CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201923Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review of NDA 201923
Review #4

Date	September 15, 2014
From	Wiley A. Chambers, M.D.
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Amendment to third action letter	March 26, 2014
Type of Application	505(b)(1)
Name	ILUVIEN (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure
Proposed Action:	Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is an active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant. ILUVIEN (fluocinolone acetonide intravitreal insert) 0.19 mg is commercially available in Europe.

ILUVIEN (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA). In this application, it was studied in two doses. Based on *in vitro* and *in vivo* data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The product was developed with a polyvinyl alcohol matrix inside a tube which can be inserted through a 25 gauge needle attached to an inserter. The applicant is seeking approval for the low dose version of ILUVIEN (0.19 mg) designed to have an initial release rate of 0.25 µg/day.

Uses of corticosteroids are known to produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

2. Background

Diabetic macular edema (DME), a serious, debilitating disease, is a cause of vision loss associated with diabetic retinopathy. While the mainstay of the treatment of diabetic retinopathy and diabetic macular edema remains the use of products to control glucose levels and HgA1c, a number of products are approved for DME including: Lucentis (ranibizumab injection) approved 8/10/2012, Eylea (aflibercept) Injection approved 7/29/2014, and Ozurdex (dexamethasone intravitreal implant) approved 6/28/2014.

As documented at an End-of-Phase 2 meeting held for IND 72,056 on September 2, 2008, the Division expressed concern that the benefits might not outweigh the risks if ILUVIEN demonstrated a safety profile which was similar to other corticosteroids. The applicant stated that they did not expect to see the development of cataracts or elevated intraocular pressure due to the low release rate.

The NDA was submitted on June 30, 2010, with the two year results of their planned three year studies. The Agency issued a Complete Response letter on December 22, 2010, citing a lack of substantial evidence to

support the efficacy, facilities that were not in compliance with cGMPs and a lack of methods, facility and controls to assure identity, strength, quality, purity and stability. From a clinical prospective, the development of cataracts during the clinical trial made it difficult to access the potential benefit of the corticosteroid.

The applicant re-submitted the application with clinical data through 3 years of study. The resubmission attempted to support the approval of the product with an endpoint at 3 years. However, when the studies failed to demonstrate a clinically significant difference at 36 months, the applicant proposed a subpopulation of patients who had reported a diagnosis of Diabetic Macular Edema (b) (4) The clinical trials had been conducted at a time when there were no approved therapies specifically indicated for DME. The subset was problematic as documented in the clinical and statistical reviews. In addition, the application did not address a way to minimize the safety concerns related to elevations in intraocular pressure which occurred with use of the implant and could persist throughout the three year implantation period. A number of manufacturing issues also continued to exist. The Agency issued a Complete Response letter November 10, 2011, citing a lack of substantial evidence to support the efficacy and insufficient information to determine the adequacy of the specifications necessary to ensure the identity, strength, quality, purity, and potency of your drug substance and drug product.

The applicant re-submitted the application a third time. From a clinical prospective, the resubmission continued to focus on a subset of patients in each trial who were reported to have had DME for an extended period of time, but had not received treatment. In this submission, the extended period of time was defined as patients who had reported a duration of diabetic macular edema greater than the median time in that trial. The subset was problematic for a number of reasons as documented in the clinical and statistical reviews. The applicant had not addressed a way to minimize the safety concerns related to elevations in intraocular pressure. The manufacturing facility was noted to be out of compliance with current Good Manufacturing Practices (cGMP). The Agency issued a Complete Response letter on October 17, 2013, citing the clinical and cGMP deficiencies.

On March 26, 2014, the applicant re-submitted the application. The applicant responded to FDA's Complete Response letter and further revised the proposed indication (b) (4) The revised indication addresses the need to attempt (b) (4)

3. CMC

The Chemistry/Manufacturing deficiencies identified during earlier submissions have been resolved including the issues related to manufacturing and testing in compliance with current Good Manufacturing Practice (cGMP). The release rate specification remains (b) (4) µg/day. It was accepted by the ONDQA Chemistry and Biopharm Reviewers and is consistent with the release rate of the test product used in the clinical trials. Re-inspection of (b) (4) a facility previously identified as being not in compliance found the facility to have corrected their deficiencies and now be incompliance with cGMP.

DRUG PRODUCT:

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)

Amount per Insert	Component	Function	Quality Standard
Empty tube measuring 3.5 mm x 0.37 mm OD, weighs approximately 0.1 mg.	Polyimide Tubing	(b) (4)	Manufacturer's specification
(b) (4)	Silicone Adhesive		Manufacturer's specification

(b) (4)

(b) (4)

Drug Product Specification (Updated March 27, 2013)

Test	Acceptance Criteria	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay- Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances Specified Identified and Unidentified Individual Impurity Release Stability (b) (4) Release Stability Unspecified Individual Impurity Release Stability Total Impurities	(b) (4) NMT NMT NMT NMT NMT NMT NMT	 CTM-200501 CTM-200562 CTM-200501
Release Rate	(b) (4)	CTM-200502
Endotoxin	(b) (4)	PTS-200566 MTM-200033
Sterility at Release	(b) (4)	(b) (4)
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

4. Nonclinical Pharmacology/Toxicology

Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. The applicant conducted several biocompatibility studies with polyimide tubing and extracts of stainless steel injection needles. The results were negative. The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber. Continuous exposures of ocular tissues for both toxicity studies were achieved via one or two injections of the insert into the eye. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations.

The panel of genotoxicity tests performed by the Sponsor included the bacterial mutation test, mammalian cell mutation test and a mouse micronucleus test. Fluocinolone acetonide did not show any evidence of genotoxic

activity in these tests when tested in accordance with regulatory guidelines. No carcinogenicity studies were conducted for ILUVIEN. Reproductive and developmental toxicity studies with ILUVIEN were not conducted.

5. Clinical/Statistical - Efficacy

The application is supported by two adequate and well controlled studies, identified as FAME studies A and B. These clinical trials were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period.

The primary endpoint described in each protocol was for either dose (0.19 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline. When the data was analyzed by the Agency, although each protocol met its primary endpoint, the results were confounded by the development of cataracts in many patients. When the studies failed to demonstrate a clinically significant difference at 36 months, the applicant proposed a subpopulation of patients who had reported a diagnosis of Diabetic Macular Edema (b) (4)

With the approval of multiple products for the treatment of DME and the demonstration in published studies that the failure to treat DME may lead to permanent visual loss, patients in the United States are expected to be treated earlier than in the past. (b) (4) In addition, while patients with a longer history of diabetic macular edema had a higher percentage of three line increases with this product, avoiding the risk of permanent visual loss associated with this longer edema history outweighs this 3 line difference in acuity. The same logic is true of treating phakic patients. While phakic patients are likely to develop cataracts during treatment and will need cataract surgery to recover their vision, the potential negative consequences of not being treated outweigh delaying treatment until the phakic patient has a cataract.

The likely rise in intraocular pressure represents a separate safety risk. To the extent that it can be predicted, it is best predicted by prior use of corticosteroids. Work by Mansour Armaly, MD and others approximately 50 years ago demonstrated genetic factors were associated with predicting IOP elevations following corticosteroid use. Prior corticosteroid use is usually considered the best predictor of future elevated IOP following corticosteroid use.

The Agency therefore recommended that the applicant's indication be modified to "ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure." The revised indication will allow clinicians to assess the response of a previously administered corticosteroid, but will not otherwise suggest a delay in treatment. The applicant has accepted this indication.

The complete response addressed the Agency observation that 11/58 or approximately 19% of the observer questionnaires in an observation study noted that there were observed difficulties with study drug administration. The applicant responded that they had received marketing authorization for ILUVIEN in several countries in Europe in 2012 and the product was launched in the United Kingdom and Germany in the spring of 2013. As part of the product launch, hands-on training was provided to the physicians along with a training kit which included an applicator (without an implant) with a 25-gauge needle, an illustrated Administration Guide, an animated Administration DVD and a Practice Eye.

For the period ending January 31, 2014, at least 269 units of ILUVIEN were used that contained the European Union instructions. Of the 269 units of ILUVIEN administered with the new instructions, 9 technical complaints were received for a technical complaint rate of 3.3%. This is a notable improvement over the technical complaint rate of 19% for issues observed with administration in the physician utilization study provided in the information to the FDA.

For the US proposed package insert, the instructions were revised to address the issues observed in the study and reported during the initial marketing in Europe and the United Kingdom.

The applicant has satisfactorily addressed the issues listed in the FDA's Complete Response Letter of October 17, 2013.

6. Safety

The results from two Fame studies (Fame A and Fame B) form the basis for the safety evaluation. The exposure of subjects was adequate. A total of 953 subjects (185, sham; 375, 0.19 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the Fame studies. The total number of treatments administered during the studies was 252, 488, and 534 in the sham, 0.19µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for the 0.19 µg/day group and 1.4 for the sham and 0.5 µg/day groups. A summary of the adverse events observed during the development and early marketing of ILUVIEN is shown below.

Common Ocular Adverse Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

Most Common Events reported	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
	0 19 FA (N=375) N (%)	0 5 FA (N=393) N (%)	0 19 FA (N=20) N (%)	0 5 FA (N=17) N (%)	0 19 FA (N=10) N (%)	0 5FA (N=7) N (%)	0 19 FA (N=14) N (%)	0 5 FA (N=6) N (%)	0 19 FA (N=120) N (%)
Cataract operation	188 (50.1)	231 (58.8)	13 (65)	5 (29.4)	3 (30)	2 (29)	3 (21)	3 (50)	5 (4.2)
Cataract	171 (45.6)	213 (54.2)	11 (55)	4 (23 5)	3 (30)	2 (29)	2 (14)	4 (67)	12 (10.0)
Intraocular pressure increased	132 (35.2)	170 (43.3)	4 (20)	7 (41.2)	1 (10)	3 (43)	3 (21)	0	15 (12.5)
Myodesopsia	67 (17.9)	68 (17.3)	7 (35)	6 (35.3)	2 (20)	1 (14)	2 (14)	1 (17)	6 (5.0)
Eye pain	51 (13.6)	65 (16.5)	4 (20)	2 (11.8)	1 (20)	0	3 (21)	1 (17)	11 (9.2)
Conjunctival hemorrhage	43 (11.5)	50 (12.7)	7 (35)	7(41.2)	2 (20)	1 (14)	1 (7)	1 (17)	28 (23.3)
Vitreous hemorrhage	41 (10.9)	48 (12.2)	0	0	0	0	0	0	8 (6.7)
Visual acuity reduced	39 (10.4)	35 (8.9)	0	1 (5.9)	0	0	1 (7)	0	6 (5.0)
Posterior capsule opacification	32 (8.5)	25 (6.4)	2 (10)	1 (5.9)	0	0	0	0	1 (0.8)
Cataract subcapsular	28 (7.5)	24 (6.1)	1 (5)	3 (17.6)	0	1 (14)	1 (7)	0	3 (2.5)
Vision blurred	28 (7.5)	20 (5.1)	1 (5)	1 (5.9)	0	0	0	0	3 (2.5)
Eye irritation	27 (7.2)	22 (5.6)	1 (5)	2 (11.8)	1 (10)	0	1 (7)	0	2 (1.7)
Vitreous detachment	26 (6.9)	20 (5.1)	2 (10)	1 (5.9)	0	1 (14)	1 (7)	0	3 (2.5)
Dry eye	23 (6.1)	22 (5.6)	1 (5)	2 (11.8)	1 (10)	1 (14)	1 (7)	1 (17)	5 (4.2)
Maculopathy	23 (6.1)	34 (8.7)	4 (20)	0	0	0	0	0	5 (4.2)
Glaucoma	19 (5.1)	18 (4.6)	1 (5)	1 (5 9)	0	0	0	0	3 (2.5)
Vitrectomy	19 (5.1)	23 (5.9)	1 (5)	0 (0.0)	0	0	0	0	0
Visual impairment	13 (3.5)	31 (7.9)	0	2 (11.8)	2 (20)	1 (14)	0	0	2 (1.7)
Trabeculectomy	10 (2.7)	22 (5.6)	1 (5)	2 (11.8)	0	0	0	0	0

Reported Systemic Events – The following systemic adverse events were reported in 5% or more of patients in the FAME Studies

	0.19 µg	0.5 µg	Sham
	(N=375)	(N=393)	(N=185)
Hypertension	44 (11.7%)	57 (14.5%)	31 (16.8%)
Anemia	33 (8.8%)	45 (11.5%)	10 (5.4%)
Headache	31 (8.3%)	21 (5.3%)	10 (5.4%)
Nausea	28 (7.5%)	30 (7.6%)	18 (9.7%)
Renal failure	27 (7.2%)	32 (8.1%)	10 (5.4%)
Pneumonia	24 (6.4%)	15 (3.8%)	5 (2.7%)
Hypercholesterolemia	24 (6.4%)	24 (6.1%)	13 (7.0%)
Gastrooesophageal reflux disease	22 (5.9%)	26 (6.6%)	11 (5.9%)
Nasopharyngitis	22 (5.9%)	24 (6.1%)	13 (7.0%)
Urinary tract infection	21 (5.6%)	23 (5.9%)	11 (5.9%)

Of the systemic events reported in more than 5% of patients, only anemia, headache, renal failure and pneumonia were reported more frequently in the 0.19 µg group than in the Sham group.

Post-Marketing Experience
ILUVIEN received marketing authorization in several countries in Europe in 2012 and was launched in the United Kingdom and Germany in the second quarter of 2013. The information provided in this safety update includes all data received as of January 31, 2014. Patient exposure is estimated based on the number of units sold as of January 31, 2014. It is assumed that (b) (4) patients were treated with ILUVIEN.

A total of ten (10) spontaneous adverse event reports were received. Eight (8) of these reports were drug administration error. Two (2) serious adverse event reports of the drug being ineffective were also reported.

Safety Summary:
The adverse event profile was consistent other ophthalmic corticosteroids.

7. Pediatrics

Pediatric subjects were not studied. It would be impossible or highly impractical to conduct a clinical study with a significant number of pediatric subjects because diabetic macular edema is rare in the pediatric population. The request to waive an assessment of pediatric patients because studies would be impossible or impractical was reviewed by the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

8. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. The DSI Clinical Inspection Summary was finalized on 12/1/10. Two sites were selected for inspection, due to enrollment of large numbers of study subjects, high number of INDs and a lack of previous inspectional history. Although regulatory violations were noted at both of these sites, given the nature of the findings, DSI considered it unlikely that data reliability

would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

Dr. Blackburn (Study C-01-05-001B /Site 001/17) failed to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Dr. Garg (Study C-01-05-001A /Site 016/ 45) failed to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided. Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name ILUVIEN under IND 72,056. The DMEPA review dated 6/15/10, did not identify any concerns, and the name was found acceptable. In a review dated 10/13/10, there were no concerns identified, and the name was found acceptable. In a review dated 8/1/14, there were no concerns identified, and the name was found acceptable. DMEPA provided tray and carton labeling comments in a review dated 8/5/14. These were combined with other discipline's comments as appropriate and sent to the applicant on 8/15/14.

9. Labeling

Labeling has been reviewed by the members of the review team and labeling recommendations were provided to the applicant in August 2014. The applicant submitted revised labeling consistent with the Agency's recommendations on August 27, 2014. I consider the labeling submitted on August 27, 2014, and listed below to be acceptable, although I note that other members of the review team have asked for additional changes.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

10. Regulatory Action

With the labeling included in this review, NDA 201923 ILUVIEN (fluocinolone acetonide intravitreal insert) 0.19 mg is recommended for approval for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

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/s/

WILEY A CHAMBERS
09/16/2014

Medical Officer Review - NDA 201923

Date	August 13, 2014
From	Martin P. Nevitt, M.P.H., M.D.
Subject	Medical Officer Review of Complete Response
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	March 26, 2014
PDUFA Goal Date	September 26, 2014
Type of Application	NDA
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Recommended:	Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well-established active ingredient currently marketed as topical dermal, otic, and ophthalmic products including an ophthalmic product where it is an intravitreal implant [i.e. Retisert (fluocinolone acetonide intravitreal implant) 0.59mg].

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal implant which releases fluocinolone acetonide (FA) and has been developed for the treatment of diabetic macular edema. Iluvien has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated by the applicant that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter. The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

Iluvien (fluocinolone acetonide intravitreal insert) is approved in Austria, France, Germany, Portugal and Spain. The UK's National Institute for Health and Care Excellence (NICE) issued a draft guidance for Iluvien (fluocinolone acetonide intravitreal insert) and recommended it for the treatment of pseudophakic patients with chronic diabetic macular edema (DME) considered unresponsive to available therapies.

2. Background

Diabetic macular edema (DME), a serious, chronic, debilitating disease, is one of the causes of vision loss associated with diabetic retinopathy.

Drugs currently approved for the treatment of DME are insulin, Lucentis (ranibizumab injection) and Ozurdex (dexamethasone intravitreal implant) 0.7 mg.

I. Applicant's Pre-NDA Regulatory History

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008 and a Pre-NDA meeting was held on March 4, 2010.

II. Original NDA submission

NDA 201923 was submitted June 30, 2010, as a Priority review with a PDUFA goal date of December 30, 2010.

A Complete Response action was taken December 22, 2010, outlining that the application could not be approved in its present form.

III. Applicant's response to Agency's December 22, 2010, Complete Response Letter

On May 12, 2011 the applicant submitted its response to the action taken on December 22, 2010, which included the requested 36 Month data.

Based on the information submitted a Complete Response action was taken on November 11, 2011, outlining that the application could not be approved in its present form.

IV. Applicant's Re-submission dated April 17, 2013

On April 17, 2013 the applicant submitted its response to the action taken on November 11, 2011, which provided additional information and modified the indication to:

(b) (4)

V. July 26, 2013 Type B Meeting

The Applicant requested a meeting with the FDA during the review of the November 11, 2011, Complete Response and a Type B meeting was granted and held on July 26, 2013.

Based on additional discussions during the review cycle with the FDA the indication was further modified to:

(b) (4)

Based on the information submitted in the April 17, 2013 submission, a Complete Response action was taken on October 10, 2013, outlining that the application could not be approved in its present form.

VI. Applicant's Re-submission dated March 26, 2014

On March 26, 2014, the applicant submitted their response to the action taken on October 10, 2013, seeking approval for its 36 month extended daily release formulation of Iluvien. In the March 26, 2014, submission, the applicant responded to FDA's Complete Response letter (refer to Section 7.0 of this reveiw) and further revised the indication to:

[redacted] (b) (4)

Reviewer's comments:

Based on this Medical Officer's review of the information submitted to this application to date, it is recommended that the applicant's proposed indication be modified to the following:

ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

3. CMC

Refer to CMC review.

4. Nonclinical Pharmacology/Toxicology

The original Pharmacology Toxicology Review finalized 11/17/10 recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 11/18/2010:

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.

6. Sterility Assurance

Refer to the Product Quality Microbiology review.

7. Clinical/Statistical – Efficacy

See previous Medical Officer reviews dated 12/20/2010, 9/13/2011 and 9/9/2013.

Background

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness $\geq$ 250 microns. The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day over 36 months.

Applicant's responses submitted March 26, 2014 to FDA's Complete Response Letter of October 10, 2013

(Note: FDA's comments within this section may be abbreviated from the Complete Response comments originally sent to the Applicant).

Comment 1 A – Appropriateness of the Study Population

FDA's Complete Response comment in October 10, 2013 letter:

You have now proposed to revise your indication (b) (4)

Applicant's comment:

The following revised indication is proposed:

(b) (4)

Reviewer's comments:

Based on this Medical Officer's review of the information submitted to this application to date, it is recommended that the applicant's proposed indication be modified to the following:

ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Based on the revised indication, Comment 1 A is no longer an outstanding issue.

Comment 1 B – Impact of IOP Increases

FDA's Complete Response comment in October 10, 2013 letter:

The results of the safety analyses of your Phase 3 clinical trials submitted to this NDA have demonstrated elevations of intraocular pressure of such magnitude as to require medical or surgical treatment.

Applicant's comment:

Increase in intraocular pressure is a class related side-effect associated with administration of corticosteroids to the eye by any route. This unwanted effect can be detected, and monitored and, in the vast majority of cases, controlled by pharmacologic treatment.

Reviewer's comments:

Those subjects previously treated with a steroid and who experienced IOP pressure spikes can be excluded from receiving Iluvien (a 36 month steroid treatment).

[redacted] (b) (4) *there is no longer an outstanding issue for Comment 1 B.*

Comment 1 C – Impact of Cataract Formation

FDA's Complete Response comment in October 10, 2013 letter:

Results of the safety analyses of your Phase 3 clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien.

Applicant's comment:

The Applicant [redacted] (b) (4) mitigates the risk of ILUVIEN associated with cataract surgery.

Reviewer's comments:

Based on this Medical Officer's review of the information submitted to this application to date, it is recommended that the applicant's proposed indication be modified to the following:

ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Steroids have a class labeling statement where it is noted that steroids cause cataract formation. It is recommended subjects who are phakic be eligible for the treatment.

[redacted] (b) (4) *there is no longer an outstanding issue for Comment 1 C.*

Comment 1 D – Analysis by the Duration of Diagnosis of Diabetic Macular Edema

FDA's Complete Response comment in October 10, 2013 letter:

You subsequently stated that you interrogated the data based on the duration of DME and analyzed two separate (complementary) subsets of patients [redacted] (b) (4)

Applicant's comment:

Given the statistically significant results for the primary efficacy endpoint in the FAME trials, and at the suggestion of the Agency, the FAME data were further interrogated to determine if a subgroup existed for which the benefit/risk calculus for ILUVIEN was favorable.
One such subgroup was based on an analysis of the primary measure of efficacy as a function of the median duration of diagnosis of DME; this resulted in a median duration of diagnosis of DME of 1.73 years.

Data from pseudophakic subjects with ≥15-letter improvement from baseline in best corrected visual acuity will be stratified by duration of diabetic macular edema subgroup (<1.73 years vs. >1.73 years), with chronic DME being defined based on the median of 1.73 years.

Reviewer's comments:

Based on this Medical Officer's review of the information submitted to this application to date, it is recommended that the applicant's proposed indication be modified to the following:

ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

(b) (4) *there is no longer an outstanding issue for Comment 1 D.*

Comment 1 E – Summary of Technical Complaints

FDA's Complete Response comment in October 10, 2013 letter:

In your current resubmission, you provided a summary of the most recent results from the use of the to-be-marketed Iluvien inserter.

We have reviewed the data provided in the submission for these additional 58 patients in whom the inserter from the third batch was used, and note that 11/58 or approximately 19% of the observer questionnaires noted that there were observed difficulties with study drug administration. Our review of these results suggests that either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties experienced by investigators in delivering the drug product.

Applicant's comment:

The applicant received marketing authorization for Iluvien in several countries in Europe in 2012 and was launched in the United Kingdom and Germany in the spring of 2013. As part of the product launch, hands-on training was provided to the physicians along with a training kit which included an applicator (without an implant) with a 25-gauge needle, an illustrated Administration Guide, an animated Administration DVD and a Practice Eye.

For the period ending January 31, 2014, at least (b) (4) units of ILUVIEN were used that contained the European Union instructions. Of the (b) (4) units of Iluvien administered with the new instructions, 9 technical complaints were received for a technical complaint rate of 3.3%. This is a notable improvement over the technical complaint rate of 19% for issues observed with administration in the physician utilization study provided in the information to the FDA.

Of the nine technical complaints, one complaint was due to the implant falling out of the needle. Two complaints were due to reports of a blunt or dull needle though microscopic examination of the returned units showed that the needles met specifications, and three complaints were related to difficulty in advancing the button.

- Issue: Implant prematurely exiting the needle prior to insertion.

Applicant comment:

Once the applicator is actuated to load the implant inside the needle, if the needle is pointed downwards, it is possible for the implant to fall out; therefore it is important to keep the applicator above the horizontal plane and to keep the protective cap on.

For the US proposed package insert, the following instructions are provided:

The protective cap on the needle should not be removed until ILUVIEN is to be injected. Prior to injection, the applicator tip must be kept above the horizontal plane to ensure that the implant is properly positioned within the applicator.

Reviewer's comments:

The instructions to be provided in the US package insert are acceptable.

- Issue: Blunt or dull needle.

Applicant comment:

During manufacturing, needles are inspected 100% to ensure they meet specifications. However, damage can occur either when the cap is placed or when removed, therefore it is important that the physician inspects the needle prior to injecting.

For the US proposed package insert, the following instruction is provided:

Carefully remove the protective cap from the needle and inspect the tip to ensure it is not bent.

Reviewer's comments:

The instructions to be provided in the US package insert are acceptable

- Issue: Resistance associated with advancement of the injector button.

Applicant Comment:

After the first step, the button should move to the UP position; it will not move forward if pushed down during the second step. The button should be slid forward completely while it is in the UP position.

For the US proposed package insert, the following instructions are provided:

To reduce the amount of air administered with the implant, the administration procedure requires two steps. Before inserting the needle into the eye, push the applicator button down and slide it to the first stop (at the curved black marks alongside the button track). At the first stop, release the button and it will move to the UP position. If the button does not rise to the UP position, do not proceed with this unit.

Gently displace the conjunctiva so that after withdrawing the needle, the conjunctival and scleral needle entry sites will not align. Care should be taken to avoid contact between the needle and the lid margin or lashes. Insert the needle in the eye. To release the implant,

while the button is in the UP position, advance the button by sliding it forward to the end of the button track and remove the needle. Note: Ensure that the button reaches the end of the track before removing the needle.

Reviewer's comments:

The instructions to be provided in the US package insert are acceptable.

- Issue: Implant not delivered inside the eye or stuck in the needle.

  Applicant Comment:

  It is important that the button is slid forward all the way to the end to ensure the implant is pushed out of the needle into the eye.

  For the US proposed package insert, the following instruction is provided:

  To release the implant, while the button is in the UP position, advance the button by sliding it forward to the end of the button track and remove the needle. Note: Ensure that the button reaches the end of the track before removing the needle.

  Reviewer's comments:

  The instructions to be provided in the US package insert are acceptable.

  Based on the information provided in this complete response, there is no longer an outstanding issue for Comment 1 C which would preclude approval of this application.

  While the technical complaint rate has been reduced, rigorous training is still recommended especially for first time users.

8. Safety

120 Day Safety Update Review

No additional safety information for the FAME studies is available.

Safety results for the FAMOUS study and Study NA-00012714 (the MAP study), an investigator-sponsored study, were submitted in Alimera's response to the FDA's second CRL and were based on final 36-month data for those studies. No additional information is available.

Safety Update information for the additional studies is provided in the following tables.

1) Study C-01-11-008 (FAME Extension Study)

The FAME Extension Study (Study C-01-11-008) is a 12 month, open-label, multi-center extension study of the safety and utility of the new applicator of ILUVIEN® (FA intravitreal implant) 0.19 mg (0.2 μg/day FA) and the safety of ILUVIEN in subjects with DME.

2) Safety Update for Study C-01-08-004 (the MAP-GA Study)

The MAP-GA study (Study C-01-08-004) was a single-center, randomized, single- masked, fellow eye comparison study of the effects of FA implants in subjects with geographic atrophy.

This study was terminated in October 2013.

3) Safety Update for Study C-01-08-006 (the FAVOR Study)

The FAVOR study (Study C-01-08-006) was a multicenter, randomized, double-masked study of the effects of 0.2 µg/day FA and 0.5 µg/day FA in subjects with central or branch retinal vein occlusion (CRVO or BRVO).

This study was terminated in October 2013.

Table 1.
Common Ocular Adverse Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
Most Common Events[1]	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)	0.2 µg/day FA (N = 20) n (%)	0.5 µg/day FA (N = 17) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 7) n (%)	0.2 µg/day FA (N = 14) n (%)	0.5 µg/day FA (N = 6) n (%)	0.2 µg/day FA (N = 120) n (%)
Cataract	171 (45.6)	213 (54.2)	11 (55.0)	4 (23.5)	3 (30.0)	2 (28.6)	2 (14.3)	4 (66.7)	12 (10.0)
Cataract operation	188 (50.1)	231 (58.8)	13 (65.0)	5 (29.4)	3 (30.0)	2 (28.6)	3 (21.4)	3 (50.0)	5 (4.2)
Cataract subcapsular	28 (7.5)	24 (6.1)	1 (5.0)	3 (17.6)	0 (0.0)	1 (14.3)	1 (7.1)	0 (0.0)	3 (2.5)
Conjunctival haemorrhage	43 (11.5)	50 (12.7)	7 (35.0)	7 (41.2)	2 (20.0)	1 (14.3)	1 (7.1)	1 (16.7)	28 (23.3)
Dry eye	23 (6.1)	22 (5.6)	1 (5.0)	2 (11.8)	1 (10.0)	1 (14.3)	1 (7.1)	1 (16.7)	5 94.2)
Eye irritation	27 (7.2)	22 (5.6)	1 (5.0)	2 (11.8)	1 (10.0)	0 (0.0)	1 (7.1)	0 (0.0)	2 (1.7)
Eye pain	51 (13.6)	65 (16.5)	4 (20.0)	2 (11.8)	2 (20.0)	0 (0.0)	3 (21.4)	1 (16.7)	11 (9.2)
Glaucoma	19 (5.1)	18 (4.6)	1 (5.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Intraocular pressure increased	132 (35.2)	170 (43.3)	4 (20.0)	7 (41.2)	1 (10.0)	3 (42.9)	3 (21.4)	0 (0.0)	15 (12.5)
Maculopathy	23 (6.1)	34 (8.7)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.2)
Myodesopsia	67 (17.9)	68 (17.3)	7 (35.0)	6 (35.3)	2 (20.0)	1 (14.3)	2 (14.3)	1 (16.7)	6 (5.0)
Posterior capsule opacification	32 (8.5)	25 (6.4)	2 (10.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Trabeculectomy	10 (2.7)	22 (5.6)	1 (5.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vision blurred	28 (7.5)	20 (5.1)	1 (5.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Visual acuity reduced	39 (10.4)	35 (8.9)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	6 (5.0)
Visual impairment	13 (3.5)	31 (7.9)	0 (0.0)	2 (11.8)	2 (20.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (1.7)
Vitrectomy	19 (5.1)	23 (5.9)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitreous detachment	26 (6.9)	20 (5.1)	2 (10.0)	1 (5.9)	0 (0.0)	1 (14.3)	1 (7.1)	0 (0.0)	3 (2.5)
Vitreous haemorrhage	41 (10.9)	48 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (6.7)

1 Ocular events with an incidence ≥ 5.0 % in either active treatment group in the integrated FAME studies. Incidence was based on occurrence in the study eye.

