Complete Response Letter:

f. Report 10066 is incomplete because the full development and validation reports for the in-vitro release methodology were not provided. Provide the following information:

- i. *Detailed method development and validation report for the in-vitro release method (justifying optimization of method parameters, e.g., choice of release medium, medium volume, temperature,*

agitation speed, maintenance of sink condition etc.) is required in the NDA submission.

ii. *In-vitro* release profiles generated for different batches and associated data set (preferably in electronic format) used to generate the *in-vitro* release profiles.

iii. Full report of the calculations involved to qualify different formulations, manufacturing sites etc.

iv. Time points in generating release profiles should continue [REDACTED] (b) (4)

v. In the formula used to calculate the amount of FA released during a 24-hour period, the injection volume as well as the volume of the medium should be considered unless justified otherwise.

Alimera Sciences, Inc. licensed the technology for Iluvien® from pSivida, Inc. (formerly Control Delivery Systems). pSivida developed the first two ophthalmic sustained drug delivery systems approved by the Food and Drug Administration (Vitraser®[®], NDA 020569 approved March 14, 1996 and Retiser®[®], NDA 021737 approved April 4, 2005). The method for determining the release rate of fluocinolone acetonide (FA) from the Iluvien inserts was adapted by pSivida from the methods they developed for Retiser and Vitraser. pSivida did not conduct a separate method development study for Iluvien but simply modified the method used for Retiser which contains the same active ingredient, fluocinolone acetonide, as Iluvien. Alimera has no right to reference the Retiser method development, although the method was validated and Validation Report DP 2006-157 070626 was included in the NDA submission (Refer to Module 3, Section 3.2.P.5.3).

The basic principle of the method is to determine the amount of drug released (b) (4)

[REDACTED]

Fluocinolone acetonide (FA) is practically insoluble in water. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Alimera is proposing to conduct a method development study as outlined in the draft protocol, [REDACTED] (b) (4)

[REDACTED]

In addition, Alimera has demonstrated an *in-vitro/in-vivo* correlation using the *in-vitro* release rate data generated using the current analytical method. The study report for Study 480271 was included in the NDA submission. A draft journal article summarizing

the *in-vitro/in-vivo* results has been included in this submission.

Does the Agency have any comments on the draft protocol for demonstrating the validity of the release rate test method?

In what manner should Alimera submit electronic *in-vitro* release rate datasets and profiles?

FDA DRAFT Response to Question 6.1:

While the draft protocol for demonstrating the validity of the release rate test method appears acceptable, final decision on the adequacy of the protocol can not be made without official review. You may submit the full protocol to the IND for the Agency to review before embarking on the study.

Some suggestions are as follows:

- *Please concentrate on a particular pH and molarity based on the in-vivo target medium (e.g., aqueous humor) instead on trying different pHs and molarities. That target condition should be in line with the IVIVC you have developed.*
- *Make sure that you have a way to monitor that your device remains submerged during the entire study period.*
- *Demonstrate accuracy and precision of your release method. This is different from accuracy and precision you need to show in your analytical (HPLC) method.*
- *Also include the IVIVC report in your IND submission for the Agency's comment.*
- *Clearly define what you want to achieve with your IVIVC.*

Endotoxin Analytical Test Procedure and Specification

Complete Response Letter:

a. The currently proposed limit (b) (4) is not applicable to the solid dose FA drug product. Without an appropriate descriptor for expressing product endotoxin limit, the acceptability of the proposed limit cannot be evaluated. Please modify the endotoxin limit value so that it is based on a per drug rod or per mg (b) (4)

b. The testing method presented in attachment MTM-200033 represented only a general SOP for LAL gel clot testing, and did not include procedures and data sets relevant to FA drug product. The stability test results (b) (4) are not acceptable without an adequate description of the endotoxin testing procedure and appropriate acceptance criteria. Please provide a description of the endotoxin testing procedure as it applies to FA drug product. The description should include the method by which the drug product rods are prepared for sampling, and the procedures and data sets for interference/enhancement testing.

