

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201923Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	201-923
Submission Date(s):	April 17, 2013
Brand Name	Iluvien™
Generic Name	Fluocinolone acetonide
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Alimera Sciences
Relevant IND(s)	NA
Submission Type; Code	Class 2 resubmission
Formulation; Strength(s)	Intravitreal insert, 0.19 mg
Indication	For the treatment of diabetic macular edema

1. EXECUTIVE SUMMARY

On December 22, 2010, the Agency issued a complete response to NDA 201,923 for Iluvien™ (fluocinolone acetonide) intravitreal insert submitted on June 30, 2010. The Applicant resubmitted a Class 2 resubmission on May 12, 2011. The Agency issued another complete response on November 10, 2011.

The current submission is a new Class 2 resubmission. The sponsor did not conduct any new clinical pharmacology studies, except that the sponsor provided the final pharmacokinetics (PK) study report C-01-06-002, which reported fluocinolone acetonide (FA) plasma and aqueous humor exposure data following intravitreal insertion beyond 18 months (i.e., Months 21, 24, 30, and 36), which was the cut-off time point in the interim PK report reviewed in the original review cycle (*Refer to the Clinical Pharmacology Review dated on November 18, 2010*). In the original review, the reviewer concurred with the sponsor's conclusion that FA plasma concentrations were below the lower limit of quantification (100 pg/mL) at all the time points from Day 7 through Month 18. (b) (4)

(b) (4)

As for the FA plasma exposure data, it was reported in the final PK report that FA plasma concentrations remained below the lower limit of quantification beyond 18 months and through Month 36 according to the same analytical method, which was expected. The reviewer is in

agreement with the sponsor's conclusions about the FA plasma PK exposure data in the final study report, and from a clinical pharmacology perspective, no substantial review is warranted in this review cycle.

1.1 Recommendation

The Clinical Pharmacology information provided by the Applicant in this latest NDA resubmission is acceptable to support the label claim with respect to fluocinolone acetonide (FA) concentrations in human plasma, and approval of Iluvien™ (fluocinolone acetonide) intravitreal insert.

The reviewer's proposed labeling changes in Appendix 2.1 are based upon the newly proposed labeling in this current resubmission and should be forwarded to the sponsor.

Yongheng Zhang, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

Philip Colangelo, Pharm.D.; Ph.D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc:

Division File: NDA 201-923/HFD-520 (CSO/Willard)/HFD-520 (MO/Nevitt)/HFD-520 (Chambers)/HFD-880 (Lazor)

2. APPENDICES

2.1. Proposed Package Insert (Original and Annotated) with Clinical Pharmacology edits (blue underline and/or strikethrough), as of October 2013

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/s/

YONGHENG ZHANG
10/07/2013

PHILIP M COLANGELO
10/07/2013

ONDQA (Biopharmaceutics) Review

NDA: 201-923 (000)
Submission Date: 03/27/2103
Product: Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg)
Type of Submission: Original NDA Resubmission
Sponsor: Alimera Sciences, Inc.
Primary Reviewer: Tapash K. Ghosh, Ph.D.
Secondary Reviewer: John Duan, Ph. D.

Background:

Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg) is a sterile sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide (FA) into the ocular vitreous chamber to treat diabetic macular edema (DME). The proposed product is an intravitreal insert which is preloaded in a specially designed inserter which allows the specialized clinician to conveniently insert this tiny FA insert into the ocular vitreous chamber.

Alimera proposed to conduct release rate testing (b) (4)

(b) (4)
When the process was transferred (b) (4)
a formal study was undertaken to verify this observation (Report 10066).

(b) (4) After (b) (4)
the inserter was placed in trays with a (b) (4) lid, the sealed trays were packaged in unit cartons (b) (4)

Therefore, Alimera proposed to conduct release rate testing (b) (4) not only because the data support the proposal but also for practical and economical reasons. (b) (4)

The *in vitro* release profile of the high dose and low dose batches manufactured at the proposed commercial manufacturing site was determined [REDACTED] (b) (4). The release rate profiles are comparable to the release rate profiles from the clinical batches. Although the mean release rates are [REDACTED] (b) (4) they were within the sponsor's proposed specifications and cover the range of the release rates of the clinical lots used in the pivotal clinical trials. According to the sponsor, this [REDACTED] (b) (4) is not expected to have changed the efficacy or safety profile of Iluvien.

During the early stages of development, pSivida set a release rate specification of [REDACTED] (b) (4) µg/day. This was the release rate specification for all the lots used in nonclinical and clinical studies. On 22 December 2010, the Agency issued a Complete Response Letter and commented that the current specification [REDACTED] (b) (4).

The sponsor proposed in this resubmission dated March 27, 2013, **the new proposed specification for release rate is** [REDACTED] (b) (4) **µg/day**. This biopharmaceutics review will address the sponsor's proposed *in-vitro* release rate determination methodology and associated results. For other CMC issues, please refer to the CMC review.

Recommendation:

The following drug product in-vitro release specification is listed in the drug product specification and will be routinely tested for stability. This specification is acceptable for stability and the sponsor's request to use the release rate [REDACTED] (b) (4) is acceptable by the Agency.

Test	Acceptance Criteria	Method
Release Rate	[REDACTED] (b) (4) µg/day	CTM-200502

Overall, the resubmission of the proposed Iluvien[®] (Fluocinolone Acetonide Intravitreal Insert 0.19 mg) is acceptable from the biopharmaceutics point of view.

Finished Product Specifications (Release and Shelf-Life/Regulatory Specifications)

In its May 2011 response to the CRL, the Sponsor proposed a release rate specification of (b) (4) µg/day. In the November 2011 CRL, the Agency did not accept this proposed specification and commented that the proposed release rate specification range should (b) (4)

The range of the release rates of the 12 batches used in clinical studies was (b) (4) µg/day (refer to Module 1, Section 1.11.1 Quality Information). The Sponsor is proposing a specification of (b) (4) µg/day, the range of the batches used in the clinical studies. The justification for this proposed specification is detailed below. Since the Sponsor's May 2011 CRL response, more release rate data have been generated from the primary stability lots which were (b) (4) batch sizes. Three (b) (4) batches were manufactured as well as a clinical batch; these were tested for release rates (see Table 2). Release rates (b) (4) were determined (see Table 3) for a total of (b) (4) release rate data (b) (4)

Based on the above analysis and information, there is justification for a specification of (b) (4) µg/day (target initial release rate of (b) (4) µg/day). However, since the lowest range in the 12 lots used in the clinical studies is (b) (4) µg/day, **the new proposed specification is (b) (4) µg/day** which is in line with the Agency's comment.

Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured (b) (4)

(b) (4)



Table 3: Release Rates (b) (4) from Study 10123

(b) (4)

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Table 4: Release Rates (b) (4) and Percent Distribution

(b) (4)

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Figure 1: Percent Distribution (b) (4) **at Different Release Rates**



Proposed Specification: (b) (4) $\mu\text{g/day}$

Summary:

The following drug product in-vitro release specification is listed in the drug product specification and will be routinely tested for stability. This specification is acceptable for stability and the sponsor's request to use the release rate (b) (4) (b) (4) is acceptable by the Agency.

Test	Acceptance Criteria	Method
Release Rate	(b) (4) $\mu\text{g/day}$	CTM-200502

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/s/

TAPASH K GHOSH
09/23/2013

JOHN Z DUAN
09/23/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	201-923
Submission Date(s):	May 12, 2011
Brand Name	Iluvien™
Generic Name	Fluocinolone acetonide
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Alimera Sciences
Relevant IND(s)	NA
Submission Type; Code	Class 2 resubmission
Formulation; Strength(s)	Intravitreal insert, 0.19 mg
Indication	For the treatment of diabetic macular edema

1. EXECUTIVE SUMMARY

On December 22, 2010, the Agency issued a complete response to the NDA 201923 submitted on June 30, 2010. In the current submission, the Applicant submitted a complete, class 2 response to the December 22, 2010, action letter.

There is no additional clinical pharmacology related information submitted in the resubmission, therefore, no review is needed from a clinical pharmacology perspective for the current review cycle. Please refer to the Clinical Pharmacology Review by Dr. Yongheng Zhang, dated on November 18, 2010, on the original submission.

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/s/

YONGHENG ZHANG
06/28/2011

PHILIP M COLANGELO
06/28/2011

ONDQA (Biopharmaceutics) Review

NDA	201-923 (000)
Applicant:	Alimera Sciences, Inc.
Type of Submission:	Complete Response to Original NDA
Proposed Trademark:	Iluvien [®]
Stamp Date	May 12, 2011
Established Name:	Fluocinolone Acetonide 0.19 mg)
Dosage Form:	Intravitreal Insert
Route of Administration:	Topical
Indication:	Diabetic macular edema
Reviewer	Tapash Ghosh, Ph. D.

Background: The Agency issued a complete response (CR) letter dated 22 December 2010 for the sponsor's original NDA submission dated June 30, 2010. In this submission, the sponsor responded to the Agency's issues raised in the CR letter. This review will deal exclusively with the Biopharmaceutics issues raised in the CR letter and the sponsor's responses.

The following is a summary of the Biopharmaceutics comments sent to the sponsor earlier and the sponsor's responses that needed to be reviewed:

Original Agency's comment #1: It is not clear how the inserts (b) (4) Overall, very little information has been presented on the "Release Rate Methodology" development and validation aspects. 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.

Sponsor's response #1: Visual check from time to time (b) (4)

Agency's new comment #1: The sponsor needs to maintain a record of visual checks performed as part of the protocol. Under that circumstance, the response is acceptable.

Original Agency's comment #2: In-vitro release profiles generated for different batches and associated data set (preferably in electronic format) used to generate the in-vitro release profiles.

Sponsor's response #2: Since the NDA submission, more release rate data have been generated from the primary stability lots which were (b) (4) batch sizes. Three (b) (4)

batches were manufactured between July and December 2010 and tested for release rates (see Table 2).

Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured [redacted] (b) (4)



[redacted] (b) (4)

Table 3: Release Rates [redacted] ^{(b) (4)} **from Study 10123**

[redacted] ^{(b) (4)}

Agency's new comment #2: The sponsor's protocol specifies the collection of samples [redacted] ^{(b) (4)}
[redacted] It is not clear from the data submitted in the above tables at what time points these samples were collected. The sponsor needs to clarify that. Also, it is not clear how many samples from each batch were tested. A detailed raw data sheet (preferably in electronic format) describing all the data used to generate the in-vitro release rates in the above tables.

Original Agency's comment #3: The sponsor's proposed Release Rates Specification of [redacted] ^{(b) (4)} $\mu\text{g/day}$ [redacted] ^{(b) (4)} The sponsor is requested [redacted] ^{(b) (4)} as they mentioned in the submission.

Sponsor's response #3: The original specification for the low dose was [redacted] ^{(b) (4)} $\mu\text{g/day}$. Since the NDA submission, more release rate data have been generated from the primary stability lots which were [redacted] ^{(b) (4)} batch sizes. Three [redacted] ^{(b) (4)} batches were manufactured between July and December 2010 and tested for release rates (see Table 2). In addition, release rates [redacted] ^{(b) (4)} from the first [redacted] ^{(b) (4)} batch were determined (see Table 3).

(b) (4)

Table 4: Release Rates (b) (4) *and Percent Distribution*

(b) (4)