Summary of IOP- and Cataract-Related Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
Event	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)
IOP-Related Events	**N=375**	**N = 393**	**N = 20**	**N = 17**	**N = 10**	**N = 7**	**N = 14**	**N = 6**	**N = 120**
IOP elevation considered an AE[1]	139 (37.1)	179 (45.5)	4 (20.0)	7 (41.2)	1 (10.0)	3 (42.9)	3 (21.4)	0 (0.0)	21 (17.5)
IOP elevation ≥ 12 mmHg from baseline	108 (28.8)	135 (34.4)	2 (10.0)	6 (35.3)	0 (0.0)	1 (14.3)	1 (7.1)	0 (0.0)	13 (10.8)
IOP elevation to over >25 mmHg	123 (32.8)	166 (42.2)	3(15.0)	8 (47.1)	0 (0.0)	2 (28.6)	3 (21.4)	0 (0.0)	25 (20.8)
IOP elevation to over >30 mmHg	69 (18.4)	90 (22.9)	1(5.0)	6 (35.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	12 (10.0)
Trabeculoplasty	5 (1.3)	10 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (0.8)
Trabeculectomy	10 (2.7)	22 (5.6)	1(5.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glaucoma surgery[2]	8 (2.1)	13 (3.3)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Vitrectomy performed for elevated IOP	1 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any surgical intervention	1 (0.5)	18 (4.8)	1 (0.5)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)

	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
Event	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)
n (%) of Phakic Subjects/Eyes									
Cataract-Related Events	**N=235**	**N = 265**	**N = 14**	**N = 8**	**N = 4**	**N = 2**	**N = 7**	**N = 4**	**N = 33**
Cataract considered to be an AE	192 (81.7)	235 (88.7)	12 (85.7)	7 (87.5)	3 (75.0)	2 (100)	3 (42.9)	4 (100)	15 (45.5)
Cataract Extraction	188 (80.0)	231 (87.2)	13 (92.9)	5 (62.5)	3 (75.0)	2 (100)	3 (42.9)	3 (75.0)	5 (15.2)

1 Includes adverse event reports of ocular hypertension and intraocular pressure increased
2 Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocyclodestruction, laser peripheral iridotomy

Post-Marketing Experience

ILUVIEN received marketing authorization in several countries in Europe in 2012 and was launched in the United Kingdom and Germany in the second quarter of 2013. The information provided in this safety update includes all data received as of January 31, 2014.

Patient exposure is estimated based on the number of units sold as of January 31, 2014. It is assumed that (b) (4) patients were treated with ILUVIEN.

A total of ten (10) spontaneous adverse event reports were received. Eight (8) of these reports were drug administration error, related to product complaints and were considered non-serious (Refer to Section 7. Comment 1 E – Summary of Technical Complaints for a complete review of these issues).

Two (2) serious adverse event reports of the drug being ineffective were also reported.

Reviewer's comments:

The adverse events of increased IOP and cataract formation are also evident in these additional trials. Based on all safety data collected to date, the safety profile of ILUVIEN is expected and typical of profiles observed with glucocorticoids.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held during this review cycle.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

None.

12. Labeling

ILUVIEN is recommended for approval with the revised labeling found in this review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION AND CONCLUSION:

Based on the risk/benefit of this drug, NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg, is recommended for approval with the following revision to the proposed indication:

ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

The recommendation for this approval is based on the risk/benefit of the drug:

- Steroids have a Class labeling effect where it is known that steroids cause IOP elevation and cataract formation. Cataract formation is a known risk of steroid therapy and subjects who are phakic are eligible for the treatment.

- The revised label reduces the risk of treating subjects who experience a spike in IOP elevation when treated with a steroid. Only subjects that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure will be recommended to have the treatment.

Only those subjects that have had previous steroid treatment for DME and did not have a clinically significant rise in intraocular pressure are recommended to receive Iluvien.

The benefits outweigh the risks in the indicated population (i.e. use in subjects that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure) with the revised package insert.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MARTIN P NEVITT
08/21/2014

WILLIAM M BOYD
08/22/2014

Summary Review for Regulatory Action #2

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review #2
NDA Number	NDA 201923
Related IND	IND 72,056
Applicant Name	Alimera Sciences, Inc.
Date of Original Submission **Complete Response Letter** **Date of Resubmission, Class 2** **Complete Response Letter #2** **Date of Resubmission, Class 2** **PDUFA Goal Date**	June 30, 2010 (priority review) December 22, 2010 May 12, 2011 November 10, 2011 April 17, 2013[1] October 17, 2013
Application Type	505(b)(1)
Proprietary Name / **Established (USAN) Name**	Iluvien Fluocinolone acetonide intravitreal insert
Formulation **Dose**	Intravitreal Insert (non-biodegradable/non-bioerodable) 0.19 mg
Proposed Indication(s)	Treatment of diabetic macular edema[2]
Action for Application	*Complete Response*

[1] The resubmission was received on April 17, 2013. An earlier document sent on March 27, 2013 was considered incomplete because it indicated that unaudited data were included in the resubmission, therefore an "acknowledge incomplete response" letter was issued by the Division on April 10, 2013. The applicant stated the information was in error, and sent a corrected submission on April 17, 2013. Of note, some of the primary reviews for this resubmission cite the March 27, 2013 date instead of the April 17, 2013 date.

[2] In the current resubmission, the applicant has proposed to revise the indication t (b) (4)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**	**Discipline-specific recommendation regarding application**
Medical Officer Review	Martin Nevitt, Bill Boyd, Wiley Chambers 12/20/2010, 9/13/2011, 9/9/2013	Deficiencies
CDTL Review	Bill Boyd 12/22/2010, 10/27/2011, 10/17/2013	Deficiencies
Deputy Director	Wiley Chambers 12/22/2010, 10/19/2011, 10/17/2013	Deficiencies
Statistical Review	Rima Izem, Yan Wang 11/30/2010, 8/1/2011, 6/20/2012 Dongliang Zhuang 9/272013	No new studies
Clinical Pharmacology Review	Yongheng Zhang, Charles Bonapace 11/18/2010, Yongheng Zhang, Philip Colangelo, 6/28/2011, 10/07/2013	Adequate
Pharmacology/Toxicology Review	Conrad Chen, Wendelyn Schmidt 11/17/2010	Adequate
OC/OMPQ/DGMPA	Juandria Williams, Tara Gooen 10/15/2013	Withhold
ONDQA/DNDQA II, Branch V Review EA	Lin Qi, Rapti Madurawe 7/22/2011, 9/30/2011 Lin Qi, Balajee Shanmugan 9/24/2013, 10/15/2013 Dorota Matecka, Stephen Miller 12/1/2010	Deficiencies – OC recommendation of Withhold
ONDQA Biopharmaceutics	Tapash Ghosh, Patrick Marroum 6/27/2011 Tapash Ghosh, John Duan 9/23/2013	Adequate
Product Quality Microbiology Review	Steven Fong, John Metcalfe 12/8/2010, 2/9/2011, 7/25/2011	Adequate
OSI/DGCPC	Kassa Ayalew, Tejashri Purohit-Sheth 12/1/2010	Adequate
OSE/DMEPA Proprietary Name	Denise Toyer 10/13/2010 (tentatively acceptable)	Adequate
CDRH Consult	Nikhil Thakur	Unacceptable
Advisors and Consultants Staff	Dermatologic and Ophthalmic Advisory Committee meeting planning underway	

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
ONDQA/DNDQA = Office of New Drug Quality Assessment, Division of New Drug Quality Assessment
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OC=Office of Compliance, OMPQ =Office of Manufacturing and Product Quality DGMPA = Division of Good Manufacturing Practice Assessment

Table of Contents:

Introduction:

The NDA 201923 application by Alimera is now in its third review cycle. The comprehensive history of this development is included in the primary reviews of the application. As summarized below, the main deficiencies identified in this application relate to (a) the clinical risk benefit interpretation where the Division has concluded that the benefit of the product does not outweigh the risk while Alimera does not agree with that interpretation and (b) manufacturing deficiencies at the [redacted] (b) (4) drug product manufacturing site which had a 16 item 483 issued and a recommendation of Withhold approval made by the Office of Compliance.

As noted in the Clinical reviews, "Diabetic macular edema (DME), a serious, chronic, debilitating disease, is one of the causes of vision loss associated with diabetic retinopathy." Thus the Division is not dismissing this condition or under-appreciating the significance of this disease, a concern expressed by the applicant.

In the September 9, 2013 amendment, Alimera proposed yet another revision to the indication; however, no new clinical studies have been submitted:

[redacted] (b) (4)

Additional issues identified include (c) change in the proposed inserter for the Illuvien insert and technical problems associated with administration of the product, (d) change in the proposed indication and absence of a clinical trial(s) in that proposed indication/patient population.

For a detailed discussion of the Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg drug development program, including preclinical and clinical studies, and product quality, the reader is referred to the individual review documents archived in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS). Briefly clinical studies of the 0.19 mg insert tested two doses based on the initial release rates of 0.2 or 0.5 µg/day, respectively, the lower dose is sought for approval.

This document summarizes some of the highlights from these reviews, provides an overview of the clinical trial results and discussion of risks and benefits, and summarizes the outstanding deficiencies which form the basis of the *Complete Response* action for this review cycle.

On October 16, 2013, the Division, OAP and OND met with the applicant to discuss the clinical and manufacturing deficiencies, and responded to the applicant's question about extending the PDUFA goal date and plans for an Advisory Committee (see meeting minutes). Briefly, the applicant was told the amendment submitted September 9, 2013 would be reviewed in the current cycle and the content did not meet "major amendment" designation; in addition the outstanding facility inspection deficiencies would not likely be addressed within this cycle. The applicant was interested in the advisory committee and there was discussion that the meeting could take place "off the clock." There was minimal discussion of the clinical deficiencies although the applicant expressed their disagreement with the Divisions of the risk/benefit interpretation of the findings and felt strongly the benefit outweighed risks for Iluvien. The applicant committed verbally to resolving the manufacturing issues with the [redacted] (b) (4). The FDA

suggested that the applicant obtain a letter of authorization from [redacted] which would then enable the FDA (Office of Compliance, the district, etc) to communicate with Alimera as well as [redacted] to resolve the manufacturing issues. After discussing options, Alimera expressed a preference to hold the advisory committee in January 2014 and not postponing it until manufacturing issues were resolved.

1. Summary and Recommendations

Based on the review of NDA 201923, including the original submission from June 30, 2010 and the resubmissions on May 12, 2011, April 17, 2013 and the amendment dated September 9, 2013, reviewers concluded that the Phase 3 clinical trials failed to show that fluocinolone acetonide intravitreal insert was safe and effective in the treatment of diabetic macular edema (DME). [redacted] Importantly, the adverse events of cataract formation and surgery, elevated IOP, trabecutomy and glaucoma progression were higher in the Iluvien group than the sham (control) group. Therefore, the risks associated with the use of Iluvien were considered to exceed the degree of benefit.

The applicant conducted an analysis of number needed to treat (NNT) and number needed to harm (NNH) in the patients with history of DME [redacted] however, the Division disagreed with the analyses and conducted an independent analysis. The Division determined that the NNT was approximately 5 patients so 1 patient would benefit, whereas the NNH was 2 patients for 1 to get cataracts and cataract surgery, about 5 for 1 to develop increased IOP. Other serious, less frequent findings were the need for surgical intervention to manage elevated IOP and increase in glaucomatous progression as reported in changes in the optic nerve cup to disc ratio.

In addition, the 483 discussed 16 observational findings and covered a range of manufacturing deficiencies at the [redacted] drug product manufacturing site, including some deficiencies identified during the 2010 and 2011 inspections that had not been addressed to date.

I concur with the review team that there are outstanding clinical and CMC deficiencies and therefore the application will be issued a *Complete Response* letter for this resubmission.

1.1 Deficiencies

The following deficiencies will be communicated to the applicant:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

Specifically, you have not provided data to support that the product is safe and effective (b) (4)

a. You have now proposed to revise your indication (b) (4)

b. The results of the safety analyses of your Phase 3 clinical trials submitted to this NDA[3] have demonstrated elevations of intraocular pressure of such magnitude as to require medical or surgical treatment. In the two trials combined, the percentage of patients in the 0.2 µg/day FA group requiring intraocular pressure (IOP) lowering medications was 38.4% (114/375) and the percentage of patients in the sham group requiring IOP lowering medications was 14.1% (26/185). The difference between the 0.2 µg/day fluocinolone acetonide (FA) group and Sham control was 24.3%. This adds an additional treatment burden to patients who already have to manage their underlying diabetes mellitus and additional risks to these patients from potential adverse drug reactions associated with the use of IOP lowering medications.

The difference between the 0.2µg/day FA and Sham control in the percentage of patients requiring surgical intervention for the reduction of their IOP was 4-5%, therefore a significant percentage of patients with IOP increases required surgical intervention. The surgical risks in these patients and the potential endophthalmitis risks associated with filtering surgery are significant additional risks.

The "Special Optic Nerve Head Assessment of the Fame Fundus Photographs by the (b) (4) - Table 6" demonstrated an imbalance at month 36 in the percentage of patients with a worsening in the vertical cup-to-disc ratio (C/D). Eleven patients out of 219 patients (5%) in the 0.2µg/day FA

[3] Two controlled clinical trials: C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B)

group had worsening of their vertical C/D, compared to only one patient out of 102 patients (1%) treated with Sham. The reported 95% confidence interval (-7.5%, -0.6%) excluded zero. This finding of glaucomatous progression of the C/D ratio in association with a three-fold increase in the rate of elevated IOP in the FA group in these 3 years trials is a concern about the relative safety of this product.

c. Results of the safety analyses of your Phase 3 clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. At 36 months follow-up, cataract progression occurred in 82% in the 0.2 µg/day FA study eyes versus 50% of the Sham group study eyes, for a difference of approximately 32%. Cataract operation occurred 80% in the 0.2 µg/day FA study eyes versus 27% of the Sham group study eyes, for a difference of approximately 53%. Many of the patients developing cataracts experienced a clinically significant loss in visual acuity, including a loss in vision of 15 letters or more, which was documented at one or more of the scheduled quarterly visits. While many patients had restoration of their visual acuity after a cataract extraction and intraocular lens placement, not all patients had improvement in their visual acuity after the surgical procedure. In addition, a number of patients failed to return for follow-up examinations after cataract removal, therefore their visual acuity after cataract surgery is unknown.

d. In support of your application you initially submitted an analysis of results based on the primary endpoint of visual acuity at 24 months, Full Analysis Set, and efficacy rates were 26-31% in the FA patients versus 15-18% in the sham control. The interpretation of these results was difficult because of the timing of the development of cataracts and the time needed for post-operative recovery. Therefore, you subsequently provided the results of the trials when 36 months of data were available. The analysis of these results showed that at Month 36, there was no statistically significant difference (benefit) in the patients with DME enrolled in your studies (FAME A and FAME B).

At 36 months, the rates for the number of subjects in the Full Analysis Set who gained ≥ 15-letters from baseline in best corrected visual acuity (BCVA) in the study eye were 28%-29% in the 0.2 µg/day FA and (b) (4)% in both Sham arms. This difference was not statistically significant. (b) (4) A was not shown to have a benefit in the treatment of DME, and had a significant risk of serious adverse reactions.

You subsequently stated that you interrogated the data based on the duration of DME and analyzed two separate (complementary) subsets of patient (b) (4) We acknowledge that this analysis is presented in your May 12, 2011, resubmission. We have previously noted that this subset analysis was not included in the protocol(s) for these

trials and was not included in the statistical analysis plan (SAP) for these trials, meaning no provision was included for statistically adjusting for additional analyses (multiplicity).

We also note that in your May 21, 2012, briefing package for the June 19, 2012, meeting you explain that this analysis by duration of DME was requested to be added by a study representative prior to unmasking of the study databases at Month 24. We note that the analysis requested in 2009 was for the effect "above and below median for duration of DME," and that your programmer noted that subgroup analyses should be completed for < median and > median. While the median analysis was provided in the May 21, 2012, submission, [redacted] (b) (4) it is not clear how the [redacted] (b) (4) analyses comply with the analysis requested in 2009.

In the analysis of these two subsets, you reported [redacted] (b) (4)

In addition, [redacted] (b) (4) these differences were not statistically significant.

However, we note that for both [redacted] (b) (4) subgroup of patients, there were comparable degrees of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population, and in both subgroups, these rates were higher in the FA groups compared to Sham control.

We interpreted these results as showing that the risk of the adverse reactions associated with the use of FA exceeded the benefit, for these subsets. This is particularly evident in [redacted] (b) (4)

[redacted] (b) (4)

e. In your current resubmission, you provided a summary of the most recent results from the use of the to-be-marketed Iluvien inserter. In this analysis, you describe that 4 patients received the insert via a "noncommercial" inserter and 117 patients received the insert via a "commercial" inserter. In the text you further explain that the first 4 patients received "the first lot," and after a design improvement a "second lot" was produced and 59 subjects were enrolled. You note that a review of technical complaints for the second lot led to an implementation of a supplementary in-process control, a "third batch" was produced and an additional 58 subjects were enrolled. We have reviewed the data provided in the submission for these additional 58 patients in whom the inserter from the third batch was used, and note that 11/58 or approximately 19% of the observer questionnaires noted that there were observed difficulties with study drug administration. Our review of these results suggests that either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties experienced by investigators in delivering the drug product.

To address the clinical and statistical deficiencies, you will need to provide data from one adequate and well controlled clinical trial that demonstrates that Iluvien, at the dose and formulation proposed for marketing and with the inserter and instructions-for-use proposed to be marketed, is safe and effective for the proposed indication you are seeking (intend to market) and the inserter can be used by practitioners with minimal technical difficulties. It is recommended that the study enroll patients who have failed to respond to a three month or more course of anti-VEGF therapy and are randomized between your drug product and continued anti-VEGF therapy. Results of the new study should be submitted with at least 12 months of follow-up for all enrolled patients. However, given the adverse reaction findings observed in the FAME studies, you should plan to obtain longer follow-up to evaluate safety, including effect on visual acuity. A meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee may be of assistance in addressing these deficiencies and providing guidance whether a patient population can be identified in which the benefits of the drug product might outweigh the risks.

2. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. All facilities and controls will need to comply with the cGMP regulations.

To address this deficiency, please amend the application with facilities that are in compliance with cGMPs or notify us in writing when all currently submitted facilities are in compliance with cGMPs.

3. The study report for Study C-01-11-008 states that a supplementary in-process control during manufacturing of the injector was added, but information on this change is not included in the submission.

To address this deficiency, specific information of this change should be submitted.

1.2 Post-Marketing Studies:

Not applicable at this time

1.3 Other Issues

The Division is working with the Advisors and Consultant Staff to plan a Dermatologic and Ophthalmic Drug Advisory Committee (DODAC) meeting for January 27, 2014.

2. Background

As noted in the Medical Officer Review, diabetic macular edema (DME), a serious, chronic, debilitating disease, is one of the causes of vision loss associated with diabetic retinopathy. There are currently no approved corticosteroids for this condition. Lucentis (ranibizumab) is a VEGF inhibitor that was approved August 10, 2012, following discussion and recommendation for approval at the DODAC on July 26, 2012.

Corticosteroids approved for intravitreal administration for different indications include:

- Ozurdex (dexamethasone intravitreal implant) 0.7 mg for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) and for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The Ozurdex insert is injected into the vitreous with a needle
- Retisert (fluocinolone acetonide intravitreal implant) 0.59mg for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. Retisert insert is surgically implanted into the posterior segment of the eye through a pars plana incision. [4]
- TRIESENCE® (triamcinolone acetonide injectable suspension) for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids and visualization during vitrectomy.

Fluocinolone acetonide is a synthetic glucocorticoid also available in topical dermal and otic products.

Dr. Nevitt reports that Iluvien (fluocinolone acetonide intravitreal insert) is approved in Austria, France, Germany, Portugal and Spain. The UK's National Institute for Health and Care Excellence (NICE) issued a draft guidance for Iluvien (fluocinolone acetonide intravitreal insert) and recommended it for the treatment of pseudophakic patients with chronic diabetic macular edema (DME) considered unresponsive to available therapies.

Iluvien is approved in Europe for the indication:

> Iluvien is indicated for the treatment of vision impairment associated with chronic diabetic macular edema considered insufficiently responsive to available therapies.

[4] Retisert was approved April 8, 2005 under NDA 21-737.

It's proposed that Iluvien be inserted into the posterior segment of the affected eye through a pars plana insertion.

Corticosteroids are associated with development of cataracts and increased intraocular pressure, and predispose patients to infection. These concerns were discussed with Alimera during the development program including the end-of-phase 2 meeting for IND 72,056 on September 2, 2008; however, the company believed that because of the low dose of fluocinolone and rate of release; they would not see these steroid-related adverse events. Now that these adverse reactions have been seen in the Iluvien clinical trials, Alimera's perspective has been that these adverse events are manageable; the cataract surgery can be performed and the IOP lowering medications can be used in patient who have these adverse reactions.

The pre-NDA meeting was held March 4, 2010 and the original NDA 201923 was submitted June 30, 2010, and given a priority review because there were no approved therapies at that time.[5] However, based on review of the application, a Complete Response letter was issued on December 22, 2010, listing clinical/statistical deficiencies such as low, clinically-insufficient efficacy, development of cataracts by 24 months, three-fold increase in IOP, and need for 36 month data to assess risk/benefit. The inserter used in clinical trials was different from the [redacted] inserter proposed for marketing, and the latter was not evaluated in clinical trials of DME. Other deficiencies were identified by the product quality, biopharmaceutics and microbiology disciplines regarding the methods to be used in, and the facilities and controls used for the manufacture, processing, packing, or holding of the drug substance and drug product; these were inadequate to preserve the identity, strength, quality, purity, and stability of the product. Specific concerns included endotoxin testing and limits, [redacted] polymorph testing of the drug substance, identification of inactive components in the drug product, in-vitro release methodology, release rate specifications, [redacted] bioburden testing, hold period, [redacted] Deficiencies were identified during inspections of the [redacted] facilities.

A Type A meeting was held February 2, 2011 which included discussion of how the deficiencies in the December 22, 2010, letter should be addressed, including the clinical trial endpoints and information on the Iluvien inserter.

The applicant sent a resubmission May 12, 2011, and the second complete response letter was issued November 10, 2011. This included both clinical and CMC deficiencies. The applicant had not demonstrated that Iluvien was safe and effective in the FAME A and FAME B studies, and had performed a post-hoc analysis of the data [redacted] The Division noted that the adverse events rates were still higher in this subset that in the control arm, and comparable to the overall study population. It was also noted that [redacted] adverse event rates were higher than in the sham (control) arm and comparable to the overall study population. Two CMC deficiencies were identified: the in-vitro release rate range [redacted] and polymorph testing method was not submitted.

[5] Since then, Lucentis was approved for the treatment of diabetic macular edema.

The applicant sent a resubmission on March 27, 2013, which was not accepted and sent a corrected submission on April 17, 2013. These submissions did not contain new clinical studies; rather, the applicant presented their perspective on the risk/benefit of the product, and submitted a June 19, 2013, briefing backgrounder for the July 26, 2013 meeting with the Agency. On September 9, 2013, the applicant submitted further discussion of the risk/benefit and asked that it be classified a major amendment and the clock be extended to allow for the scheduling of an Advisory Committee meeting. The information was reviewed in the current cycle and the submission did not constitute a major amendment as provided in the GRMP guidance. After the meeting minutes were sent to the applicant, Alimera submitted a September 10, 2013, letter disagreeing with some of the meeting minute content. During this cycle, planning for the Advisory Committee was started but the process is lengthy and the meeting is currently planned for January 27, 2014.

On October 16, 2013, the Agency met with Alimera to provide an update on the deficiencies before the PDUFA goal date. Alimera was asked to provide a letter of authorization from their contract manufacturer, [redacted] or to invite [redacted] to attend the meeting so there could be discussion of the specific manufacturing deficiencies. Alimera did not provide an LOA or invite representatives from [redacted] to the meeting, therefore they could only be told that there were outstanding manufacturing deficiencies, and no details were provided. During the meeting Alimera stated that one of their employees had been present during the Iluvien-specific portion of the inspection.

3. CMC/Product Quality Microbiology

For a complete discussion of the manufacturing of the drug product and drug substance, please refer to the reviews by Dr. Li, Dr. Ghosh and Dr Fong.

The following summary is taken from Dr. Qi's 9/24/2013 review and succinctly summarizes the previous history of this application and CMC issues:

> Iluvien®, (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a non-biodegradable [non-bioerodable] polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to insert it into the ocular vitreous chamber.
>
> The drug substance is a white or almost white, odorless, crystalline powder. It is insoluble in water but soluble in methanol. [redacted] The fluocinolone acetonide drug substance used in clinical trials for this NDA was supplied by [redacted]. The proposed commercial manufacturer is [redacted] For the chemistry manufacturing and controls information for fluocinolone acetonide drug substance, the reference is made to DMF type II [redacted] held by [redacted]
>
> See review #1 dated December 1, 2010 by Dr. Dorota Matecka for a detailed description of the

drug product and drug substance.

The original NDA dated June 28, 2010 was not approved and a complete response letter (CRL) was sent to the applicant with a list of deficiencies on December 22, 2010. Quality deficiencies identified in the CRL are in CMC review #1, biopharmaceutics review #1, and microbiology review #1. The original NDA also received a site recommendation of "Withhold" from the Office of Compliance.

The NDA resubmission dated May 12, 2011 contains a complete response to CMC deficiencies and the updated quality information. The May 12, 2011 resubmission was found inadequate by this reviewer in CMC review #3 dated September 30, 2011 and deficiencies and additional information requests were listed in the review. One CMC deficiency was sent to the sponsor in the CR letter of November 10, 2011.

The NDA resubmission dated March 27, 2013 contains complete response and supporting documents to the CMC deficiency. Upon request, available stability data, revised description of the drug product analysis procedure, and drug product performance study results were provided in an amendment dated July 2, 2013. The available stability data supports the proposed 24 months expiration dating when stored in the proposed packaging at 15-30°C (59° to 86°F) [see USP controlled Room Temperature].

The new proposed acceptance criteria of [redacted] (b) (4) µg/day for drug product *in-vitro* release rate was found acceptable by Dr. Tapash Ghosh in his review.
[The original proposed range was of [redacted] (b) (4).]

Although the CMC deficiencies from the second CR letter of November 2011 have been addressed, there is now a Compliance recommendation of Withhold for the [redacted] (b) (4) drug product manufacturing facility. The inspection was conducted [redacted] (b) (4) The 483 document from the district has 16 items listed.

[redacted] (b) (4)

(b) (4)

In summary, based on Dr. Qi and Dr. Shanmugam's CMC review, the methods validation, categorical exemption, microbiology and biopharmaceutics information is acceptable, while the CDRH consult from Dr. Nikhil Thakur found the information unacceptable (see also discussion of inserter in the Clinical section).

On October 11, 2013 the Office of Compliance issued a recommendation of "withhold" and this is documented in Dr. Qi's review of October 15, 2013, therefore the application was not recommended for approval.

The Office of Compliance reviewed the (b) (4) District Office findings from the Alimera contract manufacturing firm, (b) (4) and noted (b) (4) OC recommends the deficiencies be corrected and the firm should be inspected subsequently.

Comment:
Product Quality Reviews do not recommend approval because of the Withhold recommendation from the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

There were no additional pharmacology/toxicology studies submitted during this latest review cycle. For a complete summary, see the review by Dr. Chen. The components of the product have been reviewed. Polyvinyl alcohol has been used since the 1930's in industrial and food applications, biocompatibility studies were negative. Ocular toxicology studies (9 month and 24 months) of continuous exposure after one or two injections of insert in rabbits showed that FA appeared to induce posterior cortical/capsular cataracts at 0.5 and 1.0 microgram/day. Genotoxicity studies were negative, carcinogenicity studies and reproductive/development studies were not done.

Comment: The Pharmacology/Toxicology Reviewer recommends approval from the pharmacology/toxicology standpoint.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology studies submitted in this resubmission. Dr. Zhang summarized the systemic and ocular pharmacokinetic results from the application in the original review and recommended that systemic exposure results can be included in labeling; however, ocular levels will not be used to support a regulatory decision because the analytical methods to measure these concentrations in aqueous humor are not validated.

Dr. Zhang provides the following perspective regarding the differences between the inserter used in clinical trials compared to the to-be-marketed inserter (review 11/18/2010):

> 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 [redacted] contains 0.19 mg FA versus the clinical development product (manufactured at pSivida, Inc.) that averaged [redacted] mg. [redacted] FA is released from the polyimide tube at sub-microgram levels [redacted] (*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/da [redacted]

Comment: The Clinical Pharmacology reviewer recommends approval. The data support the labeling regarding FA concentrations in human plasma.

6. Clinical Microbiology/Immunology

Not Applicable

7. Clinical/Statistical-Efficacy

The applicant did not submit results of any new clinical studies in the current resubmission; however Alimera provided further discussion of their views about the benefits and risks of the product. Alimera continues to believe the benefits outweigh the risks, while the Division has the opposite interpretation. In the April 17, 2013 submission and the September 9, 2013 amendment, Alimera includes a calculation of number needed to treat (NNT) and number needed to harm (NNH) to support their interpretation of the risk benefit. The applicant's table is presented below:

Alimera's calculations of NNT and NNH for the FAME studies

Category	Integrated FAME Studies 0.2 µg/day FA Compared to Sham	Integrated DME Duration (b) (4) 0.2 µg/day FA Compared to Sham
Number Needed to Treat, Month 30	6.15	(b) (4)
Number Needed to Harm		
Cataract Surgery	5.22	
IOP elevation considered an AE[1]	10.79	
IOP elevation increase ≥12 mmHg	13.11	
IOP elevation to over >25 mmHg	11.76	
IOP elevation to over >30 mmHg	19.24	
Any surgical intervention for IOP	63.38	

Source: Statistical review 9/27/2013

Dr. Zhuang reviewed the calculations for this table and noted that while the NNT number was calculated using the formula (b) (4) the applicant only reported (b) (4) As reported in the Statistical Review 9/27/2013, the NNT is closer to 5 for the other time points evaluated (see table below).

Table 2: Statistical Reviewer's Summary of Number Needed to Treat

Time Point	Integrated FAME Studies			Integrated DME Duration [redacted]		
	Sham N=184	0.2 µg/day FA N=375	NNT	Sham N=112	0.2 µg/day FA N=209	NNT
Month 24, n(%)	30 (16.3)	108 (28.8)	8.00	15 (13.4)	72 (34.4)	4.75
Month 30, n(%)	28 (15.2)	118 (31.5)	**6.15**	12 (10.7)	79 (37.8)	**3.69**
Month 36, n(%)	35 (19.0)	108 (28.8)	10.2	15 (13.4)	71 (34.0)	4.86

Alimera's calculations [redacted] therefore the comparison between them is not considered appropriate.

The statistical review conducted two separate analysis of NNH:

- Using the approach Alimera used to calculate NNT, and recalculating NNH.