Alimera is preparing an analytical procedure, which will also be validated, for endotoxin testing specific to Iluvien. This method will be based on the unit, rather than by volume. The appropriate specification revision will also be made.

Will this analytical procedure, specific to the unit, address the Agency's comments?

FDA Response to Question 6.2: *A unit specific analytic procedure is acceptable. The method should provide the specific procedures and acceptance criteria to be used for Iluvien drug product, and conform to the requirements of USP <85>.*

7. SUMMARY DISCUSSION

Are there any other steps that Alimera needs to take before the application may be approved?

FDA Response to Question 7: *None currently identified.*

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
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Email address: jane.dean@fda.hhs.gov



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/s/

JANE A DEAN
01/28/2011

Reference ID: 2897903

Reference ID: 3645984

From: Cuff, Althea
Sent: Wednesday, November 03, 2010 7:31 PM
To: 'Barbara Bauschka'
Subject: 201,923 - information request

Dear Barbara,

We have the following information request from the CMC reviewer. Please respond by November 13th.

Comments for NDA 201-923:

1. Please provide information on the polymorph content in the second batch of fluocinolone acetonide drug substance (b) (4) used in clinical batches of the drug product. Please propose a limit for the polymorph content in the fluocinolone acetonide drug substance specification (e.g., NLT (b) (4)).
2. Please tighten acceptance criteria for residual solvents in the drug substance specification.
3. Please tighten the limit for total impurities to NMT (b) (4)% in drug substance specification.
4. Please clarify what is the size of the proposed commercial batch for the drug product.
5. Provide the quantitative composition of the mobile phase in the drug product HPLC procedure for related substances and assay.
6. Please include an acceptance criterion for any unspecified degradant in the drug product specification (NMT (b) (4)%).
7. Please reconcile the preclinical lots numbers (specifically lot number 311-6) with their study use (reference to toxicology studies) in Table 6 provided in section 3.2.P.5.4.

Althea M. Cuff
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of Post-Marketing Evaluation
Phone (301) 796-4061

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/s/

ALTHEA CUFF
11/03/2010

From: [Dean, Jane](#)
To: ["Barbara Bauschka";](#)
Subject: RE: NDA 201923
Date: Monday, October 25, 2010 5:39:10 PM

Thanks for the heads up, Barbara. I forwarded your email to the CMC review team so they can provide a response, especially about the issue of possible additional information requests from their discipline. At our last team meeting, there was no indication from other disciplines that more information requests would be coming.

Jane

From: Barbara Bauschka [mailto:barbara.bauschka@alimerasciences.com]
Sent: Monday, October 25, 2010 5:26 PM
To: Dean, Jane
Subject: NDA 201923

Jane:

I submitted the Stability Update through the portal this evening. This update was agreed upon during the pre-NDA meeting and contains the 12 month data for one lot, W00005152. Dr. Linda Ng confirmed to Susan Caballa last Monday, 18 Oct 2010, that Alimera should submit this information at this time.

During the same telephone conversation Dr. Ng indicated to Susan that there were comments from the Chemistry Reviewer although we have not received any. With the PDUFA data in about 2 months, receiving these comments is extremely important to allow us enough time to response to these comments. Do you have any idea when we may receive these Chemistry comments? Are there any comments expected from the other disciplines, especially Clinical and the Pre-Clinical reviewers?

Thanks for your help.

Barbara Bauschka 
Director, Regulatory Affairs
Alimera Sciences, Inc.
o: 678-527-1330
f: 678-990-5743

C: [REDACTED] (b) (6)
Skype: [REDACTED] (b) (6)

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/s/

JANE A DEAN
11/03/2010



NDA 201923

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Alimera Sciences, Inc.
6120 Windward Parkway, Suite 290
Alpharetta, Georgia 30005

ATTENTION: Barbara H. Bauschka
Director, Regulatory Affairs

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) dated June 28, 2010, received June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluocinolone Acetonide Intravitreal Insert, 0.19 mg.