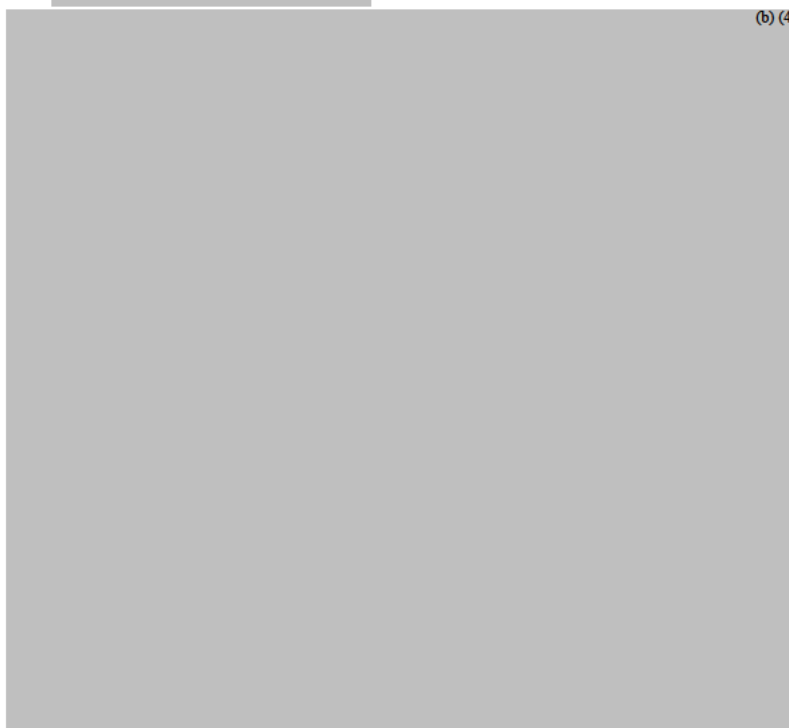


Figure 1: Percent Distribution (b) (4) **at Different Release Rates**



Based on the above analysis and information, there is justification for the proposed new specification of (b) (4) $\mu\text{g/day}$ (target initial release rate of (b) (4) $\mu\text{g/day}$).

Therefore, in response to the CRL, the new proposed specification for release rate is (b) (4) $\mu\text{g/day}$ (target initial release rate of (b) (4) $\mu\text{g/day}$). The results obtained (b) (4) will be used to release product. The Sponsor has presented this proposal (b) (4)

Agency's new comment # 3: No final concurrence can be made without data and clarification as requested in the Agency's new comment #2. However, still the proposed range (b) (4) The sponsor needs to describe the range of in-vitro release rate of the batches that were tested in the clinical studies to justify their proposed in-vitro release rate range. The release rate specifications should not allow the release of lot with release rates outside the ones tested in the clinical trials since their safety and efficacy profiles are unknown.

Recommendation: The submission lacks required information for recommending approval of the proposed Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg) from the biopharmaceutics point of view.

The following information need to be submitted::

The sponsor's new proposed range is presented below:

Release Rate	(b) (4) µg/day	CTM-200502
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No final recommendation can be made without data and clarification of the following:

The sponsor's protocol specifies the collection of samples (b) (4). However, it is not clear from the data submitted in the tables 2 and 3 at which time these samples were collected. The sponsor needs to clarify this in the future submission.

Nevertheless, still the proposed range (b) (4). The sponsor needs to describe the range of in-vitro release rate of the batches that were tested in the clinical studies to justify their proposed in-vitro release rate range. The release rate specifications should not allow the release of lot with release rates outside the ones tested in the clinical trials since their safety and efficacy profiles are unknown.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT by Patrick Marroum, Ph. D. _____

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/s/

TAPASH K GHOSH
06/27/2011

PATRICK J MARROUM
06/27/2011

ONDQA (Biopharmaceutics) Review

NDA: 201-923 (000)
Submission Date: 06/30/2010, 08/13/2010
Product: Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg)
Type of Submission: Original NDA Submission
Sponsor: Alimera Sciences, Inc.
Reviewer: Tapash K. Ghosh, Ph.D.

Background:

Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg) is a sterile sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide (FA) into the ocular vitreous chamber to treat diabetic macular edema (DME). The proposed product is an intravitreal insert which is preloaded in a especially designed inserter which allows the specialized clinician to conveniently insert this tiny FA insert into the ocular vitreous chamber.

[REDACTED] (b) (4)

Please note that the Sponsor is seeking marketing authorization on the Iluvien Low Dose; however, information on the High Dose is also provided as supporting documentation as it was integral in the development of the Low Dose.

Alimera proposed to conduct release rate testing [REDACTED] (b) (4)

[REDACTED] When the process was transferred (u) (4) a formal study was undertaken to verify this observation (Report 10066).

[REDACTED] (b) (4)

the inserter was placed in trays with a (b) (4) lid, the sealed trays were packaged in unit cartons (b) (4)

[REDACTED]

Therefore, Alimera proposed to conduct release rate testing (b) (4) not only because the data support the proposal but also for practical and economical reasons. The manufacturing steps (b) (4)

The *in vitro* (b) (4) release profile of the high dose and low dose batches manufactured at the proposed commercial manufacturing site was determined (b) (4). The release rate profiles are comparable to the release rate profiles from the clinical batches. Although the mean release rates are (b) (4) they were within the sponsor's proposed specifications and cover the range of the release rates of the clinical lots used in the pivotal clinical trials. According to the sponsor, this (b) (4) is not expected to have changed the efficacy or safety profile of Iluvien.

This biopharmaceutics review will address the sponsor's proposed *in-vitro* release rate determination methodology and associated results. For other CMC issues, please refer to the CMC review.

Recommendation:

The sponsor proposes *in-vitro* release specification (b) (4). While the sponsor's justification to use *in-vitro* release specification (b) (4) appears reasonable, Report 10066 could not be reviewed without full development and validation report for the *in-vitro* release methodology. Overall, the submission lacks required information for recommending approval of the proposed Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg) from the biopharmaceutics point of view.

The following information need to be submitted in the future submission:

- It is not clear how (b) (4) very little information has been presented on the "Release Rate Methodology" development and validation aspects. 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.
- *In-vitro* release profiles generated for different batches and associated data set (preferably in electronic format) used to generate the *in-vitro* release profiles.
- Full report of the calculation involved (f2 etc.) to qualify different formulations, manufacturing sites etc.

Without satisfactory response for the above bullets, the *in-vitro* release data submitted by the sponsor will not be reviewed in this cycle of the review.

Some of the specific comments are as follows:

- Time points in generating release profiles should continue [redacted] (b) (4)
- In the formula used to calculate the amount of FA released during a 24 hour period, as described by the sponsor and described below, the injection volume as well as the volume of the medium should be considered unless justified otherwise:

[redacted] (b) (4)

- The sponsor's proposed the Release Rates Specification of [redacted] (b) (4) $\mu\text{g}/\text{day}$ [redacted] (b) (4). The sponsor is requested [redacted] (b) (4) as they mentioned in the submission.

The above comments should be forwarded to the sponsor and the clinical division.

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Iluvien is manufactured by mixing FA with (b) (4) % polyvinyl alcohol (PVA) (b) (4)

The inserter is placed into a tray, sealed with a (b) (4) lid and placed into a carton (b) (4). The insert is inserted through the sclera into the vitreous of the eye by a physician. For the composition of the Iluvien drug product Table 1.