These results are shown in the tables below. The results do not support Alimera's claim that Iluvien offers a positive benefit to risk comparison because the NNT ([redacted] is more than the NNH (about 2) for cataract surgery, which is the predominant side-effect associated with ILUVIEN, and the NNH for elevated IOP is about 5.

Summary of Number Needed to Harm for Subjects with DME [redacted]

Category	Integrated DME Duration [redacted]				
	Sham N=112	0.2 µg/day FA N=209	Alimera's NNH	FDA's NNH	Ratio
Cataract Surgery in Phakic subjects	24/66 (36.4)	97/114 (85.1)	[redacted]	2.05	[redacted]
IOP elevation considered an AE	16 (14.3)	72 (34.4)		4.96	
IOP increase ≥12 mmHg	12 (10.7)	54 (25.8)		6.61	
IOP increase ≥25 mmHg	13 (11.6)	65 (31.1)		5.13	
IOP increase ≥30 mmHg	6 (5.4)	31 (14.8)		10.55	
Any surgical intervention for IOP	0	11 (5.3)		19.00	

- Using the approach to calculate NNT as Alimera used to calculate the NNH.

Based on this approach, the NNT [redacted] is higher than the NNH for cataract surgery [redacted]

Brief Summary of Clinical Trials:
As noted in the previous Division Director review (November 2011), two Phase 3 clinical trials were submitted, these were conducted under the same protocol but divided into C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B). The trials were conducted in the US and in various European countries.

The design and results of these clinical trials are summarized in the comprehensive clinical reviews by Dr. Nevitt, Dr. Boyd and Dr. Chambers and the comprehensive statistical review by Dr. Izem and Dr Wang.

The trials were prospective, double-masked, randomized, three-arm clinical trials conducted over 3 years. Patients with DME who received prior laser photocoagulation with retinal thickness ≥ 250 microns were enrolled and randomized to FA 0.2 mcg/day, FA 0.5 mcg/day or sham control. Subjects were allowed to have additional laser treatment at investigator discretion because the study was 3 years long.

The primary endpoint was increase in ≥ 15 letters from baseline of BCVA at 18 and 24 months. Secondary endpoints included mean BCVA.

The results show statistically significant differences in the 24 month endpoint for the ITT population with LOCF but FAME A was not significant in the population of observed patients. During the trial about 20-25% of patients discontinued due to LTFU, withdrawn consent, or death. One of the concerns identified by the Medical Officer is that in the LOCF analysis, patients who had subsequent intervention should have been counted as failures, therefore he considered the per protocol population with observed data important in the assessment of efficacy, and noted the lack of significant treatment effect in FAME A. The treatment effect for LOCF was also considered clinically low. There was significant toxicity (cataracts, increased IOP), and for many patients visual acuity declined because of cataracts.

The application was issued a *Complete Response* on December 22, 2010 in the first review cycle.

The May 12, 2011 submission contained Month 36 data. The 36-month data fail to show that Iluvien is effective in the treatment of DME. There was no significant difference in the primary endpoint of a ≥ 15-letter increase from baseline in best corrected visual acuity (BCVA) in the study eye in the FA vs. sham treated arms. The p- value is not significant for either dose in either FAME A or FAME B.

Table 1: 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	0.2 µg/day FA	0.5 µg/day FA	Sham	0.2 µg/day FA	0.5 µg/day FA
	N=95	N=190	N=196	N=90	N=186	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 (%)						
Difference[1]						
P-value[2]						

[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.
Source: Applicant's Table 3 from Efficacy Information Amendment

Dr. Izem provides additional discussion on the BCVA findings in her review:

> The primary endpoint is a responder endpoint; it only quantifies improvement from baseline BCVA that is above a threshold of 15 letters. In contrast, the secondary endpoint quantifies any change from baseline, whether they are improvements or declines from baseline BCVA. In all treatment arms, in both studies and at most time-points, some subject's BCVA increased while other subject's BCVA decreased compared to baseline. Thus, the primary and secondary endpoints together give a better picture of the low dose treatment effect and magnitude of the effect on BCVA than the primary endpoint alone.

This observation is important, because although the primary endpoint of ≥ 15-letter increase from baseline showed significant differences between treatment and control arms at some of the time points evaluated (24 months (b) (4)), this difference was not robust and not considered clinically-significant. The secondary endpoint of mean BCVA over time shows a small advantage of low dose over sham treatment in FAME B but this effect is not replicated in FAME A.

Table 8: BCVA Change from Baseline Over Time, Full Analysis Population

		Mean BCVA change from baseline			
Study	Visit	Sham	Low Dose	Difference	95% CI for difference
Fame A	Month 6	(b) (4)			
	Month 12				
	Month 18				
	Month 24	3.2	3.7	0.4	(-3.8 , 4.6)
	Month 30	(b) (4)			
	Month 36				
Fame B	Month 6				
	Month 12				
	Month 18				
	Month 24	0	5.1	5.1	(0.7 , 9.4)
	Month 30	(b) (4)			
	Month 36				

Iluvien Inserter

The inserter (b) (4) used in preclinical and clinical studies delivered an insert of fluocinolone containing (b) (4) mg, and was designed to release 0.2 micrograms/day or 0.5 microgram/day. (b) (4) This was the packaging configuration used for all the preclinical and clinical studies. Clinical trial investigators and retinal specialists who were not participants in the trials provided feedback on the inserter which resulted in several modifications being made. A new (b) (4) inserter was used in the FAVOR study C-01-09-006 (b) (4) in 8 patients. No adverse events were reported related to the procedure.

The Division recommended in the February 2, 2011 meeting scheduled after the *Complete Response* letter of 12/22/2010, that Alimera submit data on "at least 100 eyes" treated with the new Inserter before NDA approval. The Medical officer elaborates that: "The trial should be conducted in the indication intended for use." (MOR p.3)

In the latest resubmission there is information on modification of the inserter and testing of these 3 lots or batches in the FAME Extension Study (Study C-01-11-008) is an open-label, multi-center extension study of the safety and utility of the new applicator for Iluvien in subjects with DME. Subjects include those who had previously participated in the FAME studies or subjects with chronic DME considered insufficiently responsive to available therapies. The applicant writes that following the enrollment of 4 subjects with the first lot, a design improvement was implemented and a second lot was produced. After enrolling an additional 59 subjects, the study was put on hold as the second Complete Response Letter (CRL) was received from the FDA related to Alimera's submission of ILUVIEN for the treatment of DME. During (b) (4) a review of technical complaints for the second lot led to the implementation of supplementary in-process controls. The applicant writes:

The technical complaints for this lot were generally characterized (b) (4)

A third batch was produced and enrollment was completed with an additional 58 subjects. The applicant made a distinction for the statistical analysis between the first 4 subjects enrolled into the trial, called "noncommercial" and those subsequently enrolled in light of the design improvements, where the batches used after the first 4 subjects represent the "commercial" product, but did not provide separate analysis of technical complications, instead analyzing the 4 subjects in the noncommercial group, and 117 subjects in the commercial group. The results of the safety and questionnaire are provided below:

Trial C-01-01-008 (FAME Extension) Open label, multi-center extension study of Safety and Utility of the New Inserter of Iluvien

	0.2 µg/day FA			
	Commercial		Noncommercial	
Visit	Safety (N=117) n (%)	Questionnaire (N=117) n (%)	Safety (N=3) n (%)	Questionnaire (N=4) n (%)
Screening	117 (100.0)	--	3 (100.0)[a]	--
Baseline (Day 0)	--	117 (100.0)	--	4 (100.0)
Telephone call (Day 1)	117 (100.0)	--	3 (100.0)	--
Week 1	116 (99.1)	--	3 (100.0)	--
Week 3	103 (88.0)	--	3 (100.0)	--
Week 6	79 (67.5)	--	3 (100.0)	--
Month 3	56 (47.9)	--	3 (100.0)	--
Month 6	57 (48.7)	--	3 (100.0)	--
Month 9	55 (47.0)	--	3 (100.0)	--
Month 12	29 (24.8)	--	3 (100.0)	--

[a] Subject 810702 discontinued the study following a failed attempt at study drug administration.

Excerpt from Summary of Inserter Questionnaire

	0.2 µg/day FA			
	Commercial (N=117)		Noncommercial (N=4)	
Treatments Attempted	130		4	
Observer Questions	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Was sterile technique used to open the tray containing the inserter?	130 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)
Was sterile technique used to remove the inserter from the tray?	130 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)
Was the step of depressing the button down and forward to the curved black marks (to move the drug insert into the needle tip) followed?	130 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)
Was the administration of the drug insert performed as instructed? If no, please explain.	125 (96.2)	5 (3.8)	3 (75.0)	1 (25.0)
Did you observe difficulties with the study drug administration? If yes, please explain.	19 (14.6)	110 (84.6)	1 (25.0)	3 (75.0)
Do you have any other comments?	17 (13.1)	113 (86.9)	0 (0.0)	4 (100.0)

While the applicant discloses that there were technical complaints with the second lot, they do not present a separate analysis of the second lot and third batch (lot). Instead, the information from the technically deficient inserter (n=59) are pooled with the next version of the inserter (n=58) for a total of 117 "commercial" exposures in the table below, and the Inserter Questionnaire summary also does not separate the two, therefore it is not possible to say whether the technical problems have been addressed. Dr. Nevitt writes that from Summary of Physician Utilization study, "Once Iluvien is commercialized, physician training will be enhanced in order to avoid the types of issues experienced during the trial." It seems prudent that such training should be tested in the clinical trial, and this recommendation will be made to the applicant in the action letter.

Dr. Chambers examined the patient level data for the 58 patients who received drug from the inserter in the third batch and determined that investigators reported technical problems with 11/58 (19%). Given that overall investigators reported technical problems in 19/117 (14.6%) insertion procedures, (see Excerpt above), that mean 8/59 (13%) were from the second lot. This suggests that the in-process improvement to the third batch did not correct the problems with the second batch. Alimera will be asked to provide specific information on the in-process control during manufacturing of the "commercial" batches used in Study C-01-11-008.

Finally, the CDRH recommendation regarding the proposed Iluvien inserter are addressed in the Deputy Director review and the following is excerpted from his review dated 10/17/2013:

> A device consult review was received from the Center for Devices and Radiologic Health. The consult noted that engineering drawings were provided in the Original Submission (Section 3.2.P.7), along with pictures of the assembled device but stated that there was no additional testing by the applicant to demonstrate that device functionality, biocompatibility and Human Factors had been assessed. With respect to device

functionality, the consult requested that the applicant demonstrate that the length of the (b) (4) needle has been designed specifically for intravitreal implantation of the Iluvien implant, and would not inadvertently puncture other membranes within the eye during the insertion process. The clinical review team noted that the needle is one inch in length and therefore would not inadvertently puncture other membranes within the eye. The consult requested performance testing that the mechanism does not inadvertently disengage during the Iluvien implant insertion process, and during the retraction of the (b) (4) from the implant site. There was also a request to evaluate the manual slider mechanism. Study C-01-11-008 was conducted in part to evaluate the inserter and included an evaluation of the performance in an actual patient setting.

With respect to biocompatibility, the consult acknowledged that stability testing on the drug product, had characterized the impurities, and that pK/pD studies on the drug product were conducted. It also acknowledged that MSDS's and testing (b) (4) used to manufacture the final finished device had been provided, but stated that it did not meet CDRH's threshold for demonstrating that the biocompatibility concerns because CDRH relies on ISO 10993 to demonstrate that leachables/extractables and the characterization/quantification of the impurities have been assessed. While the ISO 10993 standard might be applicable for an inserter which is not product specific, in this case, only a specific drug product will be used with the inserter. The clinical testing as well as stability testing that has been performed with this specific drug product is sufficient for this particular product. If the inserter is used to deliver different drug products, the ISO 10993 standard might be appropriate. The consult raised a question about which documents were used for validation of the sterilization procedures. Sterilization issues have been reviewed by the ONDQA Sterility Assurance Reviewer. There are no outstanding sterilization issues. With respect to Human Factors, the consult also requested a comprehensive Human Factors study to assess the use-related risks and to ensure that these risks have been appropriately mitigated through testing. As noted above, if the inserter is to be used with multiple different products, this testing might be applicable; however, in this case, clinical testing with the particular drug product has been performed and evaluated.

In summary, while the CDRH consult provided comprehensive advice for the device, the division is focusing the requests on both the clinical and technical issues that impact the safety, efficacy, and function of the device for its intended use with the Iluvien (b) (4) Given the ongoing technical difficulties with the inserter, the applicant will be asked to provide details on the manufacture and in-process improvements, as well as use the inserter in a clinical trial setting and demonstrate that technical complications have been successfully minimized.

Exploratory Analysis

In the May 12, 2011 submission, the applicant proposed to modify the indication (b) (4) To support this modification, the company conducted a post-hoc subgroup analysis of a subset of the clinical trial population that the company defined (b) (4)

[redacted] (MOR, p.13)

The clinical reviewers disagreed with the way in which DME [redacted] duration was retrospectively defined, noting that *Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time. Given DME can wax and wane over time the proposed subgroup "Duration of DME [redacted]" is not defined well nor is it documented that the subjects had DME [redacted] The definition of duration of DME was not adequately assessed as a study inclusion criterion given DME can wax and wane over time.*

In the Briefing material submitted May 21, 2013 the applicant writes:

> "Although the Sponsor did not describe its planned duration of DME subgroup analysis in either its protocols or the SAP (and apologizes for this oversight), this analysis was nevertheless prospectively planned; specifically, this analysis was planned prior to unmasking of the study databases at Month 24."
>
> "The programming for the analysis to populate tables in the clinical study reports for both the A and B studies, as well as the integrated summary of efficacy (ISE) and the mock-ups of the table shells to present the results, were all completed prior to the unmasking the Month 24 database (December 1, 2009). Appendix B provides a detailed description of the process and examples of the Table Mockups and programming and demonstrates that the subgroup analysis was preplanned."
>
> **Appendix B:** "In a July 30, 2009 email, Fran Kane (FK) (Executive Director, Clinical Sciences, Alimera Sciences, Inc.) requested that Barry Kapik (BK) (Director, Biostatistics and Data Management, Clinical Sciences, Alimera Sciences, Inc.) add specific subgroups to the Integrated Summary of Efficacy (ISE) (Refer to Email, Fran Kane, July 30, 2009). The following subgroups were requested in this email: type of diabetes, PDR vs. NPDR per ETDRS classification, above and below the median for retinal thickness, and above and below the median for duration of DME."
>
> "Table 5.2.3.1 Number and Percent of Subjects with an Increase from Baseline of 15 or More Letters in Best Corrected Visual Acuity in the Study Eye by Duration of Diabetic Macular Edema
> *Programmer's note: complete for the following subgroups: < Median, ≥ Median."*
>
> "Table 5.2.3.2 Summary of Best Corrected Visual Acuity in the Study Eye by Duration of Diabetic Macular Edema
> *Programmer's note: complete for the following subgroups: < Median, ≥ Median."*
>
> "Table 5.2.3.3 Summary of Excess Center Point Thickness in the Study Eye by Duration of Diabetic Macular Edema
> *Programmer's note: complete for the following subgroups: < Median, ≥ Median".*

Compare efficacy for duration of DME ≥and < the Median. (page 168)

Assuming that patients were examined based on "above and below median duration of DME," the expectation would that that the number of patients in the below median group would equal the number of patient in the above medial group. However, (b) (4) this analysis is not consistent with the analysis requested in the email from 2009, above. (b) (4)

Alimera's Efficacy Results for FAME A (first table) and FAME B (second table) Studies, Subjects with ≥ 15 Letter Increase from baseline best corrected visual acuity (BCVA) in the Study Eye

(b) (4)

The applicant further discussed that alternative approaches to calculating the duration were considered, and provides median durations based on the completeness of information (day, month, and year of diagnosis). The complete date was known for 75% of patients and the median duration was 1.55 years. When the remaining patient information (month, year or only year) was

included, the median duration of DME was 1.73 years). As shown below, for this analysis, the number of patients in the two subgroups is balanced: 475 in the < 1.73 year subgroup and 476 patients in the ≥ 1.73 year subgroup.

Table 1: Measure of Agreement Between the Original and New Methods

Original Method	New Method	
	< 1.73 Years	≥ 1.73 Years
[redacted] (b) (4)	410 (43.1%)	6 (0.6%)
	65 (6.8%)	471 (49.5%)
kappa		0.8508
p-value		<0.0001

Based on the new analysis by < 1.73 year and > 1.73 years of duration the following Month 36 data are provided in the May 21, 2012 submission:

FAME A + B

<1.73years

Month 36	81	23	28.4	192	48	25.0	202	55	27.2
Difference						3.4			1.2
95% CI						(-8.2, 15.0)			(-10.4, 12.7)
P-value						0.447			0.795

≥1.73

Month 36	103	12	11.7	183	60	32.8	191	54	28.3
Difference						-21.1			-16.6
95% CI						(-30.3, -11.9)			(-25.5, -7.7)
P-value						<0.001			0.002

FAME A

<1.73 years

Month 36	40	12	30.0	96	26	27.1	87	25	28.7
Difference						2.9			1.3
95% CI						(-13.8, 19.7)			(-15.8, 18.4)
P-value						0.612			0.883

≥1.73 years

Month 36	54	6	11.1	93	28	30.1	107	27	25.2
Difference						-19.0			-14.1
95% CI						(-31.5, -6.5)			(-25.9, -2.4)
P-value						0.010			0.037

FAME B

<1.73 years

Month 36	41	11	26.8	96	22	22.9	115	30	26.1
Difference						3.9			0.7
95% CI						(-12.0, 19.9)			(-15.0, 16.5)
P-value						0.563			0.870

≥1.73 years

Month 36	49	6	12.2	90	32	35.6	84	27	32.1
Difference						-23.3			-19.9
95% CI						(-36.8, -9.8)			(-33.5, -6.3)
P-value						0.004			0.017

Although the above analysis follows the request from the 2009 email, I agree with the Medical Officer, Medical Team Leader, Deputy Director, and Statistical team that the applicant has failed to show persuasive evidence that the benefit outweighs the risks.
The inserter tested in patients with DME showed that technical difficulties occurred in 19% of insertion attempts for the most recent batch.

8. Safety

See comprehensive clinical reviews by Dr. Nevitt, Dr. Boyd and Dr. Chambers and the comprehensive statistical review by Dr. Izem and Dr. Wang.

During the first review cycle, all reviewers noted and commented on the significantly greater rate of serious adverse reactions seen with Iluvien treatment compared to sham treatment.

Approximately 30% of patients did not complete the study, the main reasons were loss-to-follow-up (9% to 13%), subject withdrew consent (7% to 8%) and death (6% to 8%).

8.1 Adverse events of special interest

Increased intraocular pressure:
By 36 months, increased IOP was seen in 12% (22/185) sham treated patients, 37% (139/375) low dose fluocinolone patients and 46% (179/393) high dose fluocinolone patients treated in the safety population from FAME A and FAME B.

For the proposed subgroup of patients with DME [redacted] duration, the rates were [redacted] respectively. These rates are similar to those seen in the overall safety population from these two trials.

In additional tables from clinical review of 9/9/2013, the IOP events for the "acute" DME [redacted] were actually somewhat lower in percentage than for "chronic" DME [redacted] and for both subsets the rates were higher than in the Sham control.

Table 12: Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Chronic DME and Acute DME Subgroups: Safety Population)

Category	0.2 µg/day		
	Overall FAME N = 375 n (%)	Chronic DME N = 209 n (%)	Acute DME N = 165 n (%)
Any IOP-lowering medication	144 (38.4)	75 (35.9)	69 (41.8)
IOP elevation considered an AE[1]	139 (37.1)	72 (34.4)	67 (40.6)
IOP elevation increase ≥12 mmHg	108 (28.8)	54 (25.8)	54 (32.7)
IOP elevation to over >25 mmHg	123 (32.8)	65 (31.1)	58 (35.2)
IOP elevation to over >30 mmHg	69 (18.4)	31 (14.8)	38 (23.0)

In the two trials combined, the percentage of patients in the 0.2 µg/day FA group requiring intraocular pressure (IOP) lowering medications was 38.4% (114/375) and the percentage of patients in the sham group requiring IOP lowering medications was 14.1% (26/185). The difference between the 0.2 µg/day fluocinolone acetonide (FA) group and Sham control was 24.3%.

Cataract-related adverse reactions and cataract surgery:

As show in the tables below, the rate of cataract related adverse events and cataract operations were significantly higher in the treated groups. This was true for the total safety population in FAME A and FAME B, as well as in the subgroup of patients stated to have DME [redacted] (b) (4)

Table 4: 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 operation	33 (27.3)	188 (80.0)	231 (87.2)

Source: Applicant's Table 42 from the Efficacy Information Amendment of the current submission

Table 5: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects with a DME Duration [redacted] (b) (4) (36-Month Integrated FAME Studies, Safety Population)

[redacted] (b) (4)

The rate of cataract formation and cataract surgery was higher for the "chronic" DME group compared to the Acute DME subsets, and all rates were higher in the 0.2 mcg/day versus sham control.

Table 7: Number (%) of Phakic Subjects Reporting Cataract-Related Events (Integrated FAME Studies and Chronic DME and Acute DME Subgroups: Safety Population)

Cataract Related Event	Sham n/N (%)	0.2 µg/day n/N (%)
All Phakic Subjects		
Any Cataract	61/121 (50.4)	192/235 (81.7)
Cataract Operation	33/121 (27.3)	188/235 (80.0)
Phakic Subjects with Chronic DME		
Any Cataract	34/66 (51.5)	98/114 (86.0)
Cataract Operation	24/66 (36.4)	97/114 (85.1)
Phakic Subjects with Acute DME		
Any Cataract	26/54 (48.1)	94/121 (77.7)
Cataract Operation	8/54 (14.8)	91/121 (75.2)

Reference: Refer to Module 5, 5.3.5.3, ISS-36 Month Table 5.15 and Section 9.6, Table 11.

Comment:
I agree with the Medical Officer, Medical Team Leader, Deputy Director, and Statistical team that the applicant has failed to develop a safe regimen of Iluvien. There are significant adverse reactions related to the use of Iluvien seen in the FAME A and FAME B clinical trials that make preclude approval of the product for this indication. In addition, technical difficulties were reported with the use of the inserter as delineated in the Deputy Director's review and summarized above.

9. Advisory Committee Meeting

The application was not presented before an advisory committee. Fluocinolone is not a new molecular entity, and the results from the clinical trials do not support approval of the application, because the risks of cataract formation, cataract surgery, and increased IOP outweigh the low, transient and inconsistent effect on visual acuity in the three-year trials. However, because of the ongoing discussion about the benefit versus risk interpretations (b) (4) discussion at the Dermatologic and Ophthalmic Drug Advisory Committee is planned for January 27, 2014 to help provide advice on resolving the deficiencies and provide guidance on whether a population in whom the benefits exceed the risks.

10. Pediatrics

Pediatric studies were waived because DME is rare in pediatric patients and there are insufficient numbers of patients to conduct a clinical study. The PeRC met October 4, 2010 and agreed with the waiver.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

Office of Compliance has made a recommendation of Withhold approval on October 11, 2013, because of GMP deficiencies at the [redacted] (b) (4).

11.2 Office of Scientific Investigation (OSI) Audits

Dr Ayalew notes that: "Two clinical investigator sites, one domestic and one foreign, were inspected in support of this application. Although regulatory violations were noted at both of these sites, given the nature of the findings, it is unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable." The preliminary classification of both sites was VAI; no addendum has been submitted recommending that results are not acceptable.

11.3 Financial Disclosure

Financial disclosure information was reviewed. The medical officer determined there were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies, nor did any one single investigator or site enroll a significant number of subjects.

11.4 Other Regulatory Issues

The application will be issued a *Complete Response* letter in this review cycle.

12. Labeling

The package insert and carton and container labeling have not been reviewed during this cycle because the results of the clinical trials fail to show that the potential benefit of the product outweighs the potential risks. If the deficiencies can be resolved, labeling will be reviewed.

- **Package insert (PI):** The PI is written in PLR format, to be reviewed after deficiencies addressed.
- **Carton and Container Labels**: To be reviewed after deficiencies addressed
- **Proprietary Name**: The proposed proprietary name Iluvien was reviewed and found acceptable by DMEPA; a letter stating that the name is acceptable was issued by Dr. Denise Toyer on October 13, 2010. If the outstanding deficiencies are addressed, the name will need to be re-reviewed within 90 days of the application's approval.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The deficiencies identified by the clinical, statistical, product quality, and compliance reviewers need to be addressed before the application can be approved. The application will be issued a

Complete Response letter and the deficiencies provided in Section 1.1 of this document will be included in the *Complete Response* letter.

13.2 Risk Benefit Assessment

Diabetic macular edema is one of the complications of diabetes and diabetic retinopathy. The following figures from Klein 1984 show the time course.

OPHTHALMOLOGY • DECEMBER 1984 • VOLUME 91 • NUMBER 12

DME is one complication of diabetes that affects the eye. The natural history of the broader category of diabetic retinopathy is summarized in two publications by Klein, and they report on the improvements and worsening seen over time in patients younger than 30 and older than 30 as summarized in the abstracts below:

Klein R, Arch Ophthalmol. 1989 Feb;107(2):237-43. (patients younger than 30 years)

Klein
Arch Ophthalmol. 1989 Feb;107(2):244-9. (patients 30 years or older)

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Diabetic macular edema is a serious disease for which no drug therapy is approved. The disease runs a variable course and can improve and worsen over years. Laser coagulative therapy and various products are used off label to manage the condition. Lucentis was approved in 2012 for treatment of DME. Management of underlying diabetes may also contribute to improvement in ocular changes.

The results of the Phase 3 controlled clinical trials, FAME A and FAME B showed a small and transient effect on visual acuity defined as improvement in ≥15 letters in BCVA from baseline at 24 months and (b) (4) in the ITT population with LOCF but not in the population where BCVA was assessed by observation (without LOCF) in one of the trials. Evaluation of the secondary endpoint of mean BPCA showed that while some patients gained visual acuity, others lost visual acuity and the mean BCVA was small and not considered clinically significant.

The analyses of the 24-month assessment were confounded by the development of cataracts in the majority of phakic patients; therefore 36-month data were requested. Although there was a 10% difference in the efficacy, this difference was not significant between the FA treated vs. sham-treated patients at 36 months.

In addition to lack of efficacy, there was also a lack of safety; a significantly greater rate of serious adverse reactions included increased IOP, cataracts and cataract surgery were reported in FA treated patients vs. sham treated patients.

The company reported an analysis of patients in these studies based on a calculated duration of DME (b) (4) This analysis was not included in the protocol or statistical analysis plan. (b) (4)

The applicant provided information on May 21, 2012 that the analysis by duration of DME, while not in the protocol, was requested before data unmasking. In this submission, the applicant provided another calculation for duration of DME and provided an analysis based on the median duration of DME which has been recalculated to be 1.73 years. In the analysis based on the median 1.73 years, the number of patients assigned to the < 1.73 group is 475 and the number in the ≥1.73 years is 476, which is consistent with looking "below" and "above" the median. The results of these analyses show that there is no significant difference in efficacy between Iluvien and Sham for the < 1.73 year subset, while the differences between both treatment arms and sham are significant for the ≥1.73 year subset. The adverse event profile in terms of IOP and cataracts was essentially the same in these two subgroups, again leading to the concern that the risks are greater than the benefit.

These clinical trials did not evaluate the to-be-marketed presentation of the Iluvien intravitreal inserter. A recent study of DME patients evaluated the most recent batches of the inserter and found that 19% of practitioners had technical difficulties with the most recent batch of the product: the insert did not come out of the needle, the device was judged defective, the device was difficult to depress, the needle was bent, the medication came out of the needle before it was fully depressed, and difficulty inserting the needle tip into the eye.

The applicant had embarked on the development program of Iluvien using a low intravitreal dose of 0.19 mg to be released at a starting dose of 0.25 micrograms/day for a period of [redacted] (b) (4) 36 months in the treatment of DME. They hypothesized that such low exposure would be effective and would not be associated with serious adverse reactions. The results of their clinical trials show that this dose did not result in clinically significant sustained response to treatment and was associated with very high rates of serious adverse reactions. It's not clear whether further formulation development and alterative dosing will likely result in a safe and effective product.

The applicant did provide an exploratory analysis (not included in protocol or SAP but requested in 2009 before the data were unmasked), which shows that patients with a duration of greater than or equal to 1.73 years had a significantly higher increase in BCVA with FA compared to sham of approximately 20% while those with duration less than 1.73 years had no significant difference on treatment compared to sham.

The inserter used in the most recent clinical trial and intended to be used commercially is associated with technical problems during use.

The applicant has requested a new indication [redacted] (b) (4)

Finally, there are multiple GMP deficiencies at the [redacted] (b) (4) drug manufacturing facilities that preclude approval.

13.3 Recommendation for other Postmarketing Requirements and Commitments

Not applicable 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/

RENATA ALBRECHT
10/17/2013

Deputy Division Director Review of NDA 201923

Date	October 17, 2013
From	Wiley A. Chambers, M.D.
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Amendment to second action letter	April 17, 2013
Type of Application	505(b)(1)
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	(b) (4)
Proposed Action:	Complete Response

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is an active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant. Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is commercially available in Europe.

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on *in vitro* and *in vivo* data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The product was developed with a polyvinyl alcohol matrix inside a tube which can be inserted through a 25 gauge needle attached to a specially designed inserter. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

Use of corticosteroids are known to produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

2. Background

Diabetic macular edema (DME), a chronic, debilitating disease, is a cause of vision loss associated with diabetic retinopathy. In addition to insulin therapies, Lucentis (ranibizumab injection) is approved for the treatment of DME.

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008. The Division expressed concern that the benefits might not outweigh the risks if Illuvien demonstrated a safety

profile which was similar to other corticosteroids. The applicant stated that they did not expect to see the development of cataracts or elevated intraocular pressure due to the low release rate.

The NDA was submitted on June 30, 2010. The Agency issued a Complete Response letter on December 22, 2010, citing a lack of substantial evidence to support the efficacy, facilities that were not in compliance with cGMPs and a lack of methods, facility and controls to assure identity, strength, quality, purity and stability. The applicant re-submitted the application with clinical data through 3 years of study. The Agency issues a Complete Response letter November 10, 2011, citing a lack of substantial evidence to support the efficacy and insufficient information to determine the adequacy of the specifications necessary to ensure the identity, strength, quality, purity, and potency of your drug substance and drug product. The applicant re-submitted the application a third time, which is the subject of this review.

3. CMC

The Chemistry/Manufacturing deficiencies identified during the original and second submission have been resolved with the exception of the issues related to manufacturing and testing in compliance with current Good Manufacturing Practice (cGMP). The release rate specification remains (b) (4) µg/day. It was accepted by the ONDQA Chemistry and Biopharm Reviewers and is consistent with the release rate of the test product used in the clinical trials. Re-inspection of (b) (4) a facility identified as being not in compliance with cGMP during the review of the original submission has again identified cGMP deficiencies.