We also refer to your July 15, 2010, correspondence, received July 15, 2010, requesting review of your proposed proprietary name, Iluvien. We have completed our review of the proposed proprietary name, Iluvien, and have concluded that it is acceptable.

The proposed proprietary name, Iluvien, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 15, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Raphael Rodriguez, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Denise Toyer, Pharm D
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
10/13/2010

From: Dean, Jane
Sent: Thursday, October 07, 2010 3:13 PM
To: 'Barbara Bauschka'
Subject: NDA 201923 (Iluvien) - additional information request re stats

Importance: High

Barbara, below is an additional information request from the statistics reviewer. Since we are well into the review cycle, we need a fairly rapid turn around time on this and appreciate expediting our request. Thanks!!

Jane

Request for additional exploratory analyses:

We identified four goals for which we need additional exploratory analyses. Please conduct the additional analyses and submit the results as soon as possible:

Goal 1: Assessing characteristics of subjects with missing values at visits at month 18 and visits at month 24.

For subjects with missing values on month 18 or on month 24, summarize

- 1 Baseline characteristics
- 2 Previously available BCVA measurement (mean, sd, confidence interval)

Compare these measurements to those of subjects with available data on each of these two visits.

For all subjects with at least one missing visit, assess the number of missed visits.

Goal 2: Assessing the gain in BCVA in subjects who are pseudophakic at baseline. You have characterized this gain in a pooled analysis of the data from both studies. Please analyze the gain for each study separately.

Goal 3: Assessing the risk-benefit on an individual basis at month 18 and month 24 visits in subjects who are phakic at baseline.

Provide the following:

- 1 A two-way table for improvement of BCVA from baseline to month 18 visit above or equal to 15 letters, and cataract surgery prior to visit at month 18.
- 2 A two-way table for improvement of BCVA from baseline to month 24 visit above or equal to 15 letters, and cataract surgery prior to visit at month 24.
- 3 Summary of BCVA at month 18 for those who received cataract surgery prior to visit at month 18, those who received cataract surgery after month 18, and those who did not receive cataract surgery during the study.
- 4 Summary of BCVA at month 24 for those who received cataract surgery prior to visit at month 24, those who received cataract surgery after month 24, and those who did not receive cataract surgery during the study.

Goal 4: association between cataract surgery and decline in vision in subjects who are phakic at baseline

Provide the following:

- 1 A two-way table for decline of BCVA from baseline to month 18 below 15 letters, and cataract surgery after month 18 visit.

A two way table for decline of BCVA from baseline to month 24 below 15 letters, and cataract surgery after month 24 visit.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
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Office: 301-796-1202
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/s/

JANE A DEAN
10/07/2010



NDA 201923

FILING COMMUNICATION

Alimera Sciences, Inc.
Attention: Barbara Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your new drug application (NDA) dated June 30, 2010, received June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Iluvien (flucinolone acetonide intravitreal insert) 0.19 mg.

We also refer to your submissions dated July 8, 9, 13, 15, 21, 23 and 29, and August 3, 5, 11, 13 and 31, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 4, 2010.

During our filing review of your application we identified the following potential review issue:

The development of cataracts in eyes which were phakic at baseline creates difficulty in interpreting visual acuity during months 12 to 24. It is likely that visual acuity data from the post-operative period of these patients will be needed to assess the potential benefits and risks associated with this drug product. Due to the timing of the development of the cataracts and the time needed for postoperative recovery, these visual acuity assessments may not be available in the currently submitted dataset.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision.