Table 1: Composition of Iluvien

Amount per Insert	Component	Function	Quality Standard
0.19 mg	Fluocinolone Acetonide	Active Ingredient	USP, Ph. Eur.
(b) (4)	Polyvinyl Alcohol	(b) (4)	Manufacturer's specifications
	Water for Injection		USP (b) (4)

Table 2: (b) (4)

Amount per Insert	Component	Function	Quality Standard
Not Applicable ^a	Polyimide Tubing	(b) (4)	Manufacturer's specification
(b) (4)	Silicone Adhesive		Manufacturer's specification (b) (4)

Release Rate Profile Over Time

The release kinetics (*in vitro* release rates) of the drug from the inserts was monitored for several lots used in the clinical studies. The sponsor reported the following outcome from the *in vitro* release studies.

The results of the *in vitro* (b) (4) release testing have consistently demonstrated that the batches of Iluvien used in the clinical and nonclinical studies release FA through Month 24 - 30.

Following the initial peak release, FA levels rapidly decrease through approximately Month 3 for the low dose and Month 6 for the high dose. A stable phase of release of FA of approximately 0.15 µg/day for the low dose is maintained through Month 24 while the high dose diminishes more rapidly. For the low dose at 30 months, a few samples from one clinical lot showed levels of 0.12 µg/day and at 36 months, a few samples from two lots showed traces of FA (average of 0.07 µg/day). Therefore, for the low dose, FA is released (b) (4)

(b) (4)

(b) (4)

Based on the release rates generated using the sponsor's methodology, the sponsor proposed the Release Rates Specification: (b) (4) µg/day. While the Sponsor acknowledges that the specifications (b) (4) additional data will be generated as more batches are produced at the commercial manufacturing site. With the enhanced manufacturing process, the expectation is that variability will be reduced and (b) (4) specification may be possible.

Discussion: During review of the NDA, a biopharmaceutics information request (IR) letter asking the sponsor to clarify issues listed in the IR was sent to the sponsor on July 27, 2010. In the Quality Information Amendment dated August 13, 2010, the sponsor responded to that IR. The IRs with the sponsor's responses and the reviewer's comments are described below.

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.

Sponsor's Response: The method validation report for Test Method SP-023-060 Rev. 00, "Report DP2006-157 07062006 Method Validation Report Medidur (b) (4) Inserts for Release Rate Testing – HPLC", is located in [Module 3, Section 3.2.P.5.3](#) of the dossier.

The method transfer report for Protocol 08224, "Method Transfer: Determination of Release Rate of Fluocinolone Acetonide from Iluvien Inserts by HPLC", is located in [Module 3, Section 3.2.P.5.3](#) of the dossier.

Reviewer's Comments: The method validation report for Test Method SP-023-060 Rev. 00, "Report DP2006-157 07062006 Method Validation Report Medidur (b) (4) Inserts for Release Rate Testing – HPLC", as located in [Module 3, Section 3.2.P.5.3](#) of the dossier described mostly the Analytical/HPLC method validation. The reviewer acknowledges the little description of the method as presented in the Section 7.4 under "Sample Preparation" in Doc# 10-077 - CTM-200502 as described below:

7.4 Sample Preparation



In a telephone conference with the sponsor on November 11, 2010 in presence of ONDQA RPM Ms. Althea Cuff, the sponsor mentioned that they acquired the method from another company. They attested that neither they have development/validation report from the previous company nor they have generated any new data on their own. When they were told what development/validation information is expected in the NDA submission, they requested if the information can be submitted in a post-approval amendment. The reviewer responded that it would be discussed internally before providing any answer.

The following information need to be submitted in the future submission:

- It is not clear how the inserts [REDACTED] (b) (4) [REDACTED] Overall, very little information has been presented on the “Release Rate Methodology” development and validation aspects. 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.
- *In-vitro* release profiles generated for different batches and associated data set (preferably in electronic format) used to generate the *in-vitro* release profiles.
- Full report of the calculation involved (f2 etc.) to qualify different formulations, manufacturing sites etc.

Without satisfactory response for the above bullets, the *in-vitro* release data submitted by the sponsor will not be reviewed in this cycle of the review.

Some of the specific comments are as follows:

- Time points in generating release profiles should continue [REDACTED] (b) (4) [REDACTED]
- In the formula used to calculate the amount of FA released during a 24 hour period, as described by the sponsor and described below, the injection volume as well as the volume of the medium should be considered unless justified otherwise:



(b) (4)

- The sponsor's proposed the Release Rates Specification of [redacted] (b) (4) $\mu\text{g/day}$ [redacted] (b) (4). The sponsor is requested [redacted] (b) (4) as they mentioned in the submission.

2. 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.

Sponsor's Response: A statistical analysis report, Protocol 10066 Abbreviated Statistical Report, has been provided, refer to Module 3, Section 3.2.P.5.6 of the dossier. The product used for both the "Control Group" and the "Test Group" were from the same batch.

Reviewer's Comments:

While the sponsor's justification to use *in-vitro* release specification [redacted] (b) (4) appears reasonable, Report 10066 could not be reviewed without the full development and validation report for the *in-vitro* release methodology. Without a satisfactory response for the bullets listed in IR #1, the *in-vitro* release data submitted by the sponsor will not be reviewed in this cycle of the review.

3. Provide raw *in-vitro* release data associated with Primary Stability Batches, and batches used in clinical and pre-clinical studies of Iluvien.

Sponsor's Response: The raw *in-vitro* release data for the Primary Stability Batches as well as the batches used in the clinical and pre-clinical studies of Iluvien have been provided (see Table 1).

Reviewer's Comments: Without satisfactory response for the bullets listed in IR #1, the *in-vitro* release data submitted by the sponsor will not be reviewed in this cycle of the review.

4. A follow-up email of 04 Aug 2010 also asked for clarification information.

Also, as highlighted here, there is a discrepancy between the lot #s. There is no Lot # 09-0013 reported in the Table.

Sponsor's Response: Module 3, Section 3.2.P.5.6, Table 2 has the correct information on lot numbers; the text below the table has been revised to reflect the correct lot number of 07-0013. Additionally, in Alimera's review of the information a correction was made to the result at T=24 for Lot 07-0035, with the correct result of ^{(b) (4)} μg/day now in the table.