A device consult review was received from the Center for Devices and Radiologic Health. The consult noted that engineering drawings were provided in the Original Submission (Section 3.2.P.7), along with pictures of the assembled device but stated that there was no additional testing by the applicant to demonstrate that device functionality, biocompatibility and Human Factors had been assessed. With respect to device functionality, the consult requested that the applicant demonstrate that the length of the (b) (4) needle has been designed specifically for intravitreal implantation of the Iluvien implant, and would not inadvertently puncture other membranes within the eye during the insertion process. The clinical review team noted that the needle is one inch in length and therefore would not inadvertently puncture other membranes within the eye. The consult requested performance testing that the mechanism does not inadvertently disengage during the Iluvien implant insertion process, and during the retraction of the (b) (4) from the implant site. There was also a request to evaluate the manual slider mechanism. Study C-01-11-008 was conducted in part to evaluate the inserter and included an evaluation of the performance in an actual patient setting.

With respect to biocompatibility, the consult acknowledged that stability testing on the drug product, had characterized the impurities, and that pK/pD studies on the drug product were conducted. It also acknowledged that MSDS's and testing (b) (4) used to manufacture the final finished device had been provided, but stated that it did not meet CDRH's threshold for demonstrating that the biocompatibility concerns because CDRH relies on ISO

10993 to demonstrate that leachables/extractables and the characterization/quantification of the impurities have been assessed. While the ISO 10993 standard might be applicable for an inserter which is not product specific, in this case, only a specific drug product will be used with the inserter. The clinical testing as well as stability testing that has been performed with this specific drug product is sufficient for this particular product. If the inserter is used to deliver different drug products, the ISO 10993 standard might be appropriate. The consult raised a question about which documents were used for validation of the sterilization procedures. Sterilization issues have been reviewed by the ONDQA Sterility Assurance Reviewer. There are no outstanding sterilization issues. With respect to Human Factors, the consult also requested a comprehensive Human Factors study to assess the use-related risks and to ensure that these risks have been appropriately mitigated through testing. As noted above, if the inserter is to be used with multiple different products, this testing might be applicable; however, in this case, clinical testing with the particular drug product has been performed and evaluated.

4. Nonclinical Pharmacology/Toxicology

Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. The applicant conducted several biocompatibility studies with polyimide tubing and extracts of stainless steel injection needles. The results were negative. The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber. Continuous exposures of ocular tissues for both toxicity studies were achieved via one or two injections of the insert into the eye. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations. The panel of genotoxicity tests performed by the Sponsor included the bacterial mutation test, mammalian cell mutation test and a mouse micronucleus test. Fluocinolone acetonide did not show any evidence of genotoxic activity in these tests when tested in accordance with regulatory guidelines. No carcinogenicity studies were conducted for Iluvien. Reproductive and developmental toxicity studies with Iluvien were not conducted.

5. Clinical/Statistical - Efficacy

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The 24-month data was confounded by the development of cataracts.

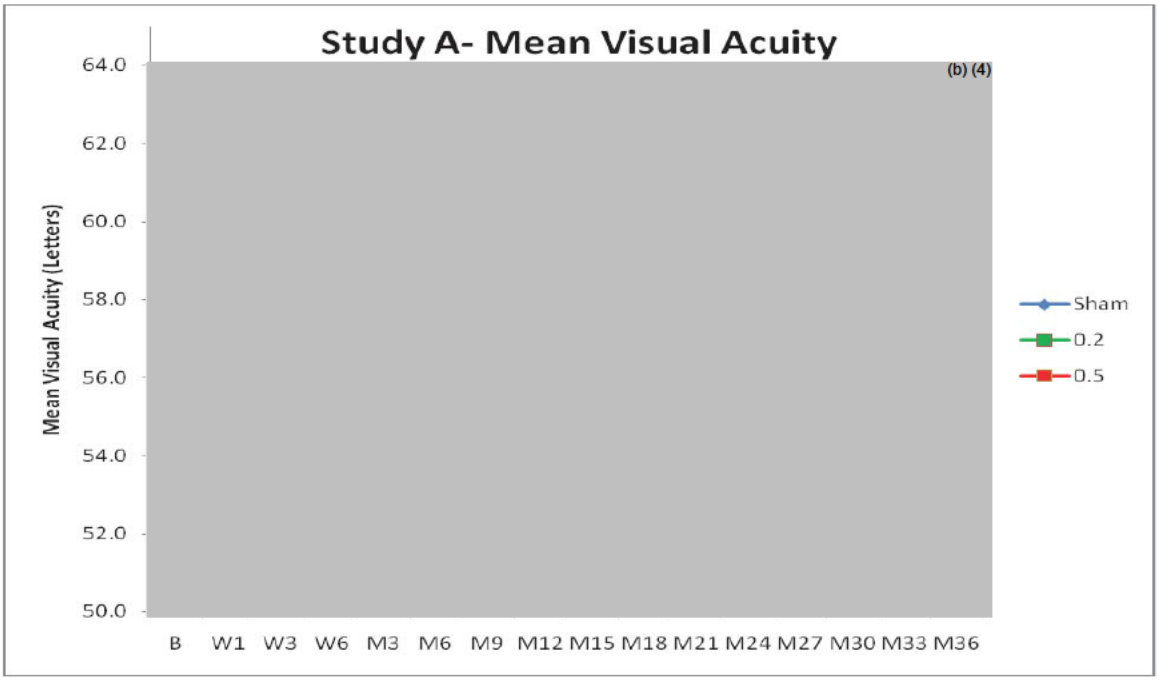
Originally, the primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline. The data was confounded by the development of cataracts in many patients and data through Month 36 was submitted. When the studies failed to demonstrate a clinically significant difference at 36 months, the applicant proposed a subpopulation of patients

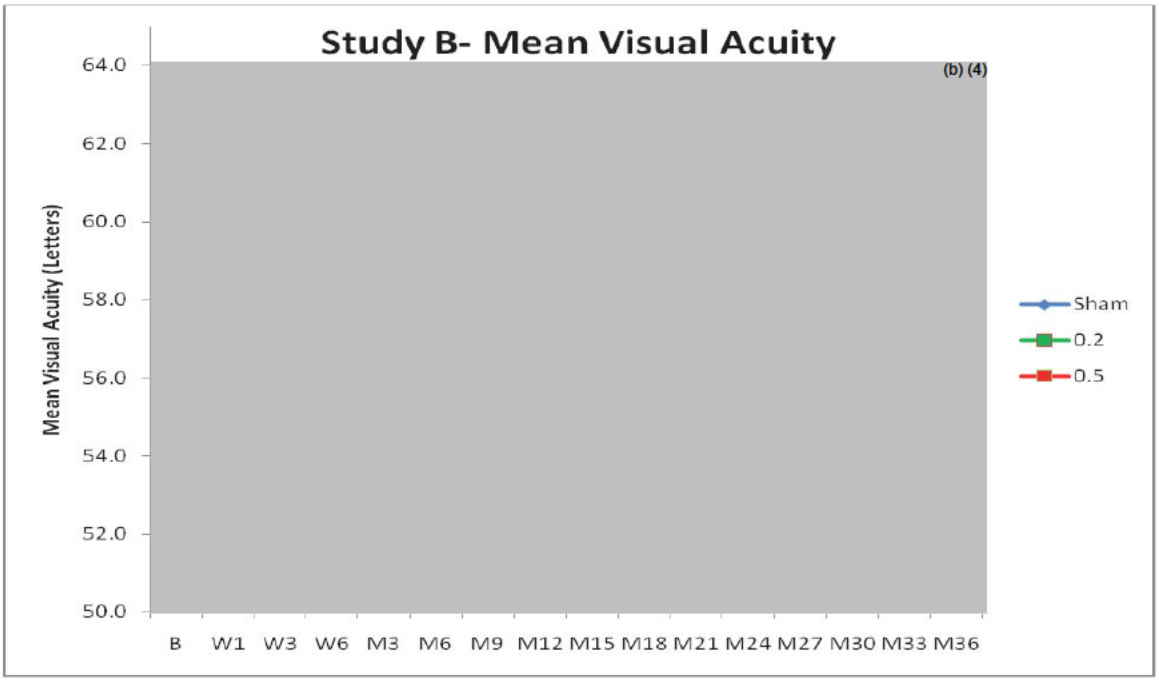
who had reported a diagnosis of Diabetic Macular Edema [redacted] (b) (4) In a Submission dated June 19, 2012, the applicant acknowledged that the subgroup based on duration of DME was not specified in the protocol or SAP for FAME A and FAME B. Instead, the applicant claims that it can be shown through the examination of emails and draft documentation that the efficacy analysis based on duration of DME was planned prior to the date of unmasking. The treatment code unmasking for both trials occurred on December 1, 2009.

The proposed subgroup has multiple issues including the lack of a statistical adjustment for multiplicity. Since the endpoint was not pre-specified as a primary or secondary endpoint or listed as an exploratory variable, the statistical plan did not include statistical adjustments for the multiplicity. DME is a disease that can wax and wane over the course of many years with varying degrees of macular involvement. [redacted] (b) (4) The proposed subgroup "Duration of DME [redacted] (b) (4)" was not specifically defined in terms of objective observations nor was it documented that the subjects had DME [redacted] (b) (4) There are a couple of missing dates, and in one patient there is documentation for both diabetic macular edema and clinically significant macular edema, fourteen months apart.

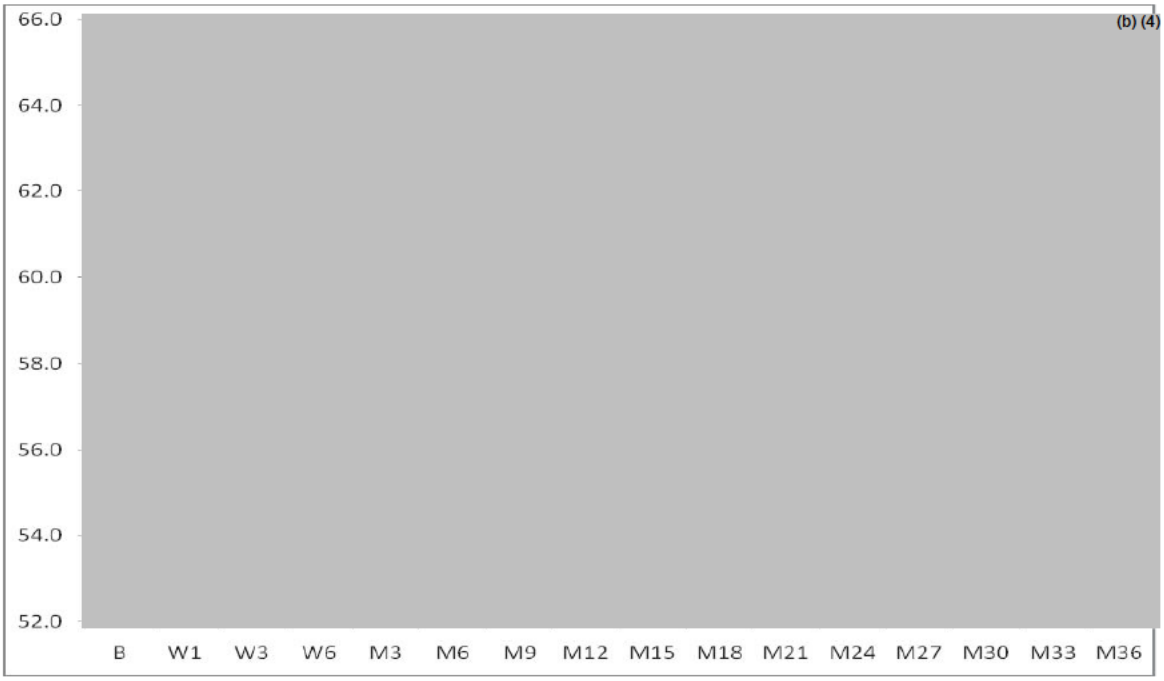
[redacted] (b) (4)

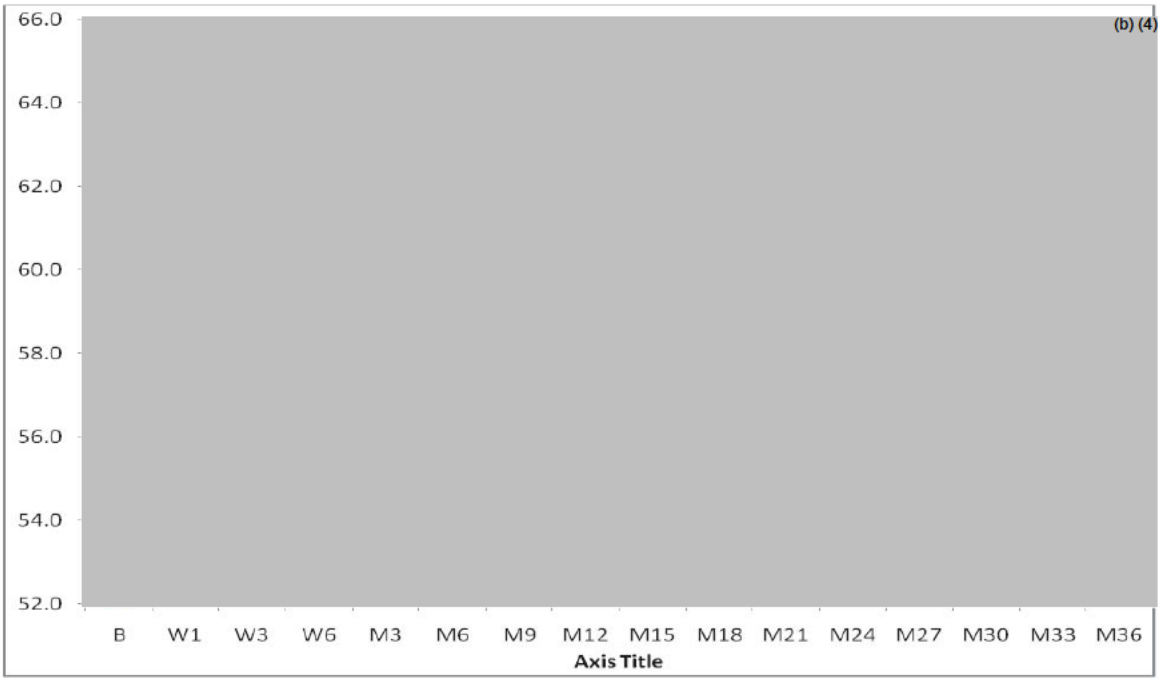
I have conducted a number of exploratory analyses which are included as the graphs which follow.



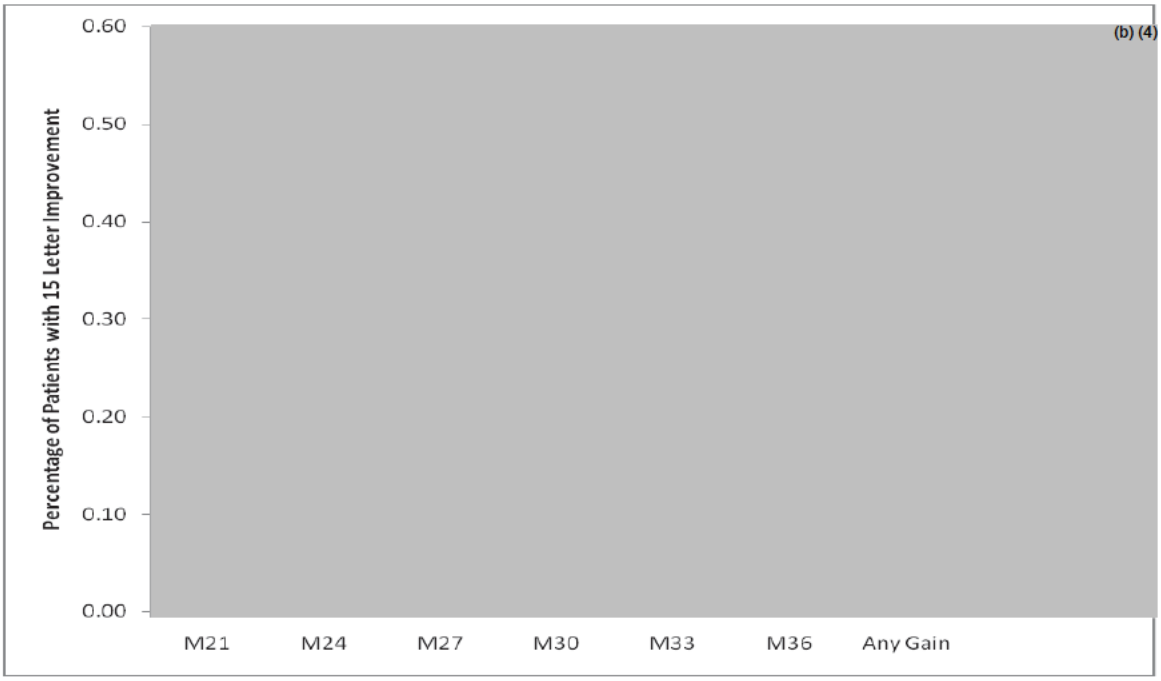


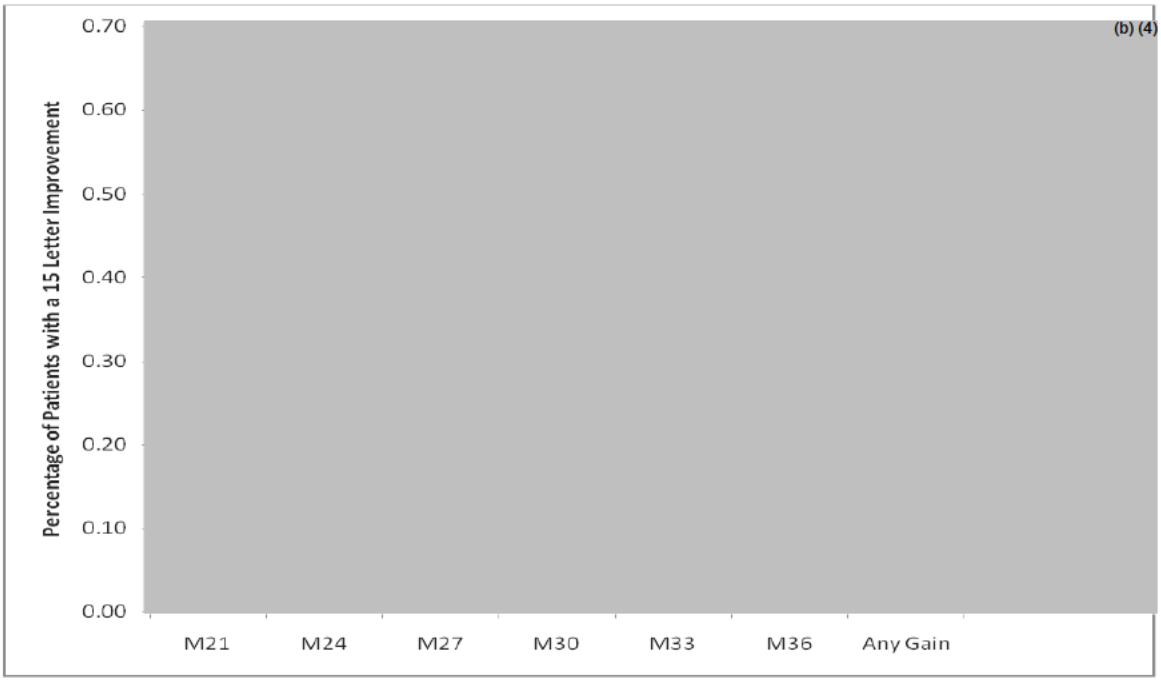
As noted in the graphs, there is an overall pattern of improvement in all groups. The two FA treatment groups demonstrate greater improvement at the end of the study, but there is a significant decrease in VA during the middle of the study presumably due to the development of cataracts.





These graphs show the mean visual acuity by treatment group, subdivided by duration of diabetic macular edema (DME) (shorter or longer than the median duration of the study). The median duration of DME (based on a historical time of first diagnosis) was approximately 1.9 years in Study A and approximately 1.6 years in Study B. (b) (4)





Treatment groups are shown by quartiles of the reported duration of diabetic macular edema. The mean duration of the first quartile was approximately 0.5 years. The mean duration of the second through fourth were approximately 1.4, 3 and 7 years, respectively. (b) (4)

(b) (4)

(b) (4)

6. Safety

The results from two Fame studies (Fame A and Fame B) form the basis for the safety evaluation. The 2 FAME studies were performed under one protocol and enrolled subjects during the same time period. The only significant difference between the studies was geographical location of the study sites. FAME A was conducted at 49 sites in 7 countries (US, Canada, 4 countries in the European Union [EU], and India). FAME B was conducted at 52 sites in 5 countries (US, India, and 3 countries in the EU). When the 2 studies enrolled subjects in the same countries, FAME A enrolled subjects in the northern portions of the countries involved, and FAME B enrolled subjects in the southern portions of the countries. The demographics of the 2 study populations were essentially the same.

The exposure of subjects was adequate. A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the Fame studies. The total number of treatments administered during the studies was 252, 488, and 534 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for the 0.2 µg/day group and 1.4 for the sham and 0.5 µg/day groups.

The completion rate was poor.

Dropouts and/or Discontinuations through Month 36 for Fame A&B

Disposition	**Sham**	**0.2 µg/day FA**	**0.5 µg/day FA**
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated[1]	185	375	393
Total completed (n, %)	126 (68.1)	272 (72.9)	279 (70.6)
Total discontinued (n,%):	59 (31.9)	102 (27.1)	116 (29.4)
Adverse events	5 (2.7)	4 (1.1)	15 (3.8)
Unsatisfactory therapeutic effect	3 (1.6)	0	1 (0.3)
Protocol violation	2 (1.1)	2 (0.5)	5 (1.3)
Subject withdrew consent	14 (7.6)	31 (8.2)	27 (6.8)
Lost to follow-up	24 (13.0)	37 (9.8)	37 (9.4)
Death	11 (5.9)	27 (7.2)	31 (7.8)
Unknown	0	1 (0.3)	0

The rate of cataract development was high.

Cataract Rate in study eye only

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)	61 (50.4)	192 (81.7)	235 (88.7)
Cataract operation	33 (27.3)	188 (80.0)	231(87.2)

Cataract formation (any type in Phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operations occurred in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. The drug's potential benefits do not overcome this significant risk in the phakic population.

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Cataract	53 (28.6)	171 (45.6)	213 (54.2)
Cataract operation	33 (17.8)	188 (50.1)	132 (58.8)
Cataract subcapsular	8 (4.3)	28 (7.5)	24 (6.1)
Conjunctival haemorrhage	20 (10.8)	43 (11.5)	50 (12.7)
Dry eye	11 (5.9)	23 (6.1)	22 (5.6)
Eye irritation	9 (4.9)	27 (7.2)	22 (5.6)
Eye pain	22 (11.9)	51 (13.6)	65 (16.5)
Glaucoma	4 (2.2)	19 (5.1)	18 (4.6)
IOP increased	21 (11.4)	132 (35.2)	170 (43.3)
Maculopathy	16 (8.6)	23 (6.1)	34 (8.7)
Myodepsia	13 (7.0)	67 (17.9)	68 (17.3)
Posterior capsule opacification	6 (3.2)	32 (8.5)	25 (6.4)
Retinal hemorrhage	11 (5.9)	9 (2.4)	17 (4.3)
Trabeculectomy	0	10 (2.7)	22 (5.6)
Vision blurred	13 (7.0)	28 (7.5)	20 (5.1)
Visual acuity reduced	17 (9.2)	39 (10.4)	35 (8.9)
Visual impairment	7 (3.8)	13 (3.5)	31 (7.9)
Vitrectomy	16 (8.6)	19 (5.1)	23 (5.9)
Vitreous detachment	12 (6.5)	26 (6.9)	20 (5.1)
Vitreous Hemorrhage	28 (15.1)	41 (10.9)	48 (12.2)

The rate of IOP elevation and glaucoma is unacceptable. The risk of increased intraocular pressure (IOP) is nearly three times higher in the drug treatment groups compared to the Sham (control) group. This adds additional risks to these patients from potential adverse drug reactions associated with the use of IOP lowering medications. The difference between Sham control and the 0.2µg/day FA in the percentage of patients requiring surgical intervention for the reduction of their IOP was 4-5%. The surgical risks in these patients and the potential

endophthalmitis risks associated with filtering surgery are significant additional risks. The drug's potential benefits do not overcome this significant risk.

The inserting procedure used in the preclinical and clinical trials was modified. The Agency requested testing of the modified insert. Study C-01-11-008 was conducted in part to evaluate the new inserter. A report of the study was submitted on March 27, 2013, along with individual listings of the study data [Electronic Submission, 5.3.5.2., List Patients With Batches and Individual Efficacy Response Data]. An initial group of approximately 59 patients were tested and based on those results supplementary in-process controls during manufacturing were added. A subsequent group of approximately 58 subjects were attempted to be implanted. In the group of 58 patients, 11 out of 58 (19%) of the observer questionnaires noted that there were observed difficulties with the study drug administration.

Subject	Lot	Question	Response	Comments
800103	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Difficult to move second step forward, Required 2nd person
800204	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Device was defective. Applicator/Kit was returned. Secondary kit used. Please consider this as "failed" attempt.
800702	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	The drug did not come out of the inserter enough to stay in the vitreous
801902	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Could not verify drug was present in barrel
803803	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Difficult to depress
803804	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Dr had to use 2 hands to push button to 2nd stage
803805	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	1st kit needle bent and med came out of needle before completely depressed. 2nd kit took two hands
803905	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Kit #244 was not used; technical complaint was issued.
806208	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	2nd kit unable to advance button to release study treatment while needle was in eye
807103	W0006366	5. Did you observe difficulties with the study drug administration? If yes, please explain.	Yes	Difficulty inserting injector tip into eye- Pressed hard to penetrate sclera
*807602	W0006366	4. Was the administration of the drug insert, performed as instructed? If no, please explain.	No	Investigational product not inserted. Investigator stated that he did not see insert in inserter. Another kit (#225) used.

*For subject 807602, Question 5 was not included in the reported data, however, Question 4 identified difficulty with the inserter.

Based on observations of those attempted procedures, it is suggest that either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties

experienced by investigators in delivering the drug product. In addition, the applicant should identify the supplementary in-process controls that were added.

7. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population. This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

8. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. The DSI Clinical Inspection Summary was finalized on 12/1/10.

Two sites were selected for inspection, one domestic and one foreign, due to enrollment of large numbers of study subjects, high number of INDs and lack of previous inspectional history. The preliminary classification of Clinical Investigator inspections of Drs. Blackburn (Kentucky) and Garg (India) are Voluntary Action Indicated (VAI). Although regulatory violations were noted at both of these sites, given the nature of the findings, DSI considered it unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

Dr. Blackburn (Study C-01-05-001B /Site 001/17) failed to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Dr. Garg (Study C-01-05-001A /Site 016/ 45) failed to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided. Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable. DMEPA again reviewed the name Iluvien for the NDA application. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle.

BIOSTATISTICS

The statistical reviewer deferred to the clinical review to weigh the benefit against the risk of this drug in the general population or in the subgroup of DME (b) (4) but the drug harms a significantly higher proportion of subjects compared to sham (the two main harms being IOP elevation and cataract development). (b) (4) However, this subgroup was determined post-hoc so any results should be considered with caution.

9. Labeling

A formal labeling review is deferred until additional data is submitted to support the application for Iluvien.

10. Regulatory Action

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended to be approved for the treatment diabetic macular edema based on the information submitted to date. The deficiencies include:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

   Specifically, data was not provided to support that the product is safe and effective (b) (4)

   a. For the proposed indication, (b) (4)

[redacted] (b) (4)

b. Results of the safety analyses demonstrated elevations of intraocular pressure of such magnitude as to require medical or surgical treatment. The difference between Sham control and the 0.2 µg/day fluocinolone acetonide (FA) in the percentage of patients requiring intraocular pressure (IOP) lowering medications was approximately 20-25%. This adds additional risks to these patients from potential adverse drug reactions associated with the use of IOP lowering medications. The difference between Sham control and the 0.2µg/day FA in the percentage of patients requiring surgical intervention for the reduction of their IOP was 4-5%. The surgical risks in these patients and the potential endophthalmitis risks associated with filtering surgery are significant additional risks.

The "Special Optic Nerve Head Assessment of the Fame Fundus Photographs by the [redacted] (b) (4) - Table 6" demonstrated an imbalance at month 36 in the percentage of patients with a worsening in the vertical cup-to-disc ratio (C/D). Eleven patients out of 219 patients (5%) in the 0.2µg/day FA group had worsening of their vertical C/D, compared to only one patient out of 102 patients (1%) treated with Sham. The reported 95% confidence interval (-7.5%, -0.6%) excluded zero. Glaucomatous progression of the C/D ratio is unusual in studies of 3 years or less, and the finding in this study is of concern.

c. Results of the safety analyses showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. At 36 months follow-up, cataract progression occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Many of the patients developing cataracts experienced a clinically significant loss in visual acuity. While many patients had restoration of their visual acuity after a cataract extraction and intraocular lens replacement, this was not true of all patients. A number of patients failed to return for follow-up examinations after cataract removal.

d. The applicant submitted an analysis of results based on a selected subgroup of patients who are said to have duration of DME [redacted] (b) (4) this analysis was not pre-specified in the protocol and was not included in the statistical analysis plan (SAP). The subgroup had been requested to be added by a study representative prior to the data lock, but the failure to include it in the protocol resulted in a failure to account for the multiplicity of adding additional subgroup analyses. The protocol and SAP defined subpopulations to be evaluated; a comparison of efficacy based on the median duration of DME was not one of the included subpopulations. This

subgroup of patients shows the same degree of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population.

e. Results of Study C-01-11-008 suggest that either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties experienced by investigators in delivering the drug product. In the group of 58 patients treated with the "to be marketed configuration," approximately 19% of the observer questionnaires noted that there were observed difficulties with the study drug administration.

To address the clinical and statistical deficiencies, the applicant should provide data from at least one adequate and well controlled clinical trial that demonstrates that Iluvien, at the dose and with the inserter proposed to be marketed, is safe and effective for the proposed indication you intend to market. It is recommended that a new study with at least 12 months of follow-up be submitted in which patients who have failed to respond to a three month or more course of anti-VEGF therapy are randomized between your drug product and continued anti-VEGF therapy.

2. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. All facilities and controls will need to comply with the cGMP regulations.

To address this deficiency, the application should be amended with facilities that are in compliance with cGMPs.

3. The study report for Study C-01-11-008 states that a supplementary in-process control during manufacturing of the injector was added.

Specific information of this change should be submitted.