If you have any questions, call Raphael Rodriquez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201923	ORIG-1	ALIMERA SCIENCES INC	FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT 0.19 mg

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/s/

WILEY A CHAMBERS
09/10/2010



NDA 201923

PRIORITY REVIEW DESIGNATION

Alimera Sciences, Inc.
Attention: Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your new drug application (NDA) dated June 28, 2010, received June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Iluvien (fluocinolone acetonide intravitreal insert) 0.19mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 9, 2010.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 12, 2010.

If you have any questions, call Raphael Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and
Ophthalmology Product
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
08/30/2010

From: [Dean, Jane](#)
To: ["Barbara Bauschka";](#)
cc: [Rodriguez, Raphael R;](#)
Subject: NDA 201923 (Iluvien) - information request
Date: Tuesday, August 24, 2010 3:56:28 PM

Hello, Barbara, we have the following information request:

Regarding "0" values for BCVA in the analysis data sets:

In the datasets analva (for study A and study B), a few subjects (about 43 across all treatments and all visits) have a study eye BCVA recorded as 0 at some visits. The define.pdf file of the original tabulation data or the analysis data set does not mention anything about 0 values. Could you please clarify what these 0 values mean?

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products

FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881

Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201923	ORIG-1	ALIMERA SCIENCES INC	FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT 0.19 mg

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/s/

JANE A DEAN
08/24/2010

From: [Dean, Jane](#)
To: ["Barbara Bauschka";](#)
cc: [Rodriguez, Raphael R;](#)
Subject: NDA 201923 (Iluvien) - information request
Date: Tuesday, August 03, 2010 3:06:19 PM

Hi, Barbara! We have the following information request. Can you please let us know what your turn around time will be to provide a response? Thanks!

From the meeting minutes in Reviewer's Guide 1.2 Section 10 Table 3:

"For each dose that is clinically and statistically superior to sham, a numerical comparison will be made to its corresponding 18 month visit. If the proportion of subjects with a ≥ 15 letter improvement from baseline in BCVA at 24 months is equal to or greater than that at 18 months, then clinical efficacy will have been demonstrated for that dose."

Please provide the above analysis for each trial for the Full Analysis, ITT and PP populations. (If already provided in the submission please designate where.) The results may be provided similar to the table provided in Section 2.5 of the Clinical Summary Section 4.3 page 16.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
08/03/2010

Cuff, Althea

From: Cuff, Althea
Sent: Tuesday, July 27, 2010 5:03 PM
To: 'Barbara Bauschka'
Subject: NDA 201,923 (Fluocinolone) - Information Request

Hi Ms. Bauschka,

Our Biopharm Reviewer has the request below. Please provide your response at your earliest convenience:

Biopharmaceutics Information Requests for Iluvien 0.19 mg (NDA201923)

1. Provide full method development and validation report for *in-vitro* release method (CTM-200502). Include the full reports of the following references as mentioned in Doc# 10-077 - CTM-200502:
 - SP-023-060 Rev. 00 - Release Rate Testing Procedures for FA in (b) (4) Inserts.
 - Protocol/Report 08224 - Method Transfer: Determination of Release Rate of Fluocinolone Acetonide from Iluvien Inserts by HPLC.
1. Include statistical analysis report with p-value associated with final report for protocol 10066. Clarify whether products for both "Control Group" and "Test Group" for protocol 10066 came from the same batch. If not, please provide batch/lot #s associated with each sample of each group.
2. Provide raw *in-vitro* release data associated with Primary Stability Batches, and batches used in clinical and pre-clinical studies of Iluvien.