Reviewer's Comments: The sponsor's response is acknowledged.

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/s/

TAPASH K GHOSH
11/29/2010

PATRICK J MARROUM
12/01/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	201-923
Submission Date(s):	June 30, 2010
Brand Name	Iluvien™
Generic Name	Fluocinolone acetonide
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Alimera Sciences
Relevant IND(s)	NA
Submission Type; Code	New formulation, priority review; 3P
Formulation; Strength(s)	Intravitreal insert, 0.19 mg
Indication	For the treatment of diabetic macular edema

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1. EXECUTIVE SUMMARY

Fluocinolone acetonide (FA) is a glucocorticoid that has been used topically as an anti-inflammatory product for more than 30 years.

The Applicant, Alimera Sciences, submitted the 505(b)(1) application for Iluvien™ (fluocinolone acetonide intravitreal insert 0.19 mg) as a sustained-release intravitreal drug delivery system to release submicrogram levels of FA in the vitreous humor for (b) (4) 36 months for the treatment of diabetic macular edema (DME). The delivery technology, which provides a controlled-release of drug directly to the back of the eye, was designed and developed by pSivida Inc, and later was licensed to the Applicant for the development of Iluvien™. An earlier intravitreal implant developed by pSivida which releases FA at similar levels (Retisert® intravitreal implant 0.59 mg FA, designed to release FA at 0.3-0.4 µg/day at steady state for about 30 months) was approved by FDA in 2005 for the treatment of non-infectious posterior uveitis. Unlike Retisert® that requires a surgical procedure, Iluvien is smaller and designed to be administered using a modified 25-gauge needle by a physician.

In support of the NDA, the Applicant conducted two Phase 3 clinical studies under the same protocol (C-01-05-001 A and B) that evaluated the safety and efficacy of 0.2 µg/day and 0.5 µg/day inserts (b) (4) in the treatment of DME. Both studies will continue through Month 36 and the Month 24 readout is included in the current submission. The Applicant also submitted one human PK interim study report (C-01-06-002) that assessed FA concentrations in human plasma (b) (4) through Month 18 (b) (4)

There is a slight difference in the total FA content between the product used in the preclinical/clinical studies and the to-be-marketed product. The to-be-marketed product (b) (4) contains 0.19 mg FA versus the clinical development product (manufactured at pSivida, Inc.) that averaged (b) (4) mg. (b) (4)

FA is released from the polyimide tube at sub-microgram levels (b) (4)

(Refer to the ONDQA Biopharmaceutics Reviewer's review). The Applicant claimed that the dose-response relationship established for both safety and efficacy (0.2 µg/day and 0.5 µg/day) supports the selection of a low dose insert. However, it should be noted that the FA release rate for the proposed product is estimated to be 0.25 µg/day (b) (4)

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable to support the label claim with respect to FA concentrations in human plasma.

The reviewer's proposed label changes in Appendix 4.1 should be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

In a human pharmacokinetic study (C-01-06-002), FA concentrations in plasma were found below the lower limit of quantitation of the assay (0.100 ng/mL) at all time points from Day 7 through Month 18 following the intravitreal administration of Iluvien (b) (4) mg FA, released at either 0.2 or 0.5 µg/day). (b) (4)

(b) (4)

(b) (4)

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

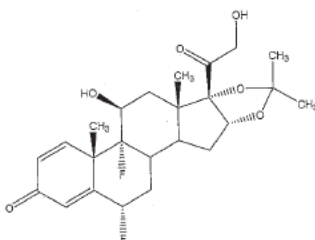
Fluocinolone Acetonide (FA) is a white or almost white, microcrystalline powder, practically insoluble in water, soluble in methanol, ethanol, chloroform, and acetone, sparingly soluble in ether.

Structural Formula: C₂₄H₃₀F₂O₆

Molecular Weight: 452.50 Dalton

CAS Index Name: (6 α , 11 β , 16 α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione

Chemical Structure:



Drug Product:

Each Iluvien consists of a light brown insert containing 0.19 mg of the active ingredient FA and the following inactive ingredients: polyvinyl alcohol and water for injection- *see* **Table 2.1.1-1**. Drug product is supplied in a single-use preloaded inserter with a 25-gauge needle. The insert is inserted through the sclera into the vitreous of the eye by a physician.

Table 2.1.1-1: Composition of Drug Product Iluvien

Amount per Insert	Component	Function	Quality Standard
0.19 mg	Fluocinolone Acetonide	Active Ingredient	USP, Ph. Eur.
(b) (4)	Polyvinyl Alcohol	(b) (4)	Manufacturer's specifications
	Water for Injection		USP, Ph. Eur.

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

FA is a glucocorticoid that has been used topically as an anti-inflammatory product for more than 30 years. Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2. Corticosteroids are capable of producing a rise in intraocular pressure.

Iluvien[®] (fluocinolone acetonide intravitreal insert) 0.19 mg is indicated for the treatment of diabetic macular edema (DME).

2.1.3. What are the proposed dosage(s) and route(s) of administration?

Iluvien[®] is inserted into the posterior segment of the affected eye through a pars plana insertion. Each intravitreal insert contains 0.19 mg of FA.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical pharmacology studies to assess the permeability, protein binding, metabolism, excretion, and drug interaction characteristics of FA were considered nonessential and not performed by the Applicant.

One human PK study (C-01-06-002) was conducted following administration of Iluvien to patients with DME to assess in vivo bioavailability. Systemic and ocular exposure of FA were assessed. The interim data is available up to Month 18. The study is still on-going at the time of the NDA submission. The final report with PK data through Month 36 will be submitted.

Two Phase 3 clinical studies under the same protocol (C-01-05-001 A and B) were conducted to provide the safety and effectiveness data on 0.2 µg/day and 0.5 µg/day FA inserts in the treatment of DME. The application includes the primary readout by Month 24. The final results will be reported when all the subjects have completed Month 36.

2.2.2. *What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?*

In the two Phase 3 studies (C-01-05-001 A and B), the primary efficacy endpoint was the percent of subjects with ≥ 15 -letter improvement in best corrected visual acuity (BCVA) letter score at Month 24. This endpoint was chosen based on input from the agency and represents a clinically relevant change in vision. The Month 36 follow-up data will be reported later to confirm the durability of the drug effectiveness and safety. This endpoint was assessed according to the standard procedure by masked, certified assessors.