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

/s/

WILEY A CHAMBERS
10/17/2013

Cross-Discipline Team Leader Review for NDA 201923

Date	October 15, 2013
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	A - Class 2 resubmission
PDUFA Goal Date	October 17, 2013
Type of Application	505(b)(1)
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	(b) (4)
Recommended:	Not Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is an active ingredient currently marketed in topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant. There is no previous marketing experience in the United States with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg and none reported from Europe where the product is commercially available.

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on *in vitro* and *in vivo* data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.

Note: In the amendment dated 9/9/2013, the applicant stated it was "formally revising the proposed indication for Iluvien in this NDA (b) (4)

(b) (4)

2. Background

Diabetic macular edema (DME), a serious, chronic, debilitating disease associated with diabetic retinopathy. In addition to various insulin products, Lucentis (ranibizumab injection) is approved for the treatment of DME; the supplemental biologics license application was approved 8/10/2012.

For a complete background and discussion regarding regulatory submissions and formal meetings with the applicant, see the Medical Officer's review, Section 2, dated 9/9/2013.

The applicant submitted an amendment to the application on 9/9/13. This amendment did not contain new efficacy information; although Iluvien is not a 505(b)(2) application, this amendment does cite the RIDE and RISE[1] studies (Phase 3, double-masked, randomized, multicenter, sham injection-controlled, 36-month [sham injection-controlled for 24 months] conducted by (b) (4) and intended to evaluate the efficacy and safety of Lucentis in patients with DME).

3. CMC

INSERTER:
History: During the development phase of this drug product (b) (4)

(b) (4)

(b) (4)

This was the packaging configuration used for all the preclinical and clinical studies. During the clinical studies, feedback was solicited from the

1 A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus (RISE); A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus (RIDE)

investigators on the inserter device. Feedback was also obtained from retinal specialists who were not part of the clinical study.

Figure 4: Iluvien Inserter Device

FAVOR study: The FAVOR study, C-01-08-006, entitled "A randomized, double-masked, pilot study of the safety and efficacy of 0.5 µg/day and 0.2 µg/day Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg in subjects with macular edema secondary to retinal vein occlusion", is an ongoing study (b) (4) The study utilized the new (b) (4) inserter and collected information from the treating physician on the performance of the inserter. In the FAVOR study no adverse events were reported related to the insertion procedure.

Open Label Trial: On March 2, 2011, IND 72,056 SDN 110 the following protocol was submitted titled, "An Open Label, Multi-center Extension Study of the Safety and Utility of the New Inserter of Iluvien (Fluocinolone Acetonide Intravitreal Insert) 0.19 mg and the Safety of Iluvien in Subjects with Diabetic Macular Edema." The applicant has provided the following data from the FAME Extension study. Subjects include those who had previously participated in the FAME studies (b) (4)

Trial C-01-01-008 (FAME Extension)
Open label, multi-center extension study of Safety and Utility of the New Inserter of Iluvien

Visit	0.2 µg/day FA			
	Commercial		Noncommercial	
	Safety (N=117) n (%)	Questionnaire (N=117) n (%)	Safety (N=3) n (%)	Questionnaire (N=4) n (%)
Screening	117 (100.0)	--	3 (100.0)[a]	--
Baseline (Day 0)	--	117 (100.0)	--	4 (100.0)
Telephone call (Day 1)	117 (100.0)	--	3 (100.0)	--
Week 1	116 (99.1)	--	3 (100.0)	--
Week 3	103 (88.0)	--	3 (100.0)	--
Week 6	79 (67.5)	--	3 (100.0)	--
Month 3	56 (47.9)	--	3 (100.0)	--
Month 6	57 (48.7)	--	3 (100.0)	--
Month 9	55 (47.0)	--	3 (100.0)	--
Month 12	29 (24.8)	--	3 (100.0)	--

[a] Subject 810702 discontinued the study following a failed attempt at study drug administration.

The clinical supplies used in this trial were comprised of 3 lots. Following the enrollment of 4 subjects with the first lot, a design improvement was implemented and a second lot was produced. After enrolling an additional 59 subjects, the study was put on hold as the second Complete Response Letter (CRL) was received from the FDA related to Alimera's submission of ILUVIEN for the treatment of DME. During (b) (4) a review of technical complaints for the second lot led to the implementation of supplementary in-process controls. A third batch was produced and enrollment was completed with an additional 58 subjects. A distinction was made during the statistical analysis between the first 4 subjects enrolled into the trial, ("noncommercial") and those subsequently enrolled in light of the design improvement, where the batches used after the first 4 subjects represent the commercial product ("commercial"). A total of 121 subjects were enrolled in this study: 4 subjects in the noncommercial group, and 117 subjects in the commercial group.

Per the applicant:

> "The technical complaints for this lot were generally characterized (b) (4)

Based on what was learned from the technical complaints and investigator interviews, upon commercialization of Iluvien, physician training will be enhanced with the following instructions, (a) do not allow the injector to fall below the horizontal plane after loading the insert with the initial advance of the button prior to insertion, this will mitigate the risk of the drug insert falling out of the inserter prior to drug administration (b) with the initial advance of the button, allow the button to completely rise upon reaching the first stop, (c) to complete the insertion once the needle is in the eye, ensure the button is advanced all the way to the final stop prior to withdrawal of the inserter.

From Summary of Physician Utilization study, "Once Iluvien is commercialized, physician training will be enhanced in order to avoid the types of issues experienced during the trial."

Initially 59 subjects were enrolled and then the trial was stopped for technical complaints. After being stopped and instituting an in-process control another 58 subjects were enrolled.

Results of Study C-01-11-008 suggest that either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties experienced by investigators in delivering the drug product. In the group of 57 patients treated with the "to be marketed configuration," approximately 19% of the observer questionnaires noted that there were observed difficulties with the study drug administration.

DRUG SUBSTANCE:

From the applicant's submission dated 6/1/2011:

Table 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
Identification by HPLC	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4),	CTM-200500
Related Substances		
(b) (4)	(b) (4) Not more than	CTM-200554
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Table 1: Specifications for Fluocinolone Acetonide (Continued)

Test	Acceptance Criteria	Analytical Method
(b) (4)	(b) (4) Not more than	
	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	(b) (4) Not more than	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4) µm	(b) (4) Not less than	(b) (4) MGR051FLU011
Particle µm	Not less than	
Particle µm	Not less than	
Polymorphism		
(b) (4)	Not less than (b) (4),	X-Ray Powder Diffraction
Microbial Limits		
Total Aerobic Count	(b) (4) Not more than	Current USP/NF <61> MTM-200155
Yeast/Mold Count	Not more than	
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
		(b) (4)

DRUG PRODUCT:

From the applicant's original submission dated 6/30/2010:

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)

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

From the applicant's submission dated 6/1/2011:

Table 1: Quality Control Specifications

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Specified Identified and Unidentified Individual Impurity		
Release	(b) (4) Not more than	CTM-200501
Stability	Not more than	
(b) (4)		
Release	Not more than	CTM-200562
Stability	Not more than	
Unspecified Individual Impurity		
Release	(b) (4) Not more than	CTM-200501
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4)	CTM-200502

Table 1: Quality Control Specifications (Continued)

Test	Specification	Method
Endotoxin	(b) (4)	PTS-200566 MTM-200033
Sterility		
Release		(b) (4)
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

From CMC review finalized 9/24/2013:

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

The new proposed acceptance criteria of (b) (4) µg/day for drug product *in-vitro* release rate was found acceptable by Dr. Tapash Ghosh in his review.

POLYMORPH TESTING

A CMC deficiency was sent in the Complete Response (CR) letter of November 10, 2011, regarding the polymorph testing method done at (b) (4) the polymorph testing site proposed in this NDA. The NDA resubmission dated March 27, 2013 contains a complete response and supporting documents for this CMC deficiency.

(b) (4)

Based on the solubility results and the release rate data from the six lots of drug products made with 3 lots of drug substance (b) (4)

Alimera still commits to a specification (b) (4)

The X-ray powder diffraction testing method is considered acceptable. System suitability acceptance criteria is not described. However, the equipment is calibrated (b) (4) for testing. Although linearity and range should be validated in the method validation, the validation results were found to support the intended use of this method since the goal of this testing is for confirmation.

EES Report

From CMC review finalized 10/15/2013:

Office of Compliance has made a determination as " Withhold" on the acceptability of the facilities on October 11, 2013 (see attached EES Report). Therefore, from the CMC perspective, this NDA is not recommended for approval.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 201923/000	**Sponsor:**	ALIMERA SCIENCES INC
Org. Code:	590		6120 WINDWARD PKY STE 290
Priority:	3		ALPHARETTA, GA 30005
Stamp Date:	30-JUN-2010	**Brand Name:**	FLUOCINOLONE ACETONIDE INTRAVITREAL INSE
PDUFA Date:	17-OCT-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	18-AUG-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; INSERT; FLUOCINOLONE ACETONIDE; .19MG

FDA Contacts:	Z. LI	Facility Reviewer		3017961798
	L. QI	Prod Qual Reviewer		3017961438
	S. FONG	Micro Reviewer	(HFD-003)	3017961501
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	D. WILLARD	Regulatory Project Mgr		3017960833
	L. NG	Team Leader	(HFA-320)	3017961426

Overall Recommendation:	WITHHOLD	on 11-OCT-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 21-SEP-2013	by EES_PROD		
	PENDING	on 08-AUG-2013	by EES_PROD		
	PENDING	on 15-JUL-2013	by EES_PROD		
	PENDING	on 22-MAY-2013	by EES_PROD		
	PENDING	on 22-MAY-2013	by EES_PROD		
	ACCEPTABLE	on 09-NOV-2011	by EES_PROD		
	PENDING	on 11-JUL-2011	by EES_PROD		
	ACCEPTABLE	on 23-JUN-2011	by EES_PROD		
	PENDING	on 24-MAY-2011	by EES_PROD		
	WITHHOLD	on 15-DEC-2010	by EES_PROD		

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: (b) (4) FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER		
Profile:	NOT ELSEWHERE CLASSIFIED	OAI Status:	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-OCT-2013		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: (b) (4) FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE RELEASE TESTER DRUG SUBSTANCE STABILITY TESTER		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	01-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE (b) (4)		
	DRUG SUBSTANCE OTHER TESTER		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-JUL-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	(b) (4)		
Profile:		OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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4. Nonclinical Pharmacology/Toxicology

The original Pharmacology Toxicology Review finalized 11/17/10 recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

From the ONDQA (Biopharmaceutics) Review finalized 9/23/13:

During the early stages of development, pSivida set a release rate specification of (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 noted that the current specification (b) (4)

The applicant proposed in this March 27, 2013, resubmission that the new proposed specification for release rate be (b) (4) µg/day.

The 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 applicant's request to use the release rate (b) (4) is acceptable by the Agency.

Test	Acceptance Criteria	Method
Release Rate	(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.

6. Sterility Assurance

Per the original Product Quality Microbiology review completed on 12/8/10:

The application is recommended for approval from a microbiology quality standpoint. There are no outstanding product quality deficiencies.

7. Clinical/Statistical - Efficacy

Note: No new efficacy data has been provided in the 4/17/13 or 9/9/13 submissions.

Efficacy

Regarding the original NDA submission dated 6/30/2010:

Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05) for the applicant's primary endpoint (i.e. proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline).

Regarding the resubmission dated 5/12/2011:

Subsequently to failing the original primary endpoint, the applicant proposed a new primary endpoint in the second Complete Response submission: Number (%) of Subjects with a ≥ 15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) The proposed new subgroup, (b) (4) had multiple issues:

1. The analysis of the proposed subgroup does not account for multiplicity because it had not pre-specified as proposed study population.
2. Diabetic macular edema (DME) is a disease that can wax and wane over the course of many years with varying degrees of macular involvement. Given the variable course of DME over time, close follow-up of patients during a period would be required to establish that patients had a "Duration of DME (b) (4) ." In the submitted studies, the determination of DME duration was made without any examinations during the period of time in question.

Regarding the resubmission dated 4/17/13:

The applicant has proposed a new indication: (b) (4) This submission contained Clinical Study Reports and post-text data tables for FAME Study C-01-05-001A, FAME Study C-01-05-001B, and Study C-01-06-002. No new efficacy data was provided.

A meeting was requested by Alimera to obtain feedback on the progress of the review and to discuss any identified deficiencies in the 4/17/ 2013, resubmission. The minutes for the meeting held 7/26/2013, were finalized in DARRTS on 8/23/13. Per those minutes:

> … Alimera proposed (b) (4)

…The Agency noted that [redacted] this continues to be an issue for this product…

Regarding the amendment dated 9/9/13:

This amendment did not contain new efficacy information.

The applicant stated it was "formally revising the proposed indication for Iluvien in this NDA [redacted]

[redacted]

There are no submitted studies to support the proposed new indication. [redacted]

Summary Statement

Iluvien has not demonstrated efficacy [redacted]

1. A post-hoc analysis demonstrated that [redacted] analysis of the subgroup of patients [redacted] did not account for multiplicity as the study population was not pre-specified as one of the many proposed analyzes in the analysis plan.
2. The proposed [redacted] has not been studied. [redacted]

8. Safety

No additional safety information for the two FAME studies is available. Reanalyses are presented. Safety Update information for the following additional studies is available:

1) Study C-01-11-008 (FAME Extension Study)

The FAME Extension Study (Study C-01-11-008) is an open-label, multi-center extension study of the safety and utility of the new applicator of ILUVIEN® (FA intravitreal implant) 0.19 mg (0.2 µg/day FA) and the safety of ILUVIEN in subjects with DME. Subjects include those who had previously participated in the FAME studies (b) (4)

Note: (b) (4) See Module 5, Section 5.3.5.2 for the protocol dated 3/1/2011.

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

The FAMOUS study (Study C-01-06-002) was an open-label, 36-month pharmacokinetic study of 0.2 µg/day FA and 0.5 µg/day FA in subjects with DME.

3) Safety Update for Study C-01-08-004 (the MAP-GA Study)

> The MAP-GA study (Study C-01-08-004) is an ongoing, single-center, randomized, single- masked, fellow eye comparison study of the effects of FA implants in subjects with geographic atrophy.

4) Safety Update for Study C-01-08-006 (the FAVOR Study)

The FAVOR study (Study C-01-08-006) is an ongoing multicenter, randomized, double-masked study of the effects of 0.2 µg/day FA and 0.5 µg/day FA in subjects with central or branch retinal vein occlusion (CRVO or BRVO).

Common Adverse Event Table

Common Ocular Adverse Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
Most Common Events[1]	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)	0.2 µg/day FA (N = 20) n (%)	0.5 µg/day FA (N = 17) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 7) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 6) n (%)	0.2 µg/day FA (N = 120) n (%)
Cataract	171 (45.6)	213 (54.2)	11 (55.0)	4 (23.5)	1 (12.5)	3 (37.5)	1 (10.0)	3 (50.0)	3 (2.5)
Cataract operation	188 (50.1)	231 (58.8)	13 (65.0)	5 (29.4)	2 (25.0)	1 (12.5)	2 (20.0)	1 (16.7)	1 (0.8)
Cataract subcapsular	28 (7.5)	24 (6.1)	1 (5.0)	3 (17.6)	1 (12.5)	0	1 (10.0)	0	0
Conjunctival haemorrhage	43 (11.5)	50 (12.7)	7 (35.0)	7 (41.2)	1 (12.5)	1 (12.5)	1 (10.0)	1 (16.7)	26 (21.7)
Dry eye	23 (6.1)	22 (5.6)	1 (5.0)	2 (11.8)	0	0	0	0	3 (2.5)
Eye irritation	27 (7.2)	22 (5.6)	1 (5.0)	2 (11.8)	0	0	0	0	2 (1.7)
Eye pain	51 (13.6)	65 (16.5)	4 (20.0)	2 (11.8)	2 (25.0)	2 (25.0)	3 (30.0)	1 (16.7)	11 (9.2)
Glaucoma	19 (5.1)	18 (4.6)	1 (5.0)	1 (5.9)	0	0	0	0	2 (1.7)
Intraocular pressure increased	132 (35.2)	170 (43.3)	4 (20.0)	7 (41.2)	1 (12.5)	1 (12.5)	2 (20.0)	0	9 (7.5)
Maculopathy	23 (6.1)	34 (8.7)	4 (20.0)	0	0	0	0	0	2 (1.7)
Myodesopsia	67 (17.9)	68 (17.3)	7 (35.0)	6 (35.3)	0	1 (12.5)	0	1 (16.7)	5 (4.2)
Posterior capsule opacification	32 (8.5)	25 (6.4)	2 (10.0)	1 (5.9)	0	0	0	0	1 (0.8)
Trabeculectomy	10 (2.7)	22 (5.6)	1 (5.0)	2 (11.8)	0	0	0	0	0
Vision blurred	28 (7.5)	20 (5.1)	1 (5.0)	1 (5.9)	0	0	0	0	2 (1.7)
Visual acuity reduced	39 (10.4)	35 (8.9)	0	1 (5.9)	0	0	0	0	4 (3.3)
Visual impairment	13 (3.5)	31 (7.9)	0	2 (11.8)	0	0	0	0	2 (1.7)
Vitrectomy	19 (5.1)	23 (5.9)	1 (5.0)	0	0	0	0	0	0
Vitreous detachment	26 (6.9)	20 (5.1)	2 (10.0)	1 (5.9)	0	1 (12.5)	1 (10.0)	0	2 (1.7)
Vitreous haemorrhage	41 (10.9)	48 (12.2)	0	0	0	0	0	0	7 (5.8)

1 Ocular events with an incidence ≥ 5.0 % in either active treatment group in the integrated FAME studies. Incidence was based on occurrence in the study eye.

The adverse events of increased IOP and cataract formation are also evident in these additional trials.

IOP

The applicant has submitted Tables comparing IOP elevation in the Acute DME cases versus Chronic DME cases.

Table 12: Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Chronic DME and Acute DME Subgroups: Safety Population)

Category	0.2 µg/day		
	Overall FAME N = 375 n (%)	Chronic DME N = 209 n (%)	Acute DME N = 165 n (%)
Any IOP-lowering medication	144 (38.4)	75 (35.9)	69 (41.8)
IOP elevation considered an AE[1]	139 (37.1)	72 (34.4)	67 (40.6)
IOP elevation increase ≥12 mmHg	108 (28.8)	54 (25.8)	54 (32.7)
IOP elevation to over >25 mmHg	123 (32.8)	65 (31.1)	58 (35.2)
IOP elevation to over >30 mmHg	69 (18.4)	31 (14.8)	38 (23.0)

Table 12: Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Chronic DME and Acute DME Subgroups: Safety Population) (Continued)

Category	0.2 µg/day		
	Overall FAME N = 375 n (%)	Chronic DME N = 209 n (%)	Acute DME N = 165 n (%)
Trabeculoplasty performed	5 (1.3)	4 (1.9)	1 (0.6)
Trabeculectomy performed	10 (2.7)	6 (2.9)	4 (2.4)
Glaucoma surgery performed[2]	8 (2.1)	5 (2.4)	3 (1.8)
Vitrectomy performed for elevated IOP	1 (0.3)	0	1 (0.6)
Any incisional surgery intervention[3]	18 (4.8)	11 (5.3)	7 (4.2)

Reference: Refer to Module 5, 5.3.5.3, ISS-36 Months, Table 5.11 and Module 1, 1.11.3, Efficacy Amendment, Sequence 0022, Section 12.4, Table ISS.10.

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

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

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

Table 3. Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Sham and 0.2 µg/day Subgroups: Safety Population)

Category	Treatment Group	
	Sham (N=185) N (%)	0.2 µg/day (N=375) N (%)
IOP elevation considered an AE[1]	22 (11.9)	139 (37.1)
IOP elevation increase ≥ 12 mm Hg	15 (8.1)	108 (28.8)
IOP elevation > 25 mm Hg	18 (9.7)	123 (32.8)
IOP elevation > 30 mm Hg	8 (4.3)	69 (18.4)
Trabeculoplasty performed	0 (0)	5 (1.3)
Trabeculectomy performed	0 (0)	10 (2.7)
Glaucoma surgery performed[2]	1 (0.5)	8 (2.1)
Vitrectomy performed for elevated IOP	0 (0)	1 (0.3)
Any surgical procedure performed	1 (0.5)	18 (4.8)

1 Includes adverse event reports of ocular hypertension and intraocular pressure increased.
2 Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocyclodestruction, and laser peripheral iridotomy. 3 Includes trabeculectomy, glaucoma surgery and vitrectomy for elevated IOP

Table 3 has the data comparing the Sham group to the 0.2 µg/day group.

The Adverse rates for increased IOP and surgeries performed for the Chronic DME 0.2 µg/day group are higher than the Sham group and remain a concern.

Cataracts

The applicant has submitted Table 7 comparing Cataract events in the Acute DME cases versus Chronic DME cases.

Table 7: Number (%) of Phakic Subjects Reporting Cataract-Related Events (Integrated FAME Studies and Chronic DME and Acute DME Subgroups: Safety Population)

Cataract Related Event	Sham n/N (%)	0.2 µg/day n/N (%)
All Phakic Subjects		
Any Cataract	61/121 (50.4)	192/235 (81.7)
Cataract Operation	33/121 (27.3)	188/235 (80.0)
Phakic Subjects with Chronic DME		
Any Cataract	34/66 (51.5)	98/114 (86.0)
Cataract Operation	24/66 (36.4)	97/114 (85.1)
Phakic Subjects with Acute DME		
Any Cataract	26/54 (48.1)	94/121 (77.7)
Cataract Operation	8/54 (14.8)	91/121 (75.2)

Reference: Refer to Module 5, 5.3.5.3, ISS-36 Month Table 5.15 and Section 9.6, Table 11.

Table 5. Incidence of Cataract events in the Study Eye of Phakic Subjects Integrated Fame Studies, Safety Studies

Category	Treatment Group	
	Sham (N=121) N (%)	0.2 µg/day (N=235) N (%)
Any cataract related event	61 (50.4)	192 (81.7)
Cataract NOS	51 (41.1)	168 (71.5)
Cataract cortical	1 (0.8)	1 (0.4)
Diabetic cataract	0 (0)	1 (0.4)
Nuclear cataract	5 (4.1)	8 (3.4)
Subcapsular Cataract	8 (6.6)	27 (11.5)
Cataract operation	33 (27.3)	188 (80.0)

Table 5 has data comparing the Sham group to the 0.2 µg/day group.

The Adverse rates for cataract events for the Chronic DME 0.2 µg/day group are higher than the Sham group and remain a concern.

Cup/Disc (C/D) Ratio Changes

A special assessment of the optic nerve head was performed on the fundus photographs obtained from subjects who were enrolled in the FAME studies. The (b) (4) performed this assessment. The purpose of this assessment was to determine the long term effects of sustained delivery of fluocinolone acetonide from intravitreal implants on the optic nerve head in subjects diagnosed with DME.

Number (%) of Subjects who had a Worsening in the Vertical Cup-to-Disc Ratio (Integrated FAME Studies: Safety Population)

	Sham		0.2 µg/day	
Time Point	N	n (%)	N	n (%)
Month 36	102	1 (1.0%)	219	11 (5.0%)
Difference (95% CI)			-4.0% (-7.5%, -0.6%)	
P-value			0.076	
Last Observation	166	2 (1.2%)	345	12 (3.5%)
Difference (95% CI)			-2.3% (-4.8%, 0.3%)	
P-value			0.134	

The applicant concludes that when the relationship between the number of study treatments and increased cupping is explored across the sham and 0.2 µg/day FA groups (Text Table 24), no trend is seen toward increased risk with increased exposure to the 0.2 µg/day FA dose.

There are several problems with the conclusions made by the applicant regarding these assessments:

Three year follow-up may be too soon to demonstrate the effect of elevated IOP on cup/disc ratio and visual fields.

Although the Table provided in the text of the submission (see above) suggests no significant difference between groups, the confidence intervals for both Iluvien doses do not cross zero at Month 36 indicating that there is a significant difference between groups (i.e. Iluvien worse than sham) in vertical cup/disc ratio. See below.

Table 5.
Summary of the Percentage of Subjects with a Worsening in the Vertical Cup-to-Disc Ratio
(Population: Intent-to-Treat)
Time Point: Month 36

	Sham (N=102)			0.2 ug/day (N=219)			0.5 ug/day (N=230)		
Visit	N	n	%	N	n	%	N	n	%
Month 36	102	1	1.0	219	11	5.0	230	11	4.8
Difference						-4.0			-3.8
95% CI						(-7.5, -0.6)			(-7.2, -0.4)
P-value						0.076			0.087

Vitrectomy and Panretinal Photocoagulation

Applicant states that treatment with ILUVIEN provides the additional benefits of reducing the need for vitrectomy and panretinal photocoagulation (PRP).

Table 6: Number (%) of Subjects Undergoing Vitrectomy and Panretinal Photocoagulation in the Integrated FAME Studies (Integrated FAME Studies: Safety Population and Subgroup with Chronic DME)

	Chronic DME		Safety Population	
	Treatment Group		Treatment Group	
Event	Sham (N=112)	0.2 µg/day (N=209)	Sham (N=185)	0.2 µg/day (N=375)
Vitrectomy, n (%)	9 (8.0)	9 (4.3) P=0.158	19 (10.3)	24 (6.4) P=0.106
Panretinal Photocoagulation, n (%)	24 (21.4)	23 (11.0) P=0.003	44 (23.8)	50 (13.3) P=0.002

Reference: Refer to Module 5, 5.3.5.3, ISE-36 Month, Table 2.3.5.3.1.A and Table 2.3.6.2 and Module 1.11.3, Efficacy Information Amendment Sequence 0022, Section 12.3, Table ISE.17 and Table ISE.20.

The difference in vitrectomy rates is not statistically significant. The difference in Panretinal Photocoagulation is not replicated in each study.

BCVA

Table 4: Between Treatment Difference in Cumulative Frequencies of Change from Baseline Best Corrected Visual Acuity at Month 36 in Subjects with Chronic DME (Integrated FAME Studies: Full Analysis Population)

Cumulative Change from Baseline	Treatment Group		Difference
	Sham (N = 112)	0.2 µg/day (N = 209)	
	n (%)	n (%)	%
≥0 Letters	68 (60.7%)	162 (77.5%)	16.8%
≥5 Letters	52 (46.4%)	141 (67.5%)	21.0%
≥10 Letters	33 (29.5%)	108 (51.7%)	22.2%
≥15 Letters	15 (13.4%)	71 (34.0%)	20.6%
≥20 Letters	6 (5.4%)	44 (21.1%)	15.7%
≥25 Letters	4 (3.6%)	25 (12.0%)	8.4%
≥30 Letters	2 (1.8%)	12 (5.7%)	4.0%

Reference: see Section 9.6, Table 25.

The primary endpoint is ≥ 15 Letters improvement in BCVA. About one in five subjects benefit over the control (Sham).

Risk Benefit

Alimera has conducted a benefit to risk assessment based on a determination of NNT (Number Needed to Treat for a benefit to be realized) and NNH (Number Needed to treat for a particular Harm associated with the therapy to occur).

The applicant has constructed the NNT and NNH component of the following table. with the NNH includes an incorrect computation which gives misleading results. NNH is reported by the applicant (b) (4)

Table 5: Overall Summary of Number Needed To Treat and Number Needed to Harm for ILUVIEN

(b) (4)

Summary Statement

At 36 Months the risk of cataract formation, cataract operation, and increased IOP are adverse events that occur at significantly high rates in the drug group when compared to the Sham group.

9. Advisory Committee Meeting

No Advisory Committee Meeting has been scheduled. There are no outstanding clinical issues which are believed to benefit from an advisory committee discussion at this time.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application was reviewed by the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed with the Division that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested in the original review cycle. The DSI Clinical Inspection Summary was finalized on 12/1/10.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided.

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable.

DMEPA again reviewed the name Iluvien for the NDA application. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable.

DDMAC
The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle.

BIOSTATISTICS
From the Biostatistics review dated 4/12/2013 regarding the 3/27/2013 Class 2 resubmission:

Alimera is applying for an indication (b) (4)

Alimera argued (b) (4)

This resubmission does not include any new efficacy data compared to previous submissions.

12. Labeling

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval (b) (4) A formal labeling review is deferred until additional data is submitted to support the application for Iluvien.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval (b) (4)

RISK BENEFIT ASSESSMENT:
There is not substantial evidence to demonstrate that the benefits of the drug outweigh its risks for either the low dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.25 µg/day) or the high dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.5 µg/day). The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema. This recommendation is based on the results from the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) studies submitted with 36 month data for the low dose version of Iluvien (0.19 mg).

At 36 months follow-up cataract formation occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes reaching a level of impairment such that cataract operations

occur in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Increased IOP occurred in 11% of the Sham group study eyes versus 35% in the 0.2 µg/day FA study eyes. The risk of increased IOP was increased 3-fold in the 0.2 µg/day FA drug group.

RECOMMENDED LANGUAGE FOR THE COMPLETE RESPONSE LETTER:

The April 17, 2013, submission constituted a complete response to our November 10, 2011, action letter. We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

   Specifically, you have not provided data to support that the product is safe and effective (b) (4)

   a. You have proposed to revise your indication (b) (4)

   b. Results of the safety analyses of your clinical trials have demonstrated elevations of intraocular pressure of such magnitude as to require medical or surgical treatment. The difference between Sham control and the 0.2 µg/day fluocinolone acetonide (FA) in the percentage of patients requiring intraocular pressure (IOP) lowering medications was approximately 20-25%. This adds additional risks to these patients from potential adverse drug reactions associated with the use of IOP lowering medications. The difference between Sham control and the 0.2µg/day FA in the percentage of patients requiring surgical intervention for the reduction of their IOP was 4-5%. The surgical risks in these patients and the potential endophthalmitis risks associated with filtering surgery are significant additional risks.

      The "Special Optic Nerve Head Assessment of the Fame Fundus Photographs by the (b) (4) Table 6" demonstrated an imbalance at month 36 in the percentage of patients with a worsening in the vertical

cup-to-disc ratio (C/D). Eleven patients out of 219 patients (5%) in the 0.2µg/day FA group had worsening of their vertical C/D, compared to only one patient out of 102 patients (1%) treated with Sham. The reported 95% confidence interval (-7.5%, -0.6%) excluded zero. Glaucomatous progression of the C/D ratio is unusual in studies of 3 years or less, and the finding in this study is of concern.

c. Results of the safety analyses of your clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. At 36 months follow-up, cataract progression occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Many of the patients developing cataracts experienced a clinically significant loss in visual acuity. While many patients had restoration of their visual acuity after a cataract extraction and intraocular lens replacement, this was not true of all patients. A number of patients failed to return for follow-up examinations after cataract removal.

d. In support of your application you have submitted an analysis of results based on a retrospectively selected subgroup of patients who are said to have duration of DM (b) (4) [redacted] this analysis as described in your June 19, 2012, briefing package was not pre-specified in the protocol and was not included in the statistical analysis plan (SAP). While the subgroup may have been requested to be added by a study representative prior to the data lock, the failure to include it in the protocol resulted in a failure to account for the multiplicity of adding additional subgroup analyses. The protocol and SAP defined subpopulations to be evaluated; a comparison of efficacy based on the median duration of DME was not one of the included subpopulations. Furthermore, we note that this subgroup of patients shows the same degree of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population.

e. Results of Study C-01-11-008 suggest that either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties experienced by investigators in delivering the drug product. In the group of 57 patients treated with the "to be marketed configuration," approximately 19% of the observer questionnaires noted that there were observed difficulties with the study drug administration.