Thanks,

Althea M. Cuff
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of Post-Marketing Evaluation
Phone (301) 796-4061

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

TERRANCE W OCHELTREE
07/27/2010

From: [Dean, Jane](#)
To: ["Barbara Bauschka";](#)
Subject: NDA 201923 (fluocinolone) - information request - please respond NLT July 29, 2010 - thanks
Date: Wednesday, July 21, 2010 1:46:43 PM

Hi, Ms. Bauschka - you will probably get this information request only once this time and it will be from me! Our chemistry reviewer has the following information request and asked if you could please provide a response by July 29, 2010:

1. (b) (4) Please provide information for the synthesis of fluocinolone. If this contained in a DMF, provide a letter of authorization that includes the DMF number, submission date and page reference.
2. Please provide the inserter device Agency approval reference. If this contained in a DMF/MAF, provide a letter of authorization that includes the DMF/MAF number, submission date and page reference.
3. Provide detail information on the composition, manufacturing, controls of the polyimide tubes and silicone adhesive. Alternately, reference to the respective DMFs with submission date and page references is acceptable. If information are already included in the NDA, provide the section and page reference.

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
07/21/2010

From: [Dean, Jane](#)
To: ["barbara.bauschka@alimerasciences.com"](mailto:barbara.bauschka@alimerasciences.com);
cc: [Rodriguez, Raphael R.](#)
Subject: NDA 201923 (fluocinolone) - information request - stat turn around please
Date: Tuesday, July 20, 2010 12:54:19 PM

Hi, Ms. Bauschka,

I'm the project manager covering for Raphael while he is away. Our statistics reviewer has the following request which will require a stat turn around please. Can you let me know when we can expect a response? Sending it by email to me is acceptable; however, you will need to formally submit your response to the NDA. Thanks!

We need the following information to reproduce your primary and secondary analyses results as well as perform additional sensitivity analyses if needed:

A) Please add the variable "Presence of Cataract at Baseline" to the baseline characteristic dataset "analdat.xpt" in folders "m5\datasets\c-01-05-001a\analysis\datasets" and "m5\datasets\c-01-05-001b\analysis\datasets". You presented results on this variable in Table 5 in the Summary of Clinical Efficacy.

B) Please add the seven variables in our list below to datasets: analva.xpt, analcs.xpt, analoct.xpt, analfa.xpt, analme.xpt, analens.xpt, analv25.xpt, and analv39.xpt in folders "m5\datasets\c-01-05-001a\analysis\datasets" and "m5\datasets\c-01-05-001b\analysis\datasets". The "efficacy variable" in our list below refers to BCVA in dataset analva.xpt, contrast sensitivity in data set analcs.xpt, optical coherence tomography in data set analoct.xpt, fundus photography in data set analfa.xpt, fluorescein angiography in data analme.xpt, lens opacity in data set analens.xpt, VFQ-25 in dataset analv25.xpt and VFQ-29 in dataset analv39.xpt.

Please add

1. A flag for ITT population
2. A flag for PP population
3. The raw **efficacy variable** measurement for each eye.
4. The **efficacy variable** measurement (for the study eye) used in the Full Analysis
5. A flag for the imputed values of the **efficacy variable** measurements used in the Full Analysis
6. The **efficacy variable** measurement (for the study eye) used in the ITT Analysis
7. A flag for the imputed values of the **efficacy variable** measurements used in the ITT Analysis

C) Please add an analysis data set with information on cataract surgery. This dataset should include the following variables:

- 1- Subject id
- 2- Treatment code
- 3- Date of surgery
- 4- Randomization date

D) Please add an analysis data set with information on disallowed medication (as defined in the protocol). This dataset should include the following variables:

- 1- Subject id
- 2- Treatment code
- 3- Name of disallowed medication
- 4- Date the disallowed medication was taken.
- 5- Randomization date
- 6- Reason the disallowed medication was taken or prescribed.

E) Please add details to the define.pdf for data set ae.xpt and the following variables: aeterm, aellt, aept, and aesoc. The define.pdf files (in folder m5\datasets\c-01-05-001a\tabulations\legacy and folder m5\datasets\c-01-05-001b\tabulations\legacy) give the exact same definition for each of these four variables, but the variables in the datasets display different information. Please give more specifications on the similarities and differences in these four variables.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
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Email address: jane.dean@fda.hhs.gov

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JANE A DEAN
07/20/2010

Dillon Parker, Maureen P

From: Dillon Parker, Maureen P
Sent: Tuesday, July 20, 2010 10:17 AM
To: 'barbara.bauschka@alimerasciences.com'
Subject: NDA 201923

Hi Ms. Bauschka,

I am covering for Raphael Rodriguez, Regulatory Project Manager for this application, while he is on leave.