2.2.3. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes, the sponsor used a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method to quantitate concentrations of FA in human plasma. (b) (4)

2.2.4. *Exposure-response*

2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.*

Dose-response for efficacy was evaluated in the two Phase 3 studies (C-01-05-001 A and B) using the FA insert with the same loading (b) (4) but two different release rates (i.e., 0.2 $\mu\text{g}/\text{day}$ and 0.5 $\mu\text{g}/\text{day}$). The data suggested that the two release rates has similar efficacy up to Month 24 (Table 2.2.4.1-1). The onset of action of FA when administered intravitreally was apparent within 1 week (Note: one week was the first point assessed in the clinical studies) based on the effect on vision and retinal thickness.

Table 2.2.4.1-1: Number (%) of Subjects with a ≥ 15 -Letter Increase from Baseline in Best Corrected Visual Acuity in the Study Eye by Treatment Group (Integrated Full Analysis Population)

(b) (4)

2.2.4.2. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.*

Dose-response for safety was evaluated in the two Phase 3 studies (C-01-05-001 A and B) using the FA insert with the same loading (b) (4) but two different release rates (i.e., 0.2 µg/day and 0.5 µg/day). The 0.5 µg/day FA intravitreal insert had a less favorable safety profile compared with the 0.2 µg/day FA intravitreal insert. In the overall analysis, the percentage of subjects who experienced an IOP-related TEAE in the study eye was lower in the 0.2 µg/day FA group (33%) versus the 0.5 µg/day FA group (44%). More subjects in the 0.5 µg/day FA group underwent an IOP-related surgical intervention (1% with sham; 4% with 0.2 µg/day FA; 7% with 0.5 µg/day FA). Median time to development or progression of a cataract was a few months shorter in the 0.2 µg/day FA group (12 months vs. 15 months).

2.2.4.3. *Does this drug prolong the QT or QTc interval?*

Cardiovascular safety and tolerability has not been evaluated following topical and intravitreal administration of FA.

2.2.4.4. *Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

Yes, the dose-response relationship established for both safety and efficacy (0.2 µg/day and 0.5 µg/day; Refer to Section 2.2.4.1 & Section 2.2.4.2) supports the selection of a low dose insert. However, it should be noted that the FA release rate for the proposed product is estimated to be 0.25 µg/day (b) (4)

(b) (4) Another potential issue regarding the proposed dosing is that the FA loading in the proposed product is 0.19 mg of FA (b) (4) evaluated in clinical trials. (Refer to the ONDQA Biopharmaceutics Reviewer's review).

2.2.5. *What are the PK characteristics of the drug and its major metabolite?*

2.2.5.1. *What are the single dose and multiple dose PK parameters?*

Systemic and ocular exposures of FA were studied in patients with DME following single intravitreal administration of FA (b) (4) insert (released at either 0.2 or 0.5 µg/day). Some subjects received a second administration after 12 months following the first administration. As reported in Study C-01-06-002, FA concentrations were below the lower limit of quantitation in plasma samples, indicating that systemic exposure of FA was minimal in subjects who received a 0.2 or 0.5 µg/day FA intravitreal insert. (b) (4)



2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Systemic and ocular exposures of FA were only studied in patients with DME.

2.2.5.3. What are the characteristics of drug absorption?

As reported in Study C-01-060992, no FA was quantifiable in plasma samples following intravitreal administration of FA intravitreal insert, indicating minimal systemic exposure following intravitreal administration.

2.2.5.4. What are the characteristics of drug distribution?



2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not performed.

2.2.5.6. What are the characteristics of drug metabolism?

No drug metabolism studies have been conducted. FA, presumably like other corticosteroids, may be metabolized primarily in the liver.

2.2.5.7. What are the characteristics of drug excretion?

No drug excretion data were available. FA, presumably like other corticosteroids, may be excreted along with its metabolite(s) by the kidneys and/or bile once absorbed into the systemic circulation.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

FA plasma concentrations were below the detection limit at all the time points analyzed following intravitreal administration of Iluvien FA (b)(4) insert in patients with DME. (b)(4)

Therefore, no definite conclusions can be drawn with respect to the degree of linearity or nonlinearity in the dose-concentration relationship.

2.2.5.9. How do the PK parameters change with time following chronic dosing?

Iluvien is designed as a long term sustained release delivery system. FA plasma concentrations were below the detection limit at all the time points analyzed following intravitreal administration of Iluvien FA (b)(4) insert in patients with DME (b)(4)

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

FA plasma concentrations were only assessed in patients with DME following intravitreal administration of Iluvien FA (b)(4) insert and found below the detection limit at all the time points analyzed. (b)(4)

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Iluvien is designed to be administered intravitreally. None of the common intrinsic factors are expected to significantly influence exposure and/or response, therefore dose adjustment based on any of these intrinsic factors is not warranted.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Not applicable.

2.4.2. Drug-drug interactions

2.4.2.1. *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

No in vitro drug metabolism studies have been conducted for FA.

2.4.2.2. *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

It is unknown whether FA is a substrate of CYP enzymes or not. It is also unknown whether FA metabolism is influenced by genetics or not.

2.4.2.3. *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

It is unknown whether FA is an inhibitor or inducer of CYP enzymes or not.

2.4.2.4. *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

It is unknown whether FA is a substrate and/or an inhibitor of P-glycoprotein transport.

2.4.2.7. *What other co-medications are likely to be administered to the target patient population?*

Numerous medications are likely to be co-administered with Iluvien including anti-VEGF therapy for DME (e.g., Pegaptanib or Ranibizumab), other corticosteroids, and anti-diabetic medicines. In the clinical studies, the concomitant medicines included anti-VEGF therapy, intraocular corticosteroids, and IOP-lowering medications.

2.4.2.8. *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

The applicant did not conduct any in vivo drug-drug interaction studies.

2.4.2.9. *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

There are potential pharmacodynamic drug-drug interactions between FA inserts and the pharmacotherapies commonly used in the treatment of DME, including anti-VEGF therapy, intraocular corticosteroids, and IOP-lowering medications.

2.4.2.10. *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

Clinical pharmacology studies to assess the permeability, protein binding, metabolism, excretion, and drug interaction characteristics of FA were considered nonessential in the NDA and not performed by the Applicant.