To address the clinical and statistical deficiencies, you will need to provide data from at least one adequate and well controlled clinical trial that demonstrates that Iluvien, at the dose and with the inserter proposed to be marketed, is safe and effective for the proposed indication you intend to market. It is recommended that a new study with at least 12 months of follow-up be submitted in which patients who have failed to respond to a three month or more course of anti-VEGF therapy are randomized between your drug product and continued anti-VEGF therapy.

2. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. All facilities and controls will need to comply with the cGMP regulations.

   To address this deficiency, please amend the application with facilities that are in compliance with cGMPs or notify us when all currently submitted facilities are in compliance with cGMPs.

3. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated 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.

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/s/

WILLIAM M BOYD
10/16/2013

WILEY A CHAMBERS
10/17/2013

Medical Officer Review - NDA 201923

Date	August 16, 2013
From	Martin P. Nevitt, M.P.H., M.D.
Subject	Medical Officer Review of Complete Response
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	April 17, 2013
PDUFA Goal Date	October 17, 2013
Type of Application	NDA
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Recommended:	Not Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic, and ophthalmic products including an ophthalmic product where it is an intravitreal implant [i.e. Retisert (fluocinolone acetonide intravitreal implant) 0.59mg].

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal implant which releases fluocinolone acetonide (FA) and has been developed for the treatment of diabetic macular edema. Iluvien has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated by the applicant that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter. The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

Iluvien (fluocinolone acetonide intravitreal insert) is approved in Austria, France, Germany, Portugal and Spain. The UK's National Institute for Health and Care Excellence (NICE) issued a draft guidance for Iluvien (fluocinolone acetonide intravitreal insert) and recommended it for the treatment of pseudophakic patients with chronic diabetic macular edema (DME) considered unresponsive to available therapies.

2. Background

Diabetic macular edema (DME), a serious, chronic, debilitating disease, is one of the causes of vision loss associated with diabetic retinopathy.

The drugs approved for DME are Insulin and Lucentis (ranibizumab injection).

I. Applicant's Pre-NDA Regulatory History

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008 and a Pre-NDA meeting was held on March 4, 2010.

II. Original NDA submission

NDA 201923 was submitted June 30, 2010, as a Priority review with a PDUFA goal date of December 30, 2010.

A Complete Response action was taken December 22, 2010, outlining that the application could not be approved in its present form. A summary of the clinical reasons for this action are described below in Complete Response (#1):

III. Agency December 22, 2010, Complete Response (# 1) Letter

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

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.

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.

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.

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.

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.

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.

IV. February 2, 2011, Type A Guidance meeting

On February 2, 2011, a Type A Guidance meeting was held with the Applicant to discuss with the Division the steps necessary for the application approval. Specifically, the following clinical issues were reiterated:

1. Alimera must demonstrate a "win" where the benefits outweigh the risks of using the drug product. Carving out a subset is suggested when the subsets can be identified prior to starting the study. 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. Demonstration of safety and efficacy to support approval of an NDA will require that at least 2 adequate and well-controlled, multi-center trials show that the benefits of the drug product outweigh its risks. To demonstrate a "win" would require statistical significance (p value ≤ 0.05) in at least two trials for the primary endpoint (the primary endpoint in the trials was defined as the proportion of subjects with a ≥ 15 letter increase in BCVA on the ETDRS eye chart at Month 24. (Given the timing of the confounding effect of cataract formation and extraction the primary endpoint would be at Month 36 and the data would be re-submitted with this time point.)

2. 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). The Division stated that the final configuration of the inserter used in the trials was required before submitting the NDA. As presented in the NDA submission, it was not clear that the final product was going to be used in the way it was actually used during the trials. When those trials are completed, Alimera can submit the results to the NDA. The trials should be conducted in the indication intended for use.

V. Applicant's response to Agency's December 22, 2010, Complete Response (#1) Letter

On May 12, 2011 the applicant submitted its response to the action taken on December 22, 2010, which included the requested 36 Month data.

Based on the information submitted a Complete Response action was taken on November 10, 2011, outlining that the application could not be approved in its present form. A summary of the clinical reasons for this action are described below in Complete Response (#2) below.

VI. Agency November 11, 2011, Complete Response Letter (# 2)

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

Specifically, based on the results of your controlled clinical trials C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. Specifically, you have not provided data to support that the product is safe and effective in the treatment of patients with diabetic macular edema (DME).

a. Results of your controlled clinical trials C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), did not demonstrate statistically and clinically significant benefit for your primary endpoint of best corrected visual acuity (BCVA) at 36 months. As we have noted previously, efficacy at earlier time points was low (26-(b) (4)% vs. 14-18%), the results were not robust as the difference between groups with respect to mean visual acuity was small and not significant. Although some beneficial effect appeared to occur during the first 6 months, the product then appeared to cause clinically significant decreases in visual acuity at month 24, and was not significantly different from sham treatment by month 36.

b. Results of the safety analyses of your clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. Furthermore, the risk of increased intraocular pressure (IOP) is nearly three times higher in the Iluvien treatment arm than the control arm. The risks of these adverse reactions are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

c. The to-be-marketed Iluvien Inserter is different from the inserter used is clinical trials, and clinical data from patients treated for diabetic macular edema with the new inserter are not provided in the application. The application only includes data on 8 patients from Study C-01-08-006 who have been enrolled in this study of macular edema in retinal vein occlusion.

d. Your have proposed to revise your indication (b) (4) In support of this revision you have submitted a post-hoc analysis of the results based on a retrospectively selected subgroup of patients who are said to have duration of DME (b) (4)

[redacted] this analysis was not pre-specified in the protocol, was not included in the statistical analysis plan (SAP), was not adjusted for multiplicity.
Furthermore, we note that this subgroup of patients shows the same degree of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population.

To address the clinical and statistical deficiencies, you will need to provide data from two controlled clinical trials that demonstrate that Iluvien, at the dose proposed to be marketed, is safe and effective for the proposed indication you intend to study and seek in labeling. Based on the current trials it appears that neither the 0.2 microgram/day nor 0.5 microgram/day dose is safe and effective, therefore your development program would likely involve new clinical trials, and should include the evaluation of the Iluvien Inserter you propose to market. If these trials are intended to involve patients with diabetic macular edema [redacted] duration, you will need to provide specific objective criteria and documentation that subjects had DME [redacted] because DME is a disease that can wax and wane over the course of many years with varying degrees of macular involvement.

VII. June 19, 2012, Type B Guidance meeting

On June 19, 2012, a Type B Guidance meeting was held with the Applicant to discuss with the Division the steps necessary for the application approval. Following the meeting the following additional comments were provided to the Applicant 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?

VIII. Current Submission dated April 17, 2013

On April 17, 2013 the applicant submitted its response to the action taken on November 11, 2011, Complete Response (#2) and is the information provided in this review.

In this submission the applicant has provided additional information and has modified the indication to:

[redacted]

(b) (4)

The Applicant requested a meeting with the FDA during the review of the Complete Response (#2) and a Type B meeting was granted and held on July 26, 2013.

3. CMC

Refer to CMC review.

4. Nonclinical Pharmacology/Toxicology

The original Pharmacology Toxicology Review finalized 11/17/10 recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 11/18/2010:

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.

6. Sterility Assurance

Refer to the Product Quality Microbiology review.

7. Clinical/Statistical – Efficacy

Note: No new efficacy data has been provided in this submission.

Background

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness $\geq$ 250 microns.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 μg/day. It was anticipated by the applicant that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

Originally, the primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline; Complete Response (#1) modified the endpoint to be evaluated at Month 36, instead of Month 24, compared to baseline.

Applicant's Response to Item #1 of the Agency's November 11, 2011, Complete Response Letter (# 2)

Primary Efficacy at 36 Months

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

Time Point	FAME Study A			FAME Study B		
	Treatment Group			Treatment Group		
	Sham	0.2 µg/day FA	0.5 µg/day FA	Sham	0.2 µg/day FA	0.5 µg/day FA
	N=95	N=190	N=196	N=90	N=186	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 (%)						
Difference[1]						
P-value[2]						

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 stratified by baseline VA.

Reviewer's comments:

Fame A and B studies do not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05).

Applicant's Response to Item #2 of the Agency's November 11, 2011, Complete Response Letter (# 2)

Primary Efficacy at 36 Months in a Post-Hoc Subgroup Analysis

The applicant subsequently performed multiple analyses and determined that the following subgroup (b) (4) at Month 36:

(b) (4)

The analyses for this subgroup follows:

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, Full Analysis Population = ITT with LOCF)

(b) (4)

(b) (4)

Reviewer's comments:

(b) (4)

The applicant is pursuing the 0.2 µg/day dose for approval.

Efficacy

Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05) for the applicant's original primary endpoint. The newly proposed primary endpoint was not adequately defined. Efficacy of this drug product has not been satisfactorily demonstrated for the original or the revised indications.

The applicant's proposed new subgroup, (b) (4) has multiple issues and concerns:

1. The a priori primary efficacy endpoint for either dose (0.2 µg/day or 0.5 µg/day) of the FA intravitreal insert was for it to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24, (b) (4) compared to baseline.

Fame A and B studies did not demonstrate statistically significant results for the original primary endpoint at either dose at 36 months (p values all > 0.05).

2. Subsequently to failing the primary endpoint, the applicant proposed the new primary endpoint:

(b) (4)

In this submission the applicant states:

(b) (4)

The Agency disagrees that there is an appropriate post-hoc multiplicity adjustment due to the failure of the 36 month evaluation.

In addition, the Agency continues to 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.

3. The endpoint was changed to the following criteria: subjects with "duration of DME (b) (4) "

> "The DME duration calculation for subjects in the FAME studies was based on (b) (4) "

Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time. Because DME can wax and wane over time, the proposed subgroup "Duration of DME (b) (4)" is not well defined nor is it well documented that the subjects had DME (b) (4)

The Definition of duration of DME was not adequately assessed as a study inclusion criterion given DME can wax and wane over time.

An additional concern is whether the date of diagnosis is based on patient memory as reported by the patient to the treating physician. Patient reported events, based on one's prior memory, are often unreliable.

4. Fame A and B studies were not performed with the final drug configuration (b) (4)

The Agency has indicated that because the injector proposed for marketing is different from the injector used in the clinical studies, Alimera should provide data on 100 eyes using the new injector. The applicant has provided the following data from the FAME Extension study.

The FAME Extension Study (Study C-01-11-008) is an open-label, multi-center extension study of the safety and utility of the new applicator of ILUVIEN® (FA intravitreal implant) 0.19 mg (0.2 µg/day FA) and the safety of ILUVIEN in subjects with DME. Subjects include those who had previously participated in the FAME studies (b) (4)

Trial C-01-01-008 (FAME Extension)
Open label, multi-center extension study of Safety and Utility of the New Inserter of Iluvien

Visit	0.2 µg/day FA			
	Commercial		Noncommercial	
	Safety (N=117) n (%)	Questionnaire (N=117) n (%)	Safety (N=3) n (%)	Questionnaire (N=4) n (%)
Screening	117 (100.0)	--	3 (100.0)[a]	--
Baseline (Day 0)	--	117 (100.0)	--	4 (100.0)
Telephone call (Day 1)	117 (100.0)	--	3 (100.0)	--
Week 1	116 (99.1)	--	3 (100.0)	--
Week 3	103 (88.0)	--	3 (100.0)	--
Week 6	79 (67.5)	--	3 (100.0)	--
Month 3	56 (47.9)	--	3 (100.0)	--
Month 6	57 (48.7)	--	3 (100.0)	--
Month 9	55 (47.0)	--	3 (100.0)	--
Month 12	29 (24.8)	--	3 (100.0)	--

[a] Subject 810702 discontinued the study following a failed attempt at study drug administration.

The clinical supplies used in this trial were comprised of 3 lots. Following the enrollment of 4 subjects with the first lot, a design improvement was implemented and a second lot was produced. After enrolling an additional 59 subjects, the study was put on hold as the second CRL was received from the FDA related to Alimera's submission of ILUVIEN for the treatment of DME. During (b) (4) a review of technical complaints for the second lot led to the

implementation of a supplementary in-process control. A third batch was produced and enrollment was completed with an additional 58 subjects. A distinction was made during the statistical analysis between the first 4 subjects enrolled into the trial, ("noncommercial") and those subsequently enrolled in light of the design improvement, where the batches used after the first 4 subjects represent the commercial product ("commercial"). A total of 121 subjects were enrolled in this study: 4 subjects in the noncommercial group, and 117 subjects in the commercial group.

Per the applicant:

> "The technical complaints for this lot were generally characterized [redacted] (b) (4)

How applicant proposes on managing Technical Issues with [redacted] (b) (4) Inserter in the future

Based on what was learned from the technical complaints and investigator interviews, upon commercialization of ILUVIEN, physician training will be enhanced with the following instructions, (a) do not allow the injector to fall below the horizontal plane after loading the insert with the initial advance of the button prior to insertion, this will mitigate the risk of the drug insert falling out of the inserter prior to drug administration (b) with the initial advance of the button, allow the button to completely rise upon reaching the first stop, (c) to complete the insertion once the needle is in the eye, ensure the button is advanced all the way to the final stop prior to withdrawal of the inserter.

From Summary of Physician Utilization study, "Once Iluvien is commercialized, physician training will be enhanced in order to avoid the types of issues experienced during the trial."

Reviewer's comments:

The applicant states 121 subjects were enrolled with 4 subjects in the noncommercial group and 117 in the commercial group. The product is not yet approved and therefore no distinction should be made between a commercial and noncommercial product since both are unapproved products.

It is concerning that initially 59 subjects were enrolled and then the trial was stopped for technical complaints. After being stopped and instituting an in-process control another 58 subjects were enrolled.

It is recommended that a minimum of 100 subjects be enrolled with the final drug formula and with its final drug [redacted] (b) (4) dispensing system. Only 58 eyes with the final configuration have been

enrolled in the Open label trial. Additionally, a control group is recommended due to the limitations of Open label trials.

Summary of Inserter Questionnaires

	0.2 µg/day FA			
	Commercial (N=117)		Noncommercial (N=4)	
Treatments Attempted	130		4	
Inserter Questions	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**
Were you able to see the drug insert in the window of the inserter?	127 (97.7)	3 (2.3)	4 (100.0)	0 (0.0)
Were the instructions in the protocol for the process of removing the ILUVIEN® Inserter from the tray and moving the drug insert into the load position adequate?	127 (97.7)	3 (2.3)	4 (100.0)	0 (0.0)
The inserter has been designed to be used either right or left handed. Were the ergonomics of the inserter acceptable to accommodate your technique?	120 (92.3)	10 (7.7)	4 (100.0)	0 (0.0)
To reduce the amount of air administered with insert, administration requires a two-step process. First, the button should be depressed and slid to the first stop (the curved black marks) before inserting the needle in the eye. At the first stop, the button will move to the UP position when the button is released. To administer the drug insert into the vitreous, the physician must push the button all the way forward with the button in the upward position. Was this clear from the instructions?	128 (98.5)	2 (1.5)	4 (100.0)	0 (0.0)
A guide with 4 mm hash marks is provided near the tip of the inserter. Is it helpful to have this guide?	85 (65.4)	45 (34.6)	3 (75.0)	1 (25.0)
Did the nature of the grips provide appropriate traction for the insertion procedure?	126 (96.9)	4 (3.1)	4 (100.0)	0 (0.0)
Overall, was the insertion device acceptable for its intended use?	114 (87.7)	16 (12.3)	3 (75.0)	1 (25.0)

Reference: See Section 14.2, Table 7; Appendix 16.2.6, Listing 16.2.6.1

	0.2 µg/day FA			
	Commercial (N=117)		Noncommercial (N=4)	
Treatments Attempted	130		4	
Observer Questions	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Was sterile technique used to open the tray containing the inserter?	130 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)
Was sterile technique used to remove the inserter from the tray?	130 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)
Was the step of depressing the button down and forward to the curved black marks (to move the drug insert into the needle tip) followed?	130 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)
Was the administration of the drug insert performed as instructed? If no, please explain.	125 (96.2)	5 (3.8)	3 (75.0)	1 (25.0)
Did you observe difficulties with the study drug administration? If yes, please explain.	19 (14.6)	110 (84.6)	1 (25.0)	3 (75.0)
Do you have any other comments?	17 (13.1)	113 (86.9)	0 (0.0)	4 (100.0)

Reviewer's comments:

From the "117 commercial" group Inserter Questionnaires:

Twelve (12) % of users reponded "No" to "Overall, was the insertion device acceptable for its intended use?"; and,
Fifteen (15) % of users responded "Yes" to "Did you observe difficulties with the study drug administration?"

There are concerns that the final configuration of this drug product is not ready for commercialization and that the applicant's proposal, "Once *Iluvien is commercialized, physician training will be enhanced in order to avoid the types of issues experienced during the trial." There is no data to support that this will be adequate to mitigate the issues observed when using this drug delivery system.*

5. Issues of IOP elevation and cataract formation

The applicant has submitted additional information regarding the agency's concern for IOP elevation observed in approximately one third of subjects and for approximately 90% of subjects developing cataracts.

Additional IOP Data

The applicant has submitted Tables 1 and 2 comparing IOP elevation in the Acute DME cases versus Chronic DME cases

Table 1. Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Chronic DME and Acute DME Subgroups: Safety Population)

Category	0.2 µg/day		
	Overall FAME N = 375 n (%)	Chronic DME N = 209 n (%)	Acute DME N = 165 n (%)
Any IOP-lowering medication	144 (38.4)	75 (35.9)	69 (41.8)
IOP elevation considered an AE[1]	139 (37.1)	72 (34.4)	67 (40.6)
IOP elevation increase ≥12 mmHg	108 (28.8)	54 (25.8)	54 (32.7)
IOP elevation to over >25 mmHg	123 (32.8)	65 (31.1)	58 (35.2)
IOP elevation to over >30 mmHg	69 (18.4)	31 (14.8)	38 (23.0)

Table 2. Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Chronic DME and Acute DME Subgroups: Safety Population)

Category	0.2 µg/day		
	Overall FAME N = 375 n (%)	Chronic DME N = 209 n (%)	Acute DME N = 165 n (%)
Trabeculoplasty performed	5 (1.3)	4 (1.9)	1 (0.6)
Trabeculectomy performed	10 (2.7)	6 (2.9)	4 (2.4)
Glaucoma surgery performed[2]	8 (2.1)	5 (2.4)	3 (1.8)
Vitrectomy performed for elevated IOP	1 (0.3)	0	1 (0.6)
Any incisional surgery intervention[3]	18 (4.8)	11 (5.3)	7 (4.2)

Reference: Ref to Module 5, 5.3.5.2, ISS 36 Months, Table 5.11 and Module 1, 1.11.2, Efficacy Amendment

1 Includes adverse event reports of ocular hypertension and intraocular pressure increased.
2 Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocyclodestruction, and laser peripheral iridotomy. 3 Includes trabeculectomy, glaucoma surgery and vitrectomy for elevated IOP.

Table 3. Number (%) of ILUVIEN-Treated Subjects with IOP-Related Events (Integrated FAME Studies, Sham and 0.2 µg/day Subgroups: Safety Population)

Category	Treatment Group	
	Sham (N=185) N (%)	**0.2 µg/day (N=375) N (%)**
IOP elevation considered an AE[1]	22 (11.9)	139 (37.1)
IOP elevation increase ≥ 12 mm Hg	15 (8.1)	108 (28.8)
IOP elevation > 25 mm Hg	18 (9.7)	123 (32.8)
IOP elevation > 30 mm Hg	8 (4.3)	69 (18.4)
Trabeculoplasty performed	0 (0)	5 (1.3)
Trabeculectomy performed	0 (0)	10 (2.7)
Glaucoma surgery performed[2]	1 (0.5)	8 (2.1)
Vitrectomy performed for elevated IOP	0 (0)	1 (0.3)
Any surgical procedure performed	1 (0.5)	18 (4.8)

1 Includes adverse event reports of ocular hypertension and intraocular pressure increased.
2 Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocyclodestruction, and laser peripheral iridotomy. 3 Includes trabeculectomy, glaucoma surgery and vitrectomy for elevated IOP

Reviewer's comments:

In the preceding Table 1 and 2, the applicant has submitted data comparing rates of Adverse events for Chronic DME versus Acute DME. Table 3 has the data comparing the Sham group to the 0.2 µg/day group.

The Adverse rates for increased IOP and surgeries performed for the Chronic DME 0.2 µg/day group are higher than the Sham group and remain a concern.

Additional Cataract Data

The applicant has submitted Table 4 comparing Cataract events in the Acute DME cases versus Chronic DME cases.

Table 4. Number (%) of Phakic Subjects Reporting Cataract-Related Events (Integrated FAME Studies and Chronic DME and Acute DME Subgroups: Safety Population)

Cataract Related Event	Sham n/N (%)	0.2 µg/day n/N (%)
All Phakic Subjects		
Any Cataract	61/121 (50.4)	192/235 (81.7)
Cataract Operation	33/121 (27.3)	188/235 (80.0)
Phakic Subjects with Chronic DME		
Any Cataract	34/66 (51.5)	98/114 (86.0)
Cataract Operation	24/66 (36.4)	97/114 (85.1)
Phakic Subjects with Acute DME		
Any Cataract	26/54 (48.1)	94/121 (77.7)
Cataract Operation	8/54 (14.8)	91/121 (75.2)

Table 5. Incidence of Cataract events in the Study Eye of Phakic Subjects Integrated Fame Studies, Safety Studies

Category	Treatment Group	
	Sham (N=121) N (%)	0.2 µg/day (N=235) N (%)
Any cataract related event	61 (50.4)	192 (81.7)
Cataract NOS	51 (41.1)	168 (71.5)
Cataract cortical	1 (0.8)	1 (0.4)
Diabetic cataract	0 (0)	1 (0.4)
Nuclear cataract	5 (4.1)	8 (3.4)
Subcapsular Cataract	8 (6.6)	27 (11.5)
Cataract operation	33 (27.3)	188 (80.0)

Reviewer's comments:

In Table 4 the applicant has submitted data comparing rates of Adverse events for Chronic DME versus Acute DME. Table 5 has the data comparing the Sham group to the 0.2 µg/day group.

The Adverse rates for cataract events for the Chronic DME 0.2 µg/day group are higher than the Sham group and remain a concern.

6. Applicant response to risk of increased IOP

IOP and Cup/Disc (C/D) Ratio Changes

A special assessment of the optic nerve head was performed on the fundus photographs obtained from subjects who were enrolled in the FAME studies. The (b) (4) performed this assessment. The purpose of this assessment was to determine the long term effects of sustained delivery of fluocinolone acetonide from intravitreal implants on the optic nerve head in subjects diagnosed with DME.

Number (%) of Subjects who had a Worsening in the Vertical Cup-to-Disc Ratio (Integrated FAME Studies: Safety Population)

	Sham		0.2 µg/day	
Time Point	**N**	**n (%)**	**N**	**n (%)**
Month 36	102	1 (1.0%)	219	11 (5.0%)
Difference (95% CI)			-4.0% (-7.5%, -0.6%)	
P-value			0.076	
Last Observation	166	2 (1.2%)	345	12 (3.5%)
Difference (95% CI)			-2.3% (-4.8%, 0.3%)	
P-value			0.134	

The applicant concludes that when the relationship between the number of study treatments and increased cupping is explored across the sham and 0.2 µg/day FA groups (Text Table 24), no trend is seen toward increased risk with increased exposure to the 0.2 µg/day FA dose.

Reviewer's comments:

Three year follow-up may be too soon to demonstrate the effect of elevated IOP on visual fields.

7. Additional Benefits of Treatment cited by applicant

BCVA by letters of vision

Between Treatment Difference in Cumulative Frequencies of Change from Baseline Best Corrected Visual Acuity at Month 36 in Subjects with Chronic DME (Integrated FAME Studies: Full Analysis Population)

Cumulative Change from Baseline	Treatment Group		Difference
	Sham (N = 112)	0.2 µg/day (N = 209)	
	n (%)	n (%)	%
≥0 Letters	68 (60.7%)	162 (77.5%)	16.8%
≥5 Letters	52 (46.4%)	141 (67.5%)	21.0%
≥10 Letters	33 (29.5%)	108 (51.7%)	22.2%
≥15 Letters	15 (13.4%)	71 (34.0%)	20.6%
≥20 Letters	6 (5.4%)	44 (21.1%)	15.7%
≥25 Letters	4 (3.6%)	25 (12.0%)	8.4%
≥30 Letters	2 (1.8%)	12 (5.7%)	4.0%

Reviewers comments:

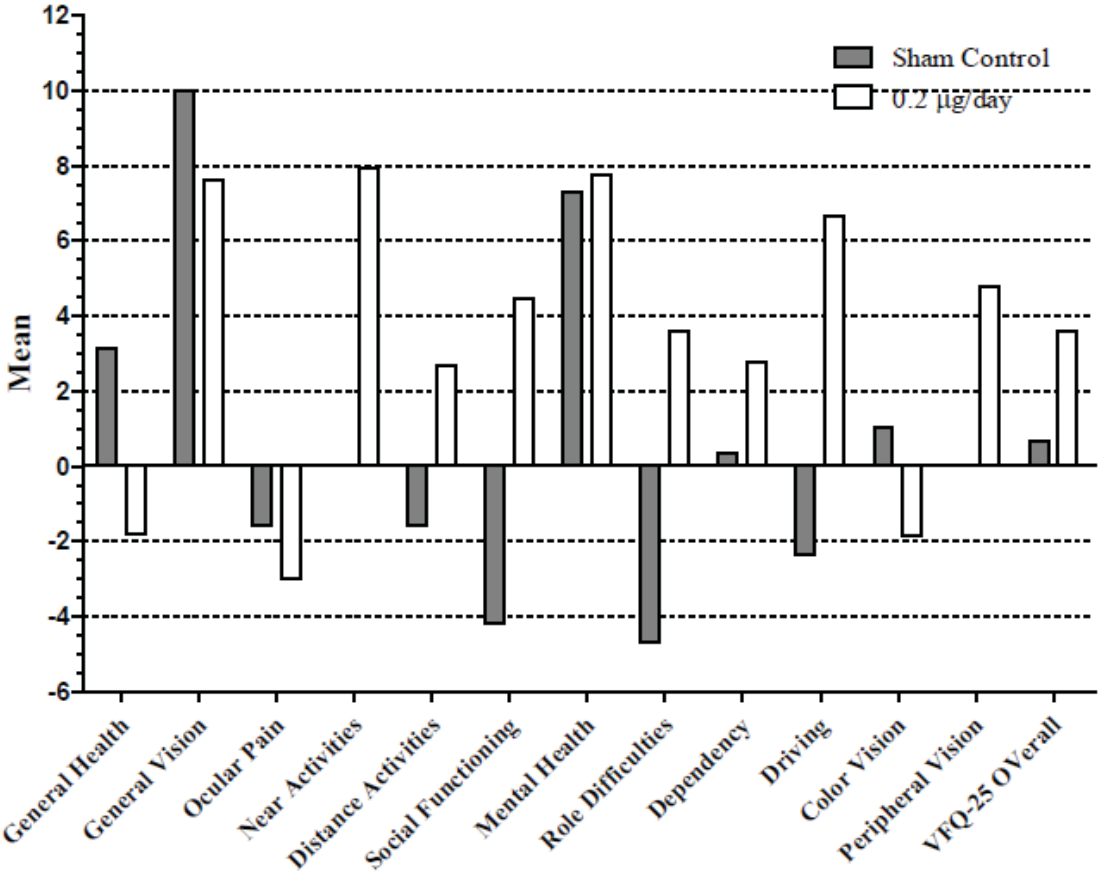
The primary endpoint is ≥ 15 Letters improvement in BCVA. When stratified by gaining Letters of vision there remains about one in five subjects who benefit over the control (Sham) which is consistent with using the primary endpoint of ≥ 15 Letters improvement in BCVA.

When stratified by gaining Letters of vision there are about one in five subjects who benefit from the therapy over the control (Sham) while 4 of 5 of all subjects will experience an iatrogenically induced Adverse Event.

National Eye Institute Visual Function Questionnaire 25 (VFQ-25)

The National Eye Institute Visual Function Questionnaire 25 (VFQ-25) was used to assess the impact of ILUVIEN on vision-related quality of life parameters.

Mean Change in the Month 36 NEI VFQ-25 Subscale Scores for Chronic DME Subjects Treated in the Best Seeing Eye (Integrated FAME Studies: Full Analysis Population)



The overall difference in mean change in VFQ-25 favored ILUVIEN by approximately 3 points.

Reviewers comments:

Visual parameters such as VFQ-25 and Visual Acuity of 20/40 or better need to be clinically relevant and clinically meaningful; the significance of an overall difference in mean change in VFQ-25 favored in the ILUVIEN group by approximately 3 points is not known.

Reduced Need for Vitrectomy and Panretinal Photocoagulation or other therapies

Applicant states that treatment with ILUVIEN provides the additional benefits of reducing the need for vitrectomy and panretinal photocoagulation (PRP).

Number (%) of Subjects Undergoing Vitrectomy and Panretinal Photocoagulation in the Integrated FAME Studies (Integrated FAME Studies: Safety Population and Subgroup with Chronic DME)

	Chronic DME		Safety Population	
	Treatment Group		Treatment Group	
Event	Sham (N=112)	0.2 µg/day (N=209)	Sham (N=185)	0.2 µg/day (N=375)
Vitrectomy, n (%)	9 (8.0)	9 (4.3) P=0.158	19 (10.3)	24 (6.4) P=0.106
Panretinal Photocoagulation, n (%)	24 (21.4)	23 (11.0) P=0.003	44 (23.8)	50 (13.3) P=0.002

Reviewer's comments:

The sample sizes are too small and the studies were not designed to determine if there is a reduction in other therapies when treated with Iluvien. All patients in both groups reportedly have laser photocoagulation prior to the study's initiation.

8. Safety

No additional safety information for the FAME studies is available. Its data is included in the table in this section with the Safety Update information for the following additional studies:

1) Study C-01-11-008 (FAME Extension Study)

The FAME Extension Study (Study C-01-11-008) is an open-label, multi-center extension study of the safety and utility of the new applicator of ILUVIEN® (FA intravitreal implant) 0.19 mg (0.2 µg/day FA) and the safety of ILUVIEN in subjects with DME. Subjects include those who had previously participated in the FAME studies (b) (4)

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

The FAMOUS study (Study C-01-06-002) was an open-label, 36-month pharmacokinetic study of 0.2 µg/day FA and 0.5 µg/day FA in subjects with DME.