I received the following request for information from the statistical reviewer. Please advise if you will not be able to provide this information by July 30th.

Thank you.
Maureen Dillon-Parker
Chief Project Management Staff
Division of Anti-Infective and Ophthalmology Products
#301-796-0706

Request for Information

RE: NDA 201923

We need the following information to reproduce your primary and secondary analyses results as well as perform additional sensitivity analyses if needed:

A) Please add the variable "Presence of Cataract at Baseline" to the baseline characteristic dataset "analdat.xpt" in folders "m5\datasets\c-01-05-001a\analysis\datasets" and "m5\datasets\c-01-05-001b\analysis\datasets".
You presented results on this variable in Table 5 in the Summary of Clinical Efficacy.

B) Please add the seven variables in our list below to datasets: analva.xpt, analcs.xpt, analoct.xpt, analfa.xpt, analme.xpt, analens.xpt, analv25.xpt, and analv39.xpt in folders "m5\datasets\c-01-05-001a\analysis\datasets" and "m5\datasets\c-01-05-001b\analysis\datasets". The "efficacy variable" in our list below refers to BCVA in dataset analva.xpt, contrast sensitivity in data set analcs.xpt, optical coherence tomography in data set analoct.xpt, fundus photography in data set analfa.xpt, fluorescein angiography in data analme.xpt, lens opacity in data set analens.xpt, VFQ-25 in dataset analv25.xpt and VFQ-29 in dataset analv39.xpt.

Please add

1. A flag for ITT population
2. A flag for PP population
3. The raw **efficacy variable** measurement for each eye.
4. The **efficacy variable** measurement (for the study eye) used in the Full Analysis
5. A flag for the imputed values of the **efficacy variable** measurements used in the Full Analysis
6. The **efficacy variable** measurement (for the study eye) used in the ITT Analysis
7. A flag for the imputed values of the **efficacy variable** measurements used in the ITT Analysis

C) Please add an analysis data set with information on cataract surgery. This dataset should include the following variables:

- 1- Subject id
- 2- Treatment code
- 3- Date of surgery
- 4- Randomization date

D) Please add an analysis data set with information on disallowed medication (as defined in the protocol). This dataset should include the following variables:

- 1- Subject id
- 2- Treatment code

- 3- Name of disallowed medication
- 4- Date the disallowed medication was taken.
- 5- Randomization date
- 6- Reason the disallowed medication was taken or prescribed.

E) Please add details to the define.pdf for data set ae.xpt and the following variables: aeterm, aellt, aept, and aesoc. The define.pdf files (in folder m5\datasets\c-01-05-001a\tabulations\legacy and folder m5\datasets\c-01-05-001b\tabulations\legacy) give the exact same definition for each of these four variables, but the variables in the datasets display different information. Please give more specifications on the similarities and differences in these four variables.

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/s/

MAUREEN P DILLON PARKER
07/20/2010



NDA 201923

NDA ACKNOWLEDGMENT

Alimera Science, Inc.
Attention: Barbara H. Bauschka
Director Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Iluvien (fluocinolone acetonide intravitreal insert) 0.19mg

Date of Application: June 28, 2010

Date of Receipt: June 30, 2010

Our Reference Number: NDA 201923

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 August 29, 2010 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/oc/datacouncil/spl.html>. 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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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 Anti-Infective 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/cder/ddms/binders.htm>.

If you have any questions, call Raphael R. Rodriguez, Senior Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
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Office of Antimicrobial Products
Center for Drug Evaluation and Research

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MAUREEN P DILLON PARKER
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