2.4.3. *What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?*

Refer to Section 2.2.4.4.

2.5. General Biopharmaceutics

Not applicable. FA is formulated in a sustained-release insert for intravitreal administration.

2.6. Analytical Section

2.6.1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

The sponsor used liquid chromatography with tandem mass spectrometry (LC/MS/MS) to quantitate FA concentrations in human plasma. (b) (4)

2.6.2. *Which metabolites have been selected for analysis and why?*

No metabolite was selected for analysis, because systemic absorption of FA is minimal following intravitreal administration and little is known about FA metabolism.

2.6.3. *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

The reported concentrations of FA in human plasma, although below the detection limit at all the timepoints, should represent total concentrations. Free concentrations in the plasma are not considered clinically relevant to the indicated efficacy following intravitreal administration.

2.6.4. *What bioanalytical methods are used to assess concentrations?*

Refer to Section 2.6.1. for further information.

2.6.4.1. *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

The standard curve in plasma ranged from 0.10 ng/mL to 25.0 ng/mL for FA. The observed plasma concentrations of FA in clinical studies were under the lower limit of quantitation. The linear regression of the curves for peak area ratios versus concentration was weighted $1/x^2$ for the standard curve.

2.6.4.2. *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The lower and upper limits of quantitation were 0.100 ng/mL and 25.0 ng/mL for FA, respectively.

2.6.4.3. *What are the accuracy, precision, and selectivity at these limits?*

The accuracy (%RE) and precision (%CV) ranges for FA were -5.6% to 10.0% and 1.8% to 9.1%, respectively.

Selectivity was demonstrated by the lack of interference by potential endogenous interfering substances in six distinct lots of human plasma.

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

FA was shown to be stable in plasma at room temperature up to 4 hours and after 3 freeze thaw cycles, in extracted samples at 4°C for 118 hours, and in reconstituted sample in the autosampler at 4°C for 6 hours.

2.6.4.5. What is the QC sample plan?

The concentrations of the QC samples consisted of 0.100, 0.300, 4.00, 15.0, and 25.0 ng/mL for FA. Between-run and within-run accuracy and precision were evaluated using replicates (n=6) from each of these concentrations.

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for detailed labeling recommendations.

4. APPENDICES

4.1. Proposed Package Insert (Original and Annotated)

5 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.2. Individual Study Review

4.2.1. Human PK study in Plasma (b) (4)

Study Number: C-01-06-002

An open label pharmacokinetic and efficacy study of 0.5 µg/day and 0.2 µg/day Fluocinolone Acetonide Intravitreal Inserts in Subjects with Diabetic Macular Edema (Phase 2b)

Dates: 20 August, 2007 to May 7, 2010 (Interim Report)

Analytical site: (b) (4)

OBJECTIVES:

The primary objective of the study was to characterize the systemic and intraocular (b) (4) concentrations of fluocinolone acetonide (FA) following intravitreal administration of 0.2 µg/day or 0.5 µg/day FA intravitreal inserts. In addition, the effect of FA on change from baseline in central retinal thickness was to be assessed. (b) (4)

FORMULATION & ADMINISTRATION

All subjects received a single intravitreal insert of FA (with the same loading (b) (4), released at either 0.2 or 0.5 µg/day) in the study eye. If progression of edema occurred, subjects could have received retreatment after 12 months. Batch Numbers: 07-0018, 07-0028, 07-0030, 07-0031, 07-0033, 07-0034, 08-0001, 08-0002, 08-0007, 08-0009, 08-0010, 08-0022, 08-0033, 08-0034, 08-0035, 08-0036, 08-0037, and 08-0038.

STUDY DESIGN:

This was an open label pharmacokinetic and efficacy study in subjects with DME. The treatment was administered to only one eye, referred to as the “study” eye. The other eye, referred to as the “non-study” eye, received any ocular treatment at the discretion of the investigator other than systemic treatments for DME or diabetic retinopathy (DR) such as Avastin®.

Of the 37 subjects randomized into the study who had a clinical diagnosis of DME, 20 subjects are in the 0.2 µg/day group and 17 subjects in the 0.5 µg/day group (**Table 1**). Subjects were eligible for retreatment after Month 12 if vision decreased or the retinal thickness increases.

The study consisted of at least 14 visits:

- Visit 1 (Day 0, screening/baseline) – eligibility visit and 1 eligible eye per qualifying subject received either the 0.2 µg/day or 0.5 µg/day FA intravitreal insert.
- The remaining visits were scheduled at Day 1, Week 1, Month 1, Month 3, and every 3 months after the Month 3 visit through Month 24, and every 6 months thereafter through Month 36 (Visit 14).
- If progression of edema occurred, the subject could have received retreatment (i.e., another implant) after 12 months. After retreatment, there were 2 post-treatment visits at 1 day and 1 week.
- This interim report includes data for all subjects through Month 18 and data from later visits on case report forms collected by August 28, 2009.

Pharmacokinetics: Plasma (b) (4) samples were obtained at baseline, Week 1, and at Months 1, 3, 6, 9, 12, 15, and 18 and additional samples collected by August 28, 2009.

Efficacy: The primary efficacy variable was the change from baseline in center point thickness in the study eye, as measured by optical coherence tomography (OCT). Secondary efficacy variables included change from baseline in best corrected visual acuity (BCVA) letter score as measured by the ETDRS chart; change from baseline in average macular volume as measured by OCT; proportion of subjects requiring treatment for DME with non-protocol therapies; change from baseline in excess average foveal thickness (microns) as assessed by OCT; and change from baseline in the level of diabetic retinopathy (DR) according to the International Clinical Diabetic Retinopathy Disease Severity Scale (0 to 4 scale).

Safety: Assessed by evaluating adverse events (AEs), vital signs, concomitant medications, Intraocular pressure (IOP), dilated ophthalmoscopy, slit lamp examination, ocular ultrasounds, and fundus photography and fluorescein angiography.