3) Safety Update for Study C-01-08-004 (the MAP-GA Study)

The MAP-GA study (Study C-01-08-004) is an ongoing, single-center, randomized, single-masked, fellow eye comparison study of the effects of FA implants in subjects with geographic atrophy.

4) Safety Update for Study C-01-08-006 (the FAVOR Study)
The FAVOR study (Study C-01-08-006) is an ongoing multicenter, randomized, double-masked study of the effects of 0.2 µg/day FA and 0.5 µg/day FA in subjects with central or branch retinal vein occlusion (CRVO or BRVO).

Common Ocular Adverse Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
Most Common Events[1]	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)	0.2 µg/day FA (N = 20) n (%)	0.5 µg/day FA (N = 17) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 7) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 6) n (%)	0.2 µg/day FA (N = 120) n (%)
Cataract	171 (45.6)	213 (54.2)	11 (55.0)	4 (23.5)	1 (12.5)	3 (37.5)	1 (10.0)	3 (50.0)	3 (2.5)
Cataract operation	188 (50.1)	231 (58.8)	13 (65.0)	5 (29.4)	2 (25.0)	1 (12.5)	2 (20.0)	1 (16.7)	1 (0.8)
Cataract subcapsular	28 (7.5)	24 (6.1)	1 (5.0)	3 (17.6)	1 (12.5)	0	1 (10.0)	0	0
Conjunctival haemorrhage	43 (11.5)	50 (12.7)	7 (35.0)	7 (41.2)	1 (12.5)	1 (12.5)	1 (10.0)	1 (16.7)	26 (21.7)
Dry eye	23 (6.1)	22 (5.6)	1 (5.0)	2 (11.8)	0	0	0	0	3 (2.5)
Eye irritation	27 (7.2)	22 (5.6)	1 (5.0)	2 (11.8)	0	0	0	0	2 (1.7)
Eye pain	51 (13.6)	65 (16.5)	4 (20.0)	2 (11.8)	2 (25.0)	2 (25.0)	3 (30.0)	1 (16.7)	11 (9.2)
Glaucoma	19 (5.1)	18 (4.6)	1 (5.0)	1 (5.9)	0	0	0	0	2 (1.7)
Intraocular pressure increased	132 (35.2)	170 (43.3)	4 (20.0)	7 (41.2)	1 (12.5)	1 (12.5)	2 (20.0)	0	9 (7.5)
Maculopathy	23 (6.1)	34 (8.7)	4 (20.0)	0	0	0	0	0	2 (1.7)
Myodesopsia	67 (17.9)	68 (17.3)	7 (35.0)	6 (35.3)	0	1 (12.5)	0	1 (16.7)	5 (4.2)
Posterior capsule opacification	32 (8.5)	25 (6.4)	2 (10.0)	1 (5.9)	0	0	0	0	1 (0.8)
Trabeculectomy	10 (2.7)	22 (5.6)	1 (5.0)	2 (11.8)	0	0	0	0	0
Vision blurred	28 (7.5)	20 (5.1)	1 (5.0)	1 (5.9)	0	0	0	0	2 (1.7)
Visual acuity reduced	39 (10.4)	35 (8.9)	0	1 (5.9)	0	0	0	0	4 (3.3)
Visual impairment	13 (3.5)	31 (7.9)	0	2 (11.8)	0	0	0	0	2 (1.7)
Vitrectomy	19 (5.1)	23 (5.9)	1 (5.0)	0	0	0	0	0	0
Vitreous detachment	26 (6.9)	20 (5.1)	2 (10.0)	1 (5.9)	0	1 (12.5)	1 (10.0)	0	2 (1.7)
Vitreous haemorrhage	41 (10.9)	48 (12.2)	0	0	0	0	0	0	7 (5.8)

1 Ocular events with an incidence ≥ 5.0 % in either active treatment group in the integrated FAME studies. Incidence was based on occurrence in the study eye.

Reviewer's comments:

The adverse events of increased IOP and cataract formation are also evident in these additional trials.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held during this review cycle.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

None.

12. Labeling

ILUVIEN is not recommended for approval [redacted] (b) (4)

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment diabetic macular edema.

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

1. Fame A and B, fail to demonstrate that the benefits of the drug product outweigh the associated risks.
2. The newly proposed primary endpoint's definition of duration DME was not adequately assessed as a study inclusion criterion. An additional concern is whether the date of diagnosis is based on patient memory as reported by the patient to the treating physician. Patient reported events, based on one's prior memory, are often unreliable.
3. The revised design (drug / dispenser) has not been adequately evaluated.
4. If the applicant chooses to pursue the indication [redacted] (b) (4)

[redacted] (b) (4)

RISK BENEFIT ASSESSMENT:

1) There is not substantial evidence to demonstrate that the benefits of the drug outweigh its risks for either the low dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.25 µg/day) or the high dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.5 µg/day). The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema. This recommendation is based on the results from the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) studies submitted with 36 month data for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day.

   Fame A and B studies did not demonstrate statistically significant results in visual function at either dose at 36 months (p values all > 0.05). The newly proposed primary endpoint was not adequately defined as a group.

   At 36 months follow-up cataract progression occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes and increased IOP occurs in 11% of the Sham group study eyes versus 35% in the 0.2 µg/day FA study eyes. The risk of increased IOP is three times the rate in the 0.2 µg/day FA drug group.

2) The inserter used in the preclinical and clinical trials was modified; use of the proposed [redacted] (b) (4) inserter is not supported by clinical data in the application.

   It was recommended that the clinical trial be 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 clinical trials supporting safety and efficacy.

   The applicant enrolled 121 subjects in an Open Label trial.

   It is concerning that initially 59 subjects were enrolled and then the trial was stopped for technical complaints. After being stopped and instituting an in-process control another 58 subjects were enrolled.

   There are concerns that the current configuration of this drug product is not ready for commercialization and that the applicant proposal, "Once Iluvien is commercialized, physician training will be enhanced in order to avoid the types of issues experienced

during the trial," will not be adequate to mitigate the issues observed with using this drug delivery system.

3) The Adverse rates for increased IOP and cataract formation and surgeries related to these adverse events are higher than the Sham group and remain a concern.

4) The primary endpoint was ≥ 15 Letters improvement in BCVA. When stratified by gaining Letters of vision there are about one in five subjects who benefit from the therapy over the control (Sham) while 4 of 5 of all subjects will experience an iatrogenically induced Adverse Event.

5) Three year follow-up is too short to demonstrate the effect of elevated IOP on visual fields.

6) Visual parameters such as VFQ-25 and Visual Acuity of 20/40 or better need to be clinically relevant and clinically meaningful; the significance of an overall difference in mean change in VFQ-25 favored in the ILUVIEN group by approximately 3 points is not known.

7) When analyzing the data based on a reduction in the number of procedures, such as fewer vitrectomies and panretinal photocoagulation, the sample sizes are too small to draw any conclusions. The studies were not designed or powered to determine if there is a statistically significant reduction in the need for other therapies for DME when previously treated with Iluvien. All patients were expected to have received adequate photocoagulation prior to drug product administration.

CONCLUSION:

Based on the risk/benefit of this drug, NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg, is not recommended for approval [redacted] (b) (4)

Additional trial(s) in pseudophakic patients adequately defined with chronic diabetic macular edema (DME) who are unresponsive to anti-VEGF therapy should be considered.

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/s/

MARTIN P NEVITT
09/05/2013

WILLIAM M BOYD
09/09/2013

Medical Officer's Review of NDA 201923
SDN 37

NDA 201923	**Submission Date:** 8/1/2012
SDN - 37	**Received Date:** 8/1/2012
	Review Date: 8/3/2012

Sponsor: Alimera Sciences, Inc.

Sponsor's address: 6120 Windward Parkway, Suite 290
Alpharetta, GA 30005
(678) 990-5740

Drug: Iluvien (fluocinolone acetonide intravitreal implant), 0.19 mg

Pharmacologic Category: corticosteroid

Dosage Form and Route of Administration: intravitreal injection

Submitted:

Alimera Sciences, Inc., in accordance with 21 CFR 314.110, would like to request an extension of time for resubmitting the application NDA 201923. This resubmission will address the issues raised in the Complete Response Letter dated November 10, 2011. Alimera requires the additional time to complete the Physician Injector Utilization Study (Protocol C-01-11-008) as well as conduct the additional analyses recommended by the Agency at the June 19, 2012 meeting. Alimera's goal is to resubmit during the first quarter of 2013.

Reviewer's comments:

It is expected that the C-01-11-008 clinical trial be 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 clinical trials supporting safety and efficacy. It is expected that at least 100 eyes will have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval.*

Recommend the extension be granted.

Recommended Regulatory Action:

Recommend the extension for NDA 201923 be granted.

Martin P. Nevitt, M.D., M.P.H.
Medical Officer

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/s/

MARTIN P NEVITT
09/19/2012

WILLIAM M BOYD
09/19/2012

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
NDA Number	NDA 201923
Related IND	IND 72,056
Applicant Name	Alimera Sciences, Inc.
Date of Original Submission **Complete Response Letter** **Date of Resubmission, Class 2** **PDUFA Goal Date**	June 30, 2010 (priority review) December 22, 2010 May 12, 2011 November 12, 2011
Application Type	505(b)(1)
Proprietary Name / **Established (USAN) Name**	Iluvien Fluocinolone acetonide intravitreal insert
Formulation **Dose**	Intravitreal Insert (non-biodegradable) 0.19 mg
Proposed Indication(s)	Treatment of diabetic macular edema
Action for Application	*Complete Response*

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**	**Discipline-specific recommendation regarding application**
Medical Officer Review	Martin Nevitt, Bill Boyd, Wiley Chambers 12/20/2010, 9/13/2011	Deficiencies
CDTL Review	Bill Boyd 12/22/2010, 10/27/2011	Deficiencies
Deputy Director	Wiley Chambers 12/22/2010, 10/19/2011	Deficiencies
Statistical Review	Rima Izem, Yan Wang 11/30/2010, 8/1/2011	Deficiencies
Clinical Pharmacology Review	Yongheng Zhang, Charles Bonapace 11/18/2010, Yongheng Zhang, Philip Colangelo, 6/28/2011	Adequate
Pharmacology/Toxicology Review	Conrad Chen, Wendelyn Schmidt 11/17/2010	Adequate
ONDQA/DNDQA II, Branch V Review	Lin Qi, Rapti Madurawe 7/22/2011, 9/30/2011 Dorota Matecka, Stephen Miller 12/1/2010	Deficiencies
ONDQA Biopharmaceutics	Tapash Ghosh, Patrick Marroum 6/27/2011	Deficiencies
Product Quality Microbiology Review	Steven Fong, John Metcalfe 12/8/2010, 2/9/2011, 7/25/2011	Adequate
OSI/DGCPC	Kassa Ayalew, Tejashri Purohit-Sheth 12/1/2010	Adequate
OSE/DMEPA Proprietary Name	Denise Toyer 10/13/2010 (tentatively acceptable)	Adequate
Advisors and Consultants Staff	None	

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
ONDQA/DNDQA = Office of New Drug Quality Assessment, Division of New Drug Quality Assessment
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
DMPQ/MAPCB/BMT = Division of Manufacturing and Product Quality/Manufacturing and PreApproval CB/ Biologics

Table of Contents:

Introduction:
For a detailed discussion of the Iluvien (fluocinolone acetonide intravitreal insert) drug development program, including preclinical and clinical studies, and product qualitly, the reader is referred to the individual review documents listed in the "Materials Reviewed" Table on page 2 and contained in the OND Action Package for this application.

This document summarizes some of the highlights from these reviews, provides an overview of the clinical trial results and discussion of risks and benefits, and summarizes the outstanding deficiencies which form the basis of the *Complete Response* action for this review cycle.

1. Summary and Recommendations

Based on the review of NDA 201923, including the original submission from June 30, 2010 and the resubmission on May 12, 2011, reviewers concluded that the Phase 3 clinical trials failed to show that fluocinolone acetonide intravitreal insert was effective in the treatment of diabetic macular edema (DME) and failed to show that the product was safe for this intended use. In addition, manufacturing deficiencies were identified for *in-vitro* release testing and polymorph testing. I concur with these recommendations and therefore the application will be issued a *Complete Response* letter for this resubmission.

1.1 Deficiencies

The following deficiencies will be communicated to the applicant:

CLINICAL TRIALS

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

   Specifically, based on the results of your controlled clinical trials C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. Specifically, you have not provided data to support that the product is safe and effective in the treatment of patients with diabetic macular edema (DME).

   a. Results of your controlled clinical trials C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), did not demonstrate statistically and clinically significant benefit for your primary endpoint of best corrected visual acuity (BCVA) at 36 months. As we have noted previously, efficacy at earlier time points was low (26-(b)(4)% vs. 14-18%), the results were not robust as the difference between groups with respect to mean visual acuity

was small and not significant. Although some beneficial effect appeared to occur during the first 6 months, the product then appeared to cause clinically significant decreases in visual acuity at month 24, and was not significantly different from sham treatment by month 36.

b. Results of the safety analyses of your clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. Furthermore, the risk of increased intraocular pressure (IOP) is nearly three times higher in the Iluvien treatment arm than the control arm. The risks of these adverse reactions are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.

c. The to-be-marketed Iluvien Inserter is different from the inserter used is clinical trials, and clinical data from patients treated for diabetic macular edema with the new inserter are not provided in the application. The application only includes data on 8 patients from Study C-01-08-006 who have been enrolled in this study of macular edema in retinal vein occlusion.

d. Your have proposed to revise your indication (b) (4) In support of this revision you have submitted a post-hoc analysis of the results based on a retrospectively selected subgroup of patients who are said to have duration of DME (b) (4) this analysis was not pre-specified in the protocol, was not included in the statistical analysis plan (SAP), was not adjusted for multiplicity. Furthermore, we note that this subgroup of patients shows the same degree of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population.

To address the clinical and statistical deficiencies, you will need to provide data from two controlled clinical trials that demonstrate that Iluvien, at the dose proposed to be marketed, is safe and effective for the proposed indication you intend to study and seek in labeling. Based on the current trials it appears that neither the 0.2 microgram/day nor 0.5 microgram/day dose is safe and effective, therefore your development program would likely involve new clinical trials, and should include the evaluation of the Iluvien Inserter you propose to market. If these trials are intended to involve patients with diabetic macular edema (b) (4) duration, you will need to provide specific objective criteria and documentation that subjects had DME (b) (4)

PRODUCT QUALITY

2. There is insufficient information to determine the adequacy of the specifications necessary to ensure the identity, strength, quality, purity, and potency of your drug substance and drug product. Specifically,

   a. The proposed *in-vitro* release rate range [redacted] (b) (4) Without the release rates of the batches that were tested in the clinical studies, the adequacy of your proposed *in-vitro* release rate cannot be determined. We suggest that the estimation of the range for the release rate be based on mean data and 90% confidence intervals around the mean. Note that the proposed release rate specification range should [redacted] (b) (4)

   In addition, your protocol for the *in vitro* drug release rate test specifies the collection of samples [redacted] (b) (4) It is not clear from the data submitted in your May 12, 2011 submission, specifically "*Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured at* [redacted] (b) (4) and "*Table 3: Release Rates from* [redacted] (b) (4) *from Study 10123*," at what time points these samples were collected and how many samples from each batch were tested. These need to be clarified. A detailed raw data sheet (preferably in electronic format) describing all the data used to generate the *in-vitro* release rates in the Tables 2 and 3 needs to be submitted.

   b. You have not provided the polymorph testing method done at [redacted] (b) (4) the polymorph testing site proposed in this NDA. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. Please provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ([redacted] (b) (4) method if applicable), operation procedures, and quantitative analysis. Please also provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

In addition, we also remind you that all manufacturing and testing facilities should be ready for inspection at the time of NDA resubmission.

1.2 Post-Marketing Studies:

Not applicable at this time

1.3 Other Issues

None at this time

2. Background

As noted in the Medical Officer Review, diabetic macular edema (DME), a serious, chronic, debilitating disease, is one of the causes of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

Fluocinolone acetonide is a synthetic glucocorticoid available in topical dermal, otic and ophthalmic products including an ophthalmic intravitreal implant, marketed as Retisert for the indication of uveitis.[2] Iluvien is not approved in any country.

Corticosteroids are associated with development of cataracts and increased intraocular pressure, and predispose patients to infection. These concerns were discussed with Alimera during the development program including the end-of-phase 2 meeting for IND 72,056 on September 2, 2008; however, the company believed that because of the low dose of fluocinolone they intended the deliver in the insert; they would not see these steroid-related adverse events.

The pre-NDA meeting was held March 4, 2010 and the original NDA 201923 was submitted June 30, 2010 and given a priority review because there are no approved therapies. However, based on review of the application, a Complete Response letter was issued on December 22, 2010 listing clinical/statistical deficiencies such as low, clinically-insufficient efficacy, development of cataracts by 24 months, three-fold increase in IOP, and need for 36 month data to assess risk/benefit. The inserter used in clinical trials was different from the (b) (4) inserter proposed for marketing, and the latter was not evaluated in clinical trials of DME. Other deficiencies were identified by the product quality, biopharmaceutics and microbiology disciplines regarding the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product; these were inadequate to preserve the identity, strength, quality, purity, and stability of the product. Specific concerns included endotoxin testing and limits, (b) (4) polymorph testing of the drug substance, identification of inactive components in the drug product, in-vitro release methodology, release rate specifications, (b) (4) bioburden testing, hold period (b) (4) Deficiencies were identified during inspections of the (b) (4) facilities.

A Type A meeting was held February 2, 2011 which included discussion of how the deficiencies in the December 22, 2010 letter should be addressed.

3. CMC/Product Quality Microbiology

For a complete discussion of the manufacturing of the drug product and drug substance, please refer to the reviews by Dr. Li, Dr. Ghosh and Dr Fong.

[2] Retisert (fluocinolone acetonide intravitreal implant) 0.59mg was approved April 8, 2005 under NDA 21-737 for the indication of chronic non-infectious uveitis affecting the posterior segment of the eye.

The Iluvien [redacted] 0.19 mg fluocinolone acetonide (FA) is designed to release 0.25 micrograms/day of product into the vitreous chamber. FA is mixed with PVA and is contained in a tube made of polyimide (a nonbiodegradable polymer) measuring 3.5 mm x 0.37 mm and weighing approximately 0.1 mg. The tube is provided within a hand piece inserter device, [redacted] pushed through a 25 gauge needle into the vitreous of the eye with the aid of the inserter device. [redacted]

As noted under Section 1.1., there are remaining deficiencies in product *in-vitro* release specifications, sampling and testing, and also on analytical procedure and method validation for polymorph testing.

Comment:
Product Quality and Biopharmaceutics reviewers recommend that the product should not be approved until the remaining deficiencies identified during this cycle are addressed. The Product Quality Microbiology deficiencies have been addressed.

4. Nonclinical Pharmacology/Toxicology

There were no additional pharmacology/toxicology studies submitted during this review cycle. For a complete summary, see the review by Dr. Chen. The components of the product have been reviewed. Polyvinyl alcohol has been used since the 1930's in industrial and food applications, biocompatibility studies were negative. Ocular toxicology studies (9 month and 24 months) of continuous exposure after one or two injections of insert in rabbits showed that FA appeared to induce posterior cortical/capsular cataracts at 0.5 and 1.0 microgram/day. Genotoxicity studies were negative, carcinogenicity studies and reproductive/development studies were not done.

Comment: The Pharmacology/Toxicology Reviewer recommends approval from the pharmacology/toxicology standpoint.

5. Clinical Pharmacology/Biopharmaceutics

Dr Zhang summarized the systemic and ocular pharmacokinetic results from the application in the original review and recommended that systemic exposure results can be included in labeling; however, ocular levels will not be used to support a regulatory decision because the analytical methods to measure these concentrations in aqueous humor are not validated.

Dr Zhang provides the following perspective regarding the differences between the inserter used in clinical trials compared to the to-be-marketed inserter:

> 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 (manufactured by [redacted]) contains 0.19 mg FA versus the clinical development product (manufactured at pSivida, Inc.) that averaged [redacted] mg. [redacted] 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/da (b) (4)

Comment: The Clinical Pharmacology reviewer recommends approval. The data support the labeling regarding FA concentrations in human plasma.

6. Clinical Microbiology/Immunology

Not Applicable

7. Clinical/Statistical-Efficacy

Two Phase 3 clinical trials were submitted, these were conducted under the same protocol but divided into C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B). The trials were conducted in the US and in various European countries.

The design and results of these clinical trials are summarized in the comprehensive clinical reviews by Dr. Nevitt, Dr. Boyd and Dr. Chambers and the comprehensive statistical review by Dr. Izem and Dr Wang.

The trials were prospective, double-masked, randomized, three-arm clinical rials conducted over 3 years. Patients with DME who received prior laser photocoagulation with retinal thickness $\geq$ 250 microns were enrolled and randomized to FA 0.2 mcg/day, FA 0.5 mcg/day or sham control. Subjects were allowed to have additional laser treatment at investigator discretion because the study was 3 years long.

The primary endpoint was increase in $\geq$ 15 letters from baseline of BCVA at 18 and 24 months. Secondary endpoints included mean BCVA.

The results show statistically significant differences in the 24 month endpoint for the ITT population with LOCF but FAME A was not significant in the population of observed patients. During the trial about 20-25% of patients discontinued due to LTFU, withdrawn consent, or death. One of the concerns identified by the Medical Officer is that in the LOCF analysis, patients who had subsequent intervention should have been counted as failures, therefore he considered the per protocol population with observed data important in the assessment of efficacy, and noted the lack of significant treatment effect in FAME A. The treatment effect for LOCF was also considered clinically low. There was significant toxicity (cataracts, increased IOP), and for many patients visual acuity declined because of cataracts.

The application was issued a *Complete Response* on December 22, 2010 in the first review cycle.

The May 12, 2011 submission contained Month 36 data. The 36-month data fail to show that Iluvien is effective in the treatment of DME. There was no significant difference in the primary endpoint of a ≥ 15-letter increase from baseline in best corrected visual acuity (BCVA) in the study eye in the FA vs. sham treated arms. The p- value is not significant for either dose in either FAME A or FAME B.

Table 1: 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	0.2 µg/day FA	0.5 µg/day FA	Sham	0.2 µg/day FA	0.5 µg/day FA
	N=95	N=190	N=196	N=90	N=186	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 (%)						
Difference[1]						
P-value[2]						

[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.

Source: Applicant's Table 3 from Efficacy Information Amendment

Dr. Izem further discussed in her review that:

> The primary endpoint is a responder endpoint; it only quantifies improvement from baseline BCVA that is above a threshold of 15 letters. In contrast, the secondary endpoint quantifies any change from baseline, whether they are improvements or declines from baseline BCVA. In all treatment arms, in both studies and at most time-points, some subject's BCVA increased while other subject's BCVA decreased compared to baseline. Thus, the primary and secondary endpoints together give a better picture of the low dose treatment effect and magnitude of the effect on BCVA than the primary endpoint alone.

This observation is important, because although the primary endpoint of ≥ 15-letter increase from baseline showed significant differences between treatment and control arms at some of the time points evaluated (24 months (b) (4)), this difference was not robust and not considered clinically-significant. The secondary endpoint of mean BCVA over time shows a small advantage of low dose over sham treatment in FAME B but this effect is not replicated in FAME A.

Table 8: BCVA Change from Baseline Over Time, Full Analysis Population

		Mean BCVA change from baseline			
Study	Visit	Sham	Low Dose	Difference	95% CI for difference
Fame A	Month 6	(b) (4)			
	Month 12				
	Month 18				
	Month 24	3.2	3.7	0.4	(-3.8 , 4.6)
	Month 30	(b) (4)			
	Month 36				
Fame B	Month 6				
	Month 12				
	Month 18				
	Month 24	0	5.1	5.1	(0.7 , 9.4)
	Month 30	(b) (4)			
	Month 36				

Iluvien Inserter

The inserter (b) (4) used in preclinical and clinical studies delivered an insert of fluocinolone containing (b) (4) mg, and was designed to release 0.2 micrograms/day or 0.5 microgram/day. Clinical trial investigators and retinal specialists who were not participants in the trials provided feedback on the inserter which resulted in several modifications being made. This modified Iluvien inserter is the one Alimera intends to market. (b) (4) The to-be-marketed inserter has not, however, been evaluated in patients with diabetic macular edema.

The Division recommended in the February 2, 2011 meeting scheduled after the *Complete Response* letter of 12/22/2010, that Alimera submit data on "at least 100 eyes" treated with the New Inserter before NDA approval. The Medical officer elaborates that: "The trial should be conducted in the indication intended for use." (MOR p.3) and both colleagues elaborate that a comparative clinical trial is needed with at least 100 enrolled eyes using the (b) (4) inserter versus at least 50 enrolled eyes using the inserter configuration from the original clinical trials.

Exploratory Analysis

In the May 12, 2011 submission, the applicant proposed to modify the indication [redacted] To support this modification, the company conducted a post-hoc subgroup analysis of a subset of the clinical trial population that the company defined [redacted] (MOR, p.13)

In the submission, the applicant acknowledges [redacted]

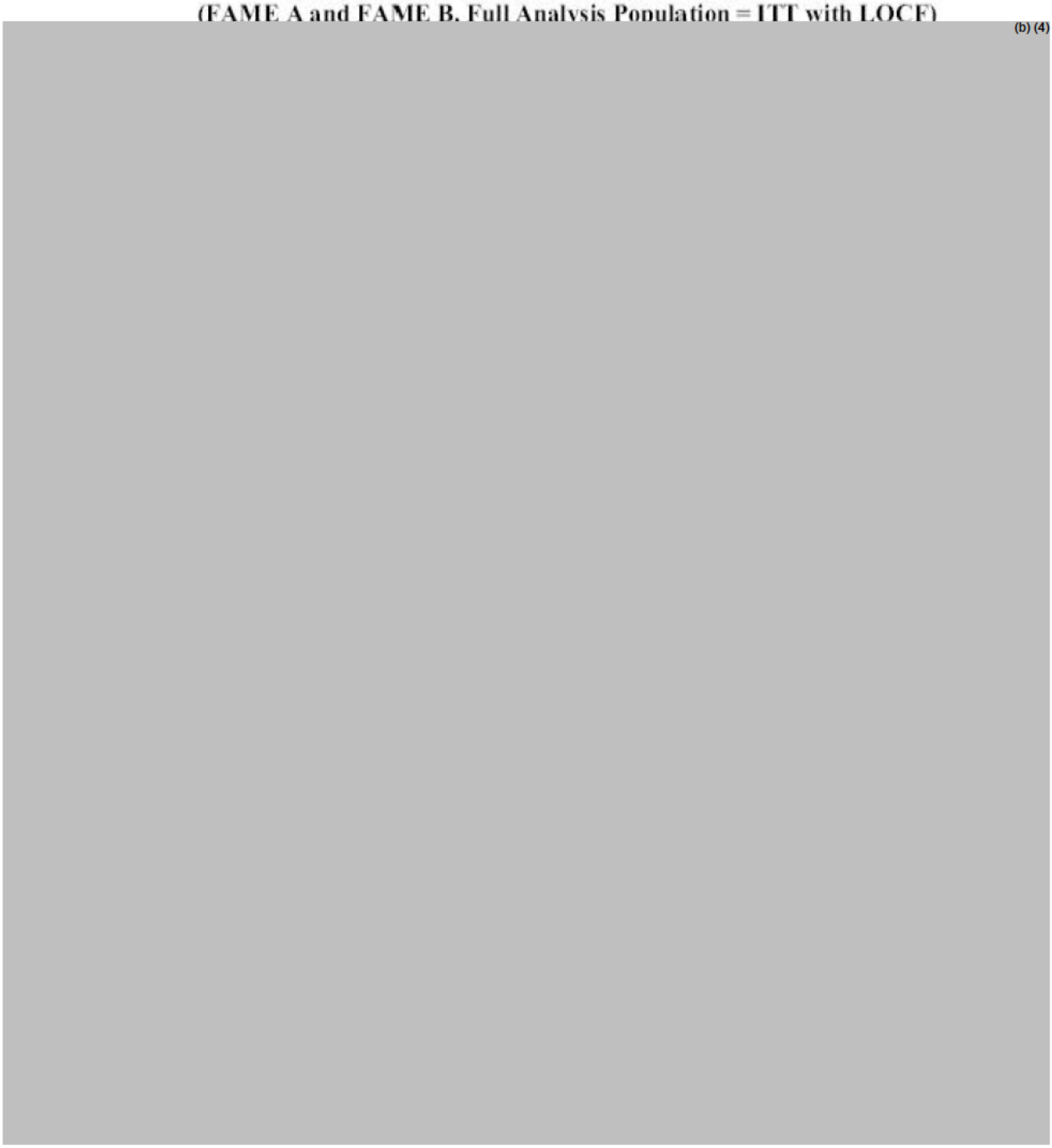
The clinical reviewers disagreed with the way in which DME [redacted] duration was retrospectively defined, noting that *Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time. Given DME can wax and wane over time the proposed subgroup "Duration of DME [redacted]" is not defined well nor is it documented that the subjects had DME [redacted] The definition of duration of DME was not adequately assessed as a study inclusion criterion given DME can wax and wane over time.*

[redacted] this analysis is flawed for the reason noted above: The population was defined retrospectively without objective criteria for the reasons noted above, the analysis was not adjusted for multiplicity, and the analysis would not support the proposed indication [redacted] However, the statistical review points out tha [redacted] this subset also has the same high rate of cataracts, cataract surgery and increased IOP noted in the population as a whole, so the risk observed with Iluvien intravitreal insert may not be outweighed by the proportion of the population that are expected to derive a benefit.

Comment:
I agree with the Medical Officer, Medical Team Leader, Deputy Director, and Statistical team that the applicant has failed to show efficacy that would support approval of the product. The [redacted] (new) inserter has not been tested in patients with DME. The exploratory analysis [redacted] is insufficient for approval and the findings would need to be corroborated, and the to-be-marketed inserter would need to be used. Even if efficacy is shown, the significant toxicity of the product would need to be taken into consideration in deciding whether the benefit of treatment outweighs the drug-associated risks of treatment.

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, Full Analysis Population = ITT with LOCF)

(b) (4)



8. Safety

See comprehensive clinical reviews by Dr. Nevitt, Dr. Boyd and Dr. Chambers and the comprehensive statistical review by Dr. Izem and Dr. Wang.

During the first review cycle, all reviewers noted and commented on the significantly greater rate of serious adverse reactions seen with Iluvien treatment compared to sham treatment.

8.1 Adverse events of special interest

Increased intraocular pressure:
By 36 months, increased IOP was seen in 12% (22/185) sham treated patients, 37% (139/375) low dose fluocinolone patients and 46% (179/393) high dose fluocinolone patients treated in the safety population from FAME A and FAME B.

For the proposed subgroup of patients with DME (b) (4) duration, the rates were (b) (4) respectively. These rates are similar to those seen in the overall safety population from these two trials.

Cataract-related adverse reactions and cataract surgery:
As show in the tables below, the rate of cataract related adverse events and cataract operations were significantly higher in the treated groups. This was true for the total safety population in FAME A and FAME B, as well as in the subgroup of patients stated to have DME (b) (4)

Table 4: 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 operation	33 (27.3)	188 (80.0)	231 (87.2)

Source: Applicant's Table 42 from the Efficacy Information Amendment of the current submission

Table 5: 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)

[redacted]

Comment:
I agree with the Medical Officer, Medical Team Leader, Deputy Director, and Statistical team that the applicant has failed to develop a safe regimen of Iluvien. There are significant adverse reactions related to the use of Iluvien seen in the FAME A and FAME B clinical trials that preclude approval of the product for this indication.

9. Advisory Committee Meeting

The application was not presented before an advisory committee. Fluocinolone is not a new molecular entity, and the results from the clinical trials do not support approval of the application, because the risks of cataract formation, cataract surgery, and increased IOP outweigh the low, transient and inconsistent effect on visual acuity in the three-year trials

10. Pediatrics

Pediatric studies were waived because DME is rare in pediatric patients and there are insufficient patients to conduct a clinical study. The PeRC met October 4, 2010 and agreed with the waiver.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

Facilities are in compliance and recommended acceptable on November 9, 2011.

11.2 Office of Scientific Investigation (OSI) Audits

Dr Ayalew notes that: "Two clinical investigator sites, one domestic and one foreign, were inspected in support of this application. Although regulatory violations were noted at both of these sites, given the nature of the findings, it is unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in

support of the NDA appear reliable." The preliminary classification of both sites was VAI; no addendum has been submitted recommending that results are not acceptable.

11.3 Financial Disclosure

Financial disclosure information was reviewed. The medical officer determined there were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies, nor did any one single investigator or site enroll a significant number of subjects.

11.4 Other Regulatory Issues

The application will be issued a *Complete Response* letter in this review cycle.

12. Labeling

The package insert and carton and container labeling have not been reviewed during this cycle because the results of the clinical trials fail to show that the product is effective and the risk of adverse reactions is higher than potential benefit. If the deficiencies identified during the first and second review cycle can be resolved, labeling will be reviewed.

- **Package insert (PI):** The PI is written in PLR format, to be reviewed after deficiencies addressed.

- **Carton and Container Labels**: To be reviewed after deficiencies addressed

- **Proprietary Name**: The proposed proprietary name Iluvien was reviewed and found acceptable by DMEPA; a letter stating that the name is acceptable was issued by Dr. Denise Toyer on October 13, 2010. If the outstanding deficiencies are addressed, the name will need to be re-reviewed within 90 days of the application's approval.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The deficiencies identified by the clinical reviewers, the statistical reviewers, the product quality, and product biopharmaceutics reviewers need to be addressed before the application can be approved. The application will be issued a *Complete Response* letter and the deficiencies provided in Section 1.1 of this document will be included in the *Complete Response* letter.

13.2 Risk Benefit Assessment

Diabetic macular edema is a serious disease for which no drug therapy is approved. The disease runs a variable course and can wax and wane over years. Laser coagulative therapy and various products are used off label to manage the condition.

The results of the Phase 3 controlled clinical trials, FAME A and FAME B showed a small and transient effect on visual acuity defined as improvement in ≥ 15 letters in BCVA from baseline at 24 months and 30 months in the ITT population with LOCF but not in the population where BCVA was assessed by observation (without LOCT) in one of the trials. Evaluation of the secondary endpoint of mean BPCA showed that while some patients gained visual acuity, others lost visual acuity and the mean BCVA was small and not considered clinically significant.

The analyses of the 24 month assessment were confounded by the development of cataracts in the majority of phakic patients; therefore 36-month data were requested. There was no significant difference in the primary endpoint outcome between FA treated vs. sham-treated patients at 36 months.

In addition to lack of efficacy, there was also a lack of safety; a significantly greater rate of serious adverse reactions included increased IOP, cataracts and cataract surgery were reported in FA treated patients vs. sham treated patients.

The company reported post hoc analyses on a retrospectively chosen subgroup of patients that was termed DME duration (b) (4) This subgroup had not been included in any of the preplanned analyses or groups in the protocol or the statistical analysis plan. This post-hoc subgroup analysis was reported to show significant effect in both FAME A and FAME B, however, the analysis was not adjusted for multiplicity. The adverse event profile in terms of IOP and cataracts was essentially the same in this subgroup, raising the question whether the benefit would outweigh risk even in this subgroup. Because this was an exploratory analysis, the results must be interpreted with caution and insufficient to serve as basis for approval at this time.

These clinical trials did not evaluate the to-be-marketed presentation of the Iluvien intravitreal inserter.

The applicant had embarked on the development program of Iluvien using a low intravitreal dose of 0.19 mg to be released at a starting dose of 0.25 micrograms/day for a period of (b) (4) 36 months in the treatment of DME. They hypothesized that such low exposure would be effective and would not be associated with serious adverse reactions. The results of their clinical trials show that this dose did not result in clinically significant sustained response to treatment and was associated with very high rates of serious adverse reactions. It's not clear whether further formulation development and alterative dosing will likely result in a safe and effective product.

13.3 Recommendation for other Postmarketing Requirements and Commitments

Not applicable at this time

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/s/

RENATA ALBRECHT
11/10/2011

Cross-Discipline Team Leader Review

Date	October 17, 2011
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	May 12, 2011
PDUFA Goal Date	November 12, 2011
Type of Application	505(b)(1)
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Recommended:	Not Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant. There is no previous marketing experience with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg as this product is not commercially available.

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) and has been developed for the treatment of Diabetic Macular Edema (DME). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.
The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

2. Background

Diabetic macular edema (DME), a serious, chronic, debilitating disease, is the primary cause of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

A Pre-NDA meeting was held for IND 72,056 on March 4, 2010.

NDA 201923 was submitted June 30, 2010 as a Priority review and a PDUFA goal date of December 30, 2010. A Complete Response action was taken December 22, 2010 outlining that the application could not be approved in its present form. A summary of the clinical reasons for this action are described below:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

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.

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.

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

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.

e. Efficacy rates are low (26-[redacted] (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.

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.

On February 2, 2011 a Type A Guidance meeting was held to discuss with the Division the steps necessary for the application approval. Specifically, the following clinical issues were reiterated:

1. Alimera must demonstrate a "win" where the benefits outweigh the risks of using the drug product. Carving out a subset is suggested when the subsets can be identified prior to starting the study. 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. Demonstration of safety and efficacy to support approval of an NDA will require that at least 2 adequate and well-controlled, multi-center trials show that the benefits of the drug product outweigh its risks. To demonstrate a "win" would require statistical significance (p value ≤ 0.05) in at least two trials for the primary endpoint (the primary endpoint in the trials was defined as the proportion of subjects with a ≥ 15 letter increase in BCVA on the ETDRS eye chart at Month 24. (Given the timing of the confounding effect of cataract formation and extraction the primary endpoint would be at Month 36 and the data would be re-submitted with this time point.)

2. 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). The Division stated that the final configuration of the inserter used in the trials was required before submitting the NDA. As presented in the NDA submission, it was not clear that the final product was going to be used in the way it was actually used during the trials. When those trials are completed, Alimera can submit the results to the NDA. The trials should be conducted in the indication intended for use.

On May 12, 2011 the applicant submitted its response to the Complete Response action taken on December 22, 2010, which included 36 Month data.

3. CMC

INSERTER:
History: During the development phase of this drug produc (b) (4)

(b) (4)

(b) (4)

This was the packaging configuration used for all the preclinical and clinical studies. During the clinical studies, feedback was solicited from the investigators on the inserter device. Feedback was also obtained from retinal specialists who were not part of the clinical study.

Figure 4: Iluvien Inserter Device

FAVOR study: The FAVOR study, C-01-08-006, entitled "A randomized, double-masked, pilot study of the safety and efficacy of 0.5 µg/day and 0.2 µg/day Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg in subjects with macular edema secondary to retinal vein occlusion", is an ongoing study (b) (4) The study utilizes the new (b) (4) inserter and collects information from the treating physician on the performance of the inserter. As of the applicant's May 12, 2011, complete response submission the FAVOR trial is ongoing and has enrolled and treated 8 subjects as of December 31, 2010. In the FAVOR study no adverse events were reported related to the insertion procedure.

There is currently no clinical data to support the use of the new (b) (4) inserter for the Iluvien drug product. The modifications to the inserter are so significant that clinical data is necessary to bridge the two different inserter configurations.

Open Label Trial: On March 2, 2011, IND 72,056 SDN 110 the following protocol was submitted titled, "An Open Label, Multi-center Extension Study of the Safety and Utility of the New Inserter of ILUVIEN (Fluocinolone Acetonide Intravitreal Insert) 0.19 mg and the Safety of ILUVIEN in Subjects with Diabetic Macular Edema." This study is to assess the safety and utility of the new Inserter for the administration of Iluvien in subjects with diabetic macular edema who have previously received either dose of Fluocinolone Acetonide (FA) Intravitreal Insert in the phase 3 FAME studies. This extension trial will be an open label retreatment study enrolling 100 subjects at 40 – 50 centers.

The trial as proposed will not satisfy the Agency's deficiency from the December 22, 2010, Complete Response Letter; use of the proposed (b) (4) inserter is still not supported by clinical data in the application. Per the February 2, 2011 a Type A Guidance meeting, it is expected that the clinical trial be 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 clinical trials supporting safety and efficacy. It is expected that at least 100 eyes will have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval. In addition, the Inclusion Criteria as proposed for the trial are not acceptable. Criterion #2 (In the judgment of the Investigator, the subject will benefit from retreatment with Iluvien) is too vague. The protocol should specify exactly what inclusion parameters identify subjects as candidates for retreatment.

DRUG SUBSTANCE:
From the applicant's submission dated 11/11/10:

Table 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
Identification by HPLC	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4)	CTM-200500
Related Substances		
(b) (4)	Not more than (b) (4)	CTM-200500
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Test	Acceptance Criteria	Analytical Method
(b) (4)	Not more than (b) (4)	
	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	Not more than (b) (4)	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4) µm	Not less than (b) (4)	(b) (4) MGR051FLU011
Particle µm	Not less than	
Particle µm	Not less than	
Polymorphism		
(b) (4)	Not less than (b) (4)	Contract Laboratory[c] High Resolution X-Ray Powder Diffraction and/or Differential Scanning Calorimety
Microbial Limits		
Total Aerobic Count	Not more than (b) (4)	Current USP/NF <61> MTM-200155
Yeast/Mold Count	Not more than	
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
		(b) (4)

DRUG PRODUCT:

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)

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

Table 1: Quality Control Specifications

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Specified Identified and Unidentified Individual Impurity		
Release	(b) (4) Not more than	CTM-200501
Stability	Not more than	
Unspecified Individual Impurity		
Release	(b) (4) Not more than	
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4)	CTM-200502
Endotoxin		MTM-200033
Sterility		
Release		(b) (4)
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

From CMC's review 9/30/2011:

From the ONDQA viewpoint, NDA 201-923 is not recommended for approval. The site recommendation on a new testing facility has not been made for this application by the Office of Compliance as of the date of this review. The action letter for this resubmission should contain the following or similar language:

> All facilities and controls will need to comply with the cGMP regulations. Please amend the application with facilities that are in compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.

Cited deficiencies from the final CMC review this cycle:

1. Without the data and clarification as requested in Comment #3 below, we cannot make any final recommendation regarding the acceptability of the proposed specification range for the *in-vitro* release rate. Provide the release rates of the batches that were tested in the clinical studies to justify your proposed *in-vitro* release rate. We consider the proposed range (b) (4) We suggest that the estimation of the range for the release rate be based on mean data and 90% confidence intervals around the mean. Note that the proposed release rate specification range should (b) (4)

2. You have not provided the polymorph testing method done at (b) (4) the polymorph testing site proposed in this NDA.

    a. Provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ((b) (4) method if applicable), operation procedures, and quantitative analysis.
    b. Provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA.

In addition, we request that you address the following issues in a submission to your NDA.

3. Your protocol for the *in vitro* drug release rate test specifies the collection of samples at (b) (4) are collected. It is not clear from the data submitted in your May 12, 2011 submission, specifically "*Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured at* (b) (4) " and "*Table 3: Release Rates from* (b) (4) *from Study 10123*," at what time points these samples were collected. This needs to be clarified. In addition, 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 Tables 2 and 3 needs to be submitted.

4. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

5. Because the resubmission dated May 12, 2011 provided updated analytical procedures and method validation reports for the drug product, provide the following updates and information:

    a. List under specified impurities, each degradant reported in the drug product specification identified by its name or relative retention tim (b) (4)

b. Specify how impurities [redacted] (b) (4) are to be "combined reported" in the drug product specification.

c. The method transfer report-08202 recommends [redacted] (b) (4) Update CTM - 200501 to include the [redacted] (b) (4) information.

d. Explain the [redacted] (b) (4) RSD results observed on accuracy, precision, and intermediate precision for assay in the validation report (DP2006-156) compared to those in the method transfer report (08202).

e. For the in-vitro drug release test, we recommend you maintain a record of the visual checks being performed as part of the protocol.

6. No updated stability data were submitted in the May 12, 2011, resubmission. Submit all available stability data.

4. Nonclinical Pharmacology/Toxicology

The original Pharmacology Toxicology Review finalized 11/17/10 recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 11/18/2010:

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.

From the ONDQA (Biopharmaceutics) Review finalized 6/27/11:

The submission lacks required information for recommending approval of the proposed [drug product] from the biopharmaceutics point of view.

The applicant's new proposed range is presented below:

Release Rate	[redacted] (b) (4)	µg/day	CTM-200502

The applicant's protocol specifies the collection of samples [redacted] (b) (4) However, it is not clear from the data submitted in the Tables 2 (Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured at [redacted] (b) (4)) and Table

3 (Release Rates from [redacted] (b) (4) from Study 10123) at which time these samples were collected.

The proposed [release rate] range [redacted] (b) (4)
The applicant 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 [redacted] (b) (4)

6. Sterility Assurance

Per the original Product Quality Microbiology review completed on 12/8/10:

The application is recommended for approval from a microbiology quality standpoint. There are no outstanding product quality deficiencies.

7. Clinical/Statistical - Efficacy

From the Medical Officer Review finalized 9/13/2011:

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness $\geq$ 250 microns.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

Originally, the primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a $\geq$ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline; the current Complete Response modified the endpoint to be evaluated at Month 36, instead of Month 24, compared to baseline.

Primary Efficacy at 36 Months

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

Time Point	FAME Study A			FAME Study B		
	Treatment Group			Treatment Group		
	Sham	0.2 µg/day FA	0.5 µg/day FA	Sham	0.2 µg/day FA	0.5 µg/day FA
	N=95	N=190	N=196	N=90	N=186	N=199
Month 18, n (%)	[redacted]					(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 (%)	[redacted]					(b) (4)
Difference[1]						
P-value[2]						
Month 36, n (%)						
Difference[1]						
P-value[2]						

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 stratified by baseline VA.

Fame A and B studies do not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05).

Primary Efficacy at 36 Months in a Post-Hoc Subgroup Analysis

The applicant subsequently performed multiple analyses [redacted] (b) (4)

[redacted] (b) (4)

The analyses for this subgroup are as follows:

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, Full Analysis Population = ITT with LOCF)

(b) (4)

(b) (4)

(b) (4)

Efficacy Summary Statement

Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05) for the applicant's original primary endpoint. The newly proposed primary endpoint was not adequately defined. Efficacy of this drug product has not been satisfactorily demonstrated for the original or the revised indications.

The applicant's proposed new subgroup, (b) (4) has multiple issues and concerns:

1. The a priori primary efficacy endpoint for either dose (0.2 µg/day or 0.5 µg/day) of the FA intravitreal insert was for it to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24, or Month 36, compared to baseline.

Fame A and B studies did not demonstrate statistically significant results for the original primary endpoint at either dose at 36 months (p values all > 0.05).

2. Subsequently to failing the primary endpoint, the applicant proposed the new primary endpoint: Number (%) of Subjects with a ≥ 15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4)

The analysis of the proposed subgroup lacks a statistical adjustment for multiplicity.

This newly proposed endpoint was not a pre-specified primary or secondary endpoint or listed as an exploratory variable. Even for planned secondary / exploratory variables no statistical adjustment was taken.

3. The endpoint was changed to the following criteria: subjects with "duration of DME (b) (4) "

The duration of DME was defined by the applicant as follows: (b) (4)

Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time. Given DME can wax and wane over time the proposed subgroup "Duration of DME (b) (4)" is not defined well nor is it documented that the subjects had DME (b) (4)

The Definition of duration of DME was not adequately assessed as a study inclusion criterion given DME can wax and wane over time.

4. Fame A and B studies were not performed with the final drug configuration ((b) (4) Inserter).

In addition to the eight eyes treated in the FAVOR study, the applicant has submitted results from a questionnaire completed by 31 physicians from a wet lab demonstration and has also submitted a protocol to enroll 100 eyes in an open label extension study with subjects from Fame A and B studies. There is no clinical data provided from this new protocol in this May 12, 2011, submission.

Prior to approval of a drug, it is recommended that at least one clinical study include treatment of patients with the proposed final market formulation. Neither Fame A or Fame B were performed with the final drug/dispenser configuration ((b) (4) Inserter). Per the applicant's complete reponse of May 12, 2011, as of December 31, 2010, there have been eight eyes treated with the final drug/dispenser configuration in another of the sponsor's studies – the retinal vein occlusion study (FAVOR). It is recommended that at least a minimum of 100 eyes be treated with the final drug/dispenser formulation for this drug product

5. The applicant has proposed the following revised indicaton (b) (4)

Because (b) (4) the drug can not be labelled as suggested by the applicant.

6. Clinical results when comparing similar groups for Primary Efficacy at 36 Months:

i. Lens Status: Phakic at Baseline and Pseudophakic at Month 36
ii. Lens Status: Phakic at Baseline and Month 36
iii. Lens Status: Pseudophakic at Baseline and Month 36
iv. An integrated analysis of FAME A and B in a subgroup of subjects with no confounding variables.[1]

(b) (4)

To examine the duration of therapeutic effect of a single dose of FA insert without the confounding effects of cataracts, additional laser treatments and disallowed therapies, the applicant performed the additional subgroup analysis for the percentage of subjects with ≥15 letter improvement from baseline in the subgroup of subjects who were pseudophakic at baseline and received 1 study treatment and no laser or disallowed therapies during the study.

[1] Tables for these 36 month results are found in the Medical Officer's review, pages 14-16, dated 9/13/2011.

When controlling for the confounding effects of cataracts, additional laser treatments and disallowed therapies, the integrated analysis of the Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (nor at any of the time points listed at 18 months or more), (p values all > 0.05).

8. Safety

From the Medical Officer Review finalized 9/13/2011:

The 36 Month results from the two Fame studies (Fame A and Fame B) form the basis for the safety evaluation.

Exposure in Study Treatments:
36 Month Integrated Fame A and B Studies (Total n = 953)

Study Treatments	Sham (N=185)	0.2 µg/day FA (N=375)	0.5 µg/day FA (N=393)
Number of Treatments Completed			
Number of Treatments	252	488	534
Number of Subjects Receiving at Least 1 Treatment	185	375	393
Mean (SD)	1.4 (0.7)	1.3 (0.6)	1.4 (0.6)
Median	1.0	1.0	1.0
Minimum, Maximum	(1.0, 6.0)	(1.0, 4.0)	(1.0, 4.0)
Number of Treatments Completed by Frequency, n (%)			
1 Treatment	132 (71.4)	279 (74.4)	278 (70.7)
2 Treatments	4 (23.8)	81 (21.6)	91 (23.2)
3 Treatments	6 (3.3)	13 (3.5)	22 (5.6)
4 Treatments	2 (1.1)	2 (0.5)	2 (0.5)
> 4 Treatments	1 (0.5)	0	0

A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the Fame studies. The total number of treatments administered during the studies was 252, 488, and 534 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for the 0.2 µg/day group and 1.4 for the sham and 0.5 µg/day groups.

Dropouts and/or Discontinuations
36 Month Integrated Studies (Fame A and B)

Disposition	Sham	0.2 µg/day FA	0.5 µg/day FA
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated[1]	185	375	393
Total completed (n, %)	126 (68.1)	272 (72.9)	279 (70.6)
Total discontinued (n,%):	59 (31.9)	102 (27.1)	116 (29.4)
Adverse events	5 (2.7)	4 (1.1)	15 (3.8)

Disposition	Sham	0.2 µg/day FA	0.5 µg/day FA
Unsatisfactory therapeutic effect	3 (1.6)	0	1 (0.3)
Protocol violation	2 (1.1)	2 (0.5)	5 (1.3)
Subject withdrew consent	14 (7.6)	31 (8.2)	27 (6.8)
Lost to follow-up	24 (13.0)	37 (9.8)	37 (9.4)
Death	11 (5.9)	27 (7.2)	31 (7.8)
Unknown	0	1 (0.3)	0

1. This represents the set of subjects included in the safety population.

Overall, 277 (29%) subjects discontinued the trial, primarily due to loss to follow-up (10%). withdrawn consent (8%), or death (7%).Of the 277 subjects who discontinued the study, 43 (16%) subjects discontinued during the first 12 months of the study, and 97 (35%) subjects discontinued during the second year of the study. Overall, discontinuations rates were similar throughout the three treatment groups.

Ocular Adverse Events Leading to Discontinuation
Integrated Studies (Fame A and B)

Treatment Group	Subject No.	Adverse Event
Sham	102404	Vision loss (OU)
0.2 µg/day FA	100403	Chemical eye injury
0.2 µg/day FA	101634	Endophthalmitis
0.2 µg/day FA	105645	Eye infection fungal
0.5 µg/day FA	100313	Intraocular pressure increased
0.5 µg/day FA	10221	Trabeculectomy
0.5 µg/day FA	104921	Cataract
0.5 µg/day FA	109406	Glaucoma, Trabeculectomy, Iris incarceration
0.5 µg/day FA	109502	Retinal detachment

In the Integrated Analysis at 36 Months by dose in the Fame A and B studies, 621 (77%) of the 953 subjects who received drug therapy were phakic at baseline and at risk for primary cataract formation.

Cataract-Related Events in Phakic Subjects
36 Month Integrated Studies (Fame A and B)
Study eye only

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)	61 (50.4)	192 (81.7)	235 (88.7)
Cataract operation	33 (27.3)	188 (80.0)	231(87.2)

The percentage of phakic subjects who developed a cataract or had a cataract operation was lower in the sham group compared to the 0.2 µg/day FA and 0.5 µg/day FA groups. Fifty percent

of the sham group compared with 82% of the 0.2 µg/day FA and 89% of the 0.5 µg/day FA had a cataract with 27% of the sham group compared to 80% of the 0.2 µg/day and 87% of the FA 0.2 µg/day FA groups requiring a cataract operation during the 36 month study period.

The risks of cataract formation and cataract operation are significant by 36 months after the drug treatment and this risk appears to be dose and time dependent.

Common (≥ 5%) Ocular Adverse Events by Treatment Group: 36 Month Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Cataract	53 (28.6)	171 (45.6)	213 (54.2)
Cataract operation	33 (17.8)	188 (50.1)	132 (58.8)
Cataract subcapsular	8 (4.3)	28 (7.5)	24 (6.1)
Conjunctival haemorrhage	20 (10.8)	43 (11.5)	50 (12.7)
Dry eye	11 (5.9)	23 (6.1)	22 (5.6)
Eye irritation	9 (4.9)	27 (7.2)	22 (5.6)
Eye pain	22 (11.9)	51 (13.6)	65 (16.5)
Glaucoma	4 (2.2)	19 (5.1)	18 (4.6)
IOP increased	21 (11.4)	132 (35.2)	170 (43.3)
Maculopathy	16 (8.6)	23 (6.1)	34 (8.7)
Myodepsia	13 (7.0)	67 (17.9)	68 (17.3)
Posterior capsule opacification	6 (3.2)	32 (8.5)	25 (6.4)
Retinal hemorrhage	11 (5.9)	9 (2.4)	17 (4.3)
Trabeculectomy	0	10 (2.7)	22 (5.6)
Vision blurred	13 (7.0)	28 (7.5)	20 (5.1)
Visual acuity reduced	17 (9.2)	39 (10.4)	35 (8.9)
Visual impairment	7 (3.8)	13 (3.5)	31 (7.9)
Vitrectomy	16 (8.6)	19 (5.1)	23 (5.9)
Vitreous detachment	12 (6.5)	26 (6.9)	20 (5.1)
Vitreous Hemorrhage	28 (15.1)	41 (10.9)	48 (12.2)

Overall, the most common ocular adverse events were cataract operation (47%), cataract (46%), increased intraocular pressure (34%) and myodesopsia (16%). Several events had a lower incidence in the sham group with the most notable observed differences being for cataract operation (18%, sham; 50%, 0.2 µg/day FA; 59%, 0.5 µg/day FA); cataract (29%, sham; 46%, 0.2 µg/day FA; 54%, 0.5 µg/day FA); and increased intraocular pressure (11%, sham; 35%, 0.2 µg/day FA; 43%, 0.5 µg/day FA). Similar trends were observed for myodesopsia (7%, sham; 18%, 0.2 µg/day FA; 17%, 0.5 µg/day FA), posterior capsular opacification (3%, sham; 9%, 0.2 µg/day FA; 6%, 0.5 µg/day FA,) and glaucoma (2%, sham; 5%, 0.2 µg/day FA; 5%, 0.5 µg/day FA). The only cases of trabeculectomy occurred in the active treatment groups (3%, 0.2 µg/day FA; 6%, 0.5 µg/day FA).

Safety Summary Statement

At 36 months the risk of cataract formation, cataract operation, and increased IOP are adverse events that continue to occur at significantly high rates in the drug group when compared to the Sham group.

Cataract formation (any type in Phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes.

Increased IOP occurs in 11% of the Sham group versus 35% in the 0.2 µg/day FA. The risk of increased IOP is three times the rate in the 0.2 µg/day FA drug group.

Safety Summary Statement

At 36 Months the risk of cataract formation, cataract operation, and increased IOP are adverse events that occur at significantly high rates in the drug group when compared to the Sham group.

9. Advisory Committee Meeting

No Advisory Committee Meeting has been scheduled. There are no outstanding clinical issues which are believed to benefit from an advisory committee discussion at this time.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested in the original review cycle. The DSI Clinical Inspection Summary was finalized on 12/1/10.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided.

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable.

DMEPA again reviewed the name Iluvien for the NDA application. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable.

DDMAC
The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle.

BIOSTATISTICS
From the Biostatistics review dated 8/1/2011:

The review finds that the applicant did not demonstrate (b) (4)

In conclusion, we defer to the clinical review to weigh the benefit against the risk of this drug in the general population or in the subgroup of DME (b) (4) but the drug harms a significantly higher proportion of subjects compared to sham. The two main harms considered here are IOP elevation or cataract surgery. (b) (4) However, this subgroup was determined post-hoc so any results should be considered with caution. The statistical review cannot weigh the benefit of BCVA gain versus the risk of cataract surgery or elevated IOP and we defer to the clinical review team to weigh these outcomes against each other.

12. Labeling

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment diabetic macular edema.

A formal labeling review is deferred until additional data is submitted to support the application for Iluvien.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment diabetic macular edema.

RISK BENEFIT ASSESSMENT:
There is not substantial evidence to demonstrate that the benefits of the drug outweigh its risks for either the low dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.25 µg/day) or the high dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.5 µg/day). The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema. This recommendation is based on the results from the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) studies submitted with 36 month data for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day.

At 36 months follow-up cataract formation occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes and Increased IOP occurs in 11% of the Sham group study eyes versus 35% in the 0.2 µg/day FA study eyes. The risk of increased IOP is three times the rate in the 0.2 µg/day FA drug group.

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended (b) (4). Specifically,

1) Fame A and B, the confirmatory clinical trials, failed their original primary endpoint (p values > 0.05).
2) When evaluating for the newly proposed primary endpoint there was a lack of statistical adjustment for multiplicity.
3) The newly proposed primary endpoint's definition of duration DME was not adequately assessed as a study inclusion criterion.
4) There were not results from patients treated with the proposed final market formulation (drug/dispenser) in a minimum of 100 treated eyes.
5) The drug can not be labeled as proposed by the applicant.
6) When evaluating for the newly proposed primary endpoint analysis based on similar pre/post op groups no statistically significant results (based on a p value of 0.5) at 36 Months were demonstrated.

Recommended language for a second Complete Response letter follows:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

    a) Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05) for your original primary endpoint. Your newly proposed primary endpoint, i.e. Number (%) of Subjects with a ≥ 15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) was not adequately defined. Efficacy of this drug product has not been satisfactorily demonstrated for the either original or the revised indications.

    b) Your proposed new subgroup, (b) (4) has multiple issues and concerns:

        1. The analysis of the proposed subgroup lacks a statistical adjustment for multiplicity.

        2. This newly proposed endpoint was not a pre-specified primary or secondary endpoint or listed as an exploratory variable. Even for planned secondary / exploratory variables no statistical adjustment was taken, as noted in your Complete Response submission of May 12, 2011.

        3. Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time. Given DME can wax and wane over time the proposed subgroup "Duration of DME (b) (4)" is not defined well nor is it documented that the subjects had DME (b) (4)

        4. The Definition of duration of DME was not adequately assessed as a study inclusion criterion given DME can wax and wane over time.

    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. In addition to the eight eyes treated in the FAVOR study, you have has submitted results from a questionnaire completed by 31 physicians from a wet lab demonstration and has also submitted a protocol to enroll 100 eyes in an open label extension study with subjects from Fame A and B studies.

    There is no clinical data provided from this new protocol in this May 12, 2011, submission. It is expected that the clinical trial be a comparative study with at

least 100 eyes enrolled into the trial using the [redacted] inserter versus at least 50 eyes enrolled using the inserter configuration utilized in the clinical trials supporting safety and efficacy. It is expected that at least 100 eyes will have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval.

d) The risk of increased intraocular pressure (IOP) is nearly three times higher in the drug treatment groups compared to the Sham (control) group in the 36-month data. Additional clinical data will need to demonstrate that the drug's benefits will be able to overcome this significant risk

e) Cataract formation (any type in Phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Additional clinical data will need to demonstrate that the drug's benefits will be able to overcome this significant risk

3. Your protocol specifies the collection of samples [redacted] It is not clear from the data submitted in your May 12, 2011 submission, specifically Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured at [redacted] and Table 3: Release Rates