Reviewer’s comments: *A placebo control group was not included since efficacy and safety comparisons were secondary goals. Because the number of patients enrolled in the study (n=37) was small, the study may not be sufficiently powered to discern the differences in PK, efficacy and safety between two treatments, i.e., the 0.2 µg/day and 0.5 µg/day FA intravitreal inserts. This review only focuses on the PK part of the study.*

Table 1: Demographic Characteristics (ITT population)

Demographics	Treatment Group		
	0.2 µg/day FA (N = 20)	0.5 µg/day FA (N = 17)	Total (N = 37)
Gender, n (%)			
Male	10 (50.0)	11 (64.7)	21 (56.8)
Female	10 (50.0)	6 (35.3)	16 (43.2)
Age (yrs)			
Mean (SD)	66.6 (9.4)	67.4 (10.3)	66.9 (9.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (5.0)	0	1 (2.7)
Non-Hispanic or Latino	19 (95.0)	17 (100.0)	36 (97.3)
Race, n (%)			
White	17 (85.0)	15 (88.2)	32 (86.5)
Black/African American	3 (15.0)	0	3 (8.1)
American Indian/Alaskan Native	0	2 (11.8)	2 (5.4)
Iris Color, n (%)			
Brown	8 (40.0)	8 (41.7)	16 (43.2)
Hazel	2 (10.0)	3 (17.6)	5 (13.5)
Green	0	1 (5.9)	1 (2.7)
Blue	10 (50.0)	5 (29.4)	15 (40.5)
Iris Color Group, n (%)			
Light	12 (60.0)	9 (52.9)	21 (56.8)
Dark	8 (40.0)	8 (47.1)	16 (43.2)

ASSAY METHODOLOGY:

Plasma samples were assayed for FA using a validated LC/MS/MS method. The validated concentration ranged from 0.100 ng/mL to 25.0 ng/mL. (b) (4)

The concentrations of FA in (b) (4) were measured against a calibration curve and QC samples prepared in human plasma.

Criterion	Fluocinolone Acetonide	Comments
Conc. range, ng/mL	0.100 – 25.0	satisfactory
LLOQ, ng/mL	0.100	satisfactory
Linearity, r ²	0.997	satisfactory
Accuracy, % RE	-5.6 – 10.0 ^a -2.4 – 6.8 ^b	satisfactory
Precision, % CV	1.8 – 9.1 ^a 2.1 – 5.2 ^b	satisfactory
Recovery	Evaluated for analyte and internal standard at two QC concentrations (low and high)	satisfactory
Specificity	Interference by endogenous compounds evaluated	satisfactory
Stability	Stable in plasma at room temperature up to 4 hours and after 3 freeze thaw cycles; extracted samples at 4°C for 118 hours, reconstituted sample on autosampler at 4°C for 6 hours.	satisfactory

^a, QC samples at 0.1, 0.3, 4.0, 15.0, 25.0 ng/mL; ^b, calibration standards.

Internal standard: Triamcinolone-6-d1 acetonide-d6.

Reference: Study report No. 07-8965

DATA ANALYSIS

Non-compartmental analysis was used to estimate C_{max} and AUC. The concentration-time profile was plotted.

Reviewer's comments: Because the bioanalytical method to quantify FA concentrations (b) (4) validated, the conclusions derived from this part of PK analyses are for internal discussion only, and not to be used to drive any regulatory decisions including labeling language.

RESULTS:

Human Plasma

Plasma concentrations of FA at all the sampling points were below the LOQ (0.10 ng/mL). No further analysis was performed.

(b) (4)

SAFETY RESULTS:

The safety results (18-month report indicate that FA intravitreal inserts are generally safe and well tolerated in subjects with DME. The most common TEAEs were eye disorders and surgical and medical procedures involving the eye. Common drug-related TEAEs, all of which occurred in the study eye, included cataract, cataract operation, increased intraocular pressure, and subcapsular cataract. Approximately 25% of the subjects had at least 1 drug-related SAE, most of which were cataract operation in the study eye. AE profiles were generally comparable between the 2 dose groups, although the incidence of increased intraocular pressure was higher in the 0.5 µg/day FA group. The one case of serious increased intraocular pressure also occurred in the high dose group.

SPONSORS CONCLUSIONS:

As expected, no FA was quantifiable in plasma samples, indicating that systemic exposure of FA was minimal in subjects who received a 0.2 or 0.5 µg/day FA intravitreal insert. (b) (4)

[Redacted]

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study C-01-06-002 adequately assessed the systemic exposure of FA following administration of a 0.2 or 0.5 µg/day FA intravitreal insert in patients with DME. The sponsor's conclusion of minimal systemic exposure following the administration is valid. (b) (4)

[Redacted] The reviewer has additional comments as follows:

[Redacted] (b) (4)

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

/s/

YONGHENG ZHANG
11/17/2010

CHARLES R BONAPACE
11/18/2010

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 201923
 Drug Name: ILUVIEN® (fluocinolone acetonide intravitreal insert, 0.19 mg)
 Applicant: Alimera Sciences
 Submission Date: 30JUN2010
 Filing Date: 30AUG2010
 PDUFA Date: 20DEC2010
 OCP Primary Reviewer: Kimberly L. Bergman, PharmD
 OCP Team Leader: Charles Bonapace, PharmD

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<i>Fileability:</i> <i>Is the Clinical Pharmacology section of the application fileable?</i> <i>(if 'NO', please comment as to why it is not fileable)</i>	<i>X</i>			
<i>Fileability Review Components</i>				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Clinical pharmacology studies submitted in this application: C-01-06-002 (plasma ^{(b) (4)} PK in DME patients); 480271 (IVIVC)
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The insert intended for market contains 0.19 mg FA versus the product used in clinical studies, containing ^{(b) (4)} FA (see comment below)
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Complete bioanalytical reports for C-01-06-002 included in this submission: 07-8965 (validation) and 07-8967 (bioanalytical)
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PK data in listing format in Appendix 16.2.5 in Clinical Study Report C-01-06-002
<u>Additional Comments:</u> DME = diabetic macular edema FA = fluocinolone acetonide				

PVA = polyvinyl alcohol

Comment: There is a slight difference in the total FA content between the product used in the preclinical and clinical studies and the product to be marketed. The to-be-marketed product (b) (4) contains 0.19 mg FA versus the clinical development product (manufactured at pSivida, Inc.) that averaged (b) (4) mg. (b) (4) FA is released from the polyimide tube at sub-microgram levels (b) (4)

This will be a review issue for CMC/ONDQA.

OCP Primary Reviewer

Date

OCP Team Leader

Date

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

/s/

KIMBERLY L BERGMAN
10/06/2010

CHARLES R BONAPACE
10/06/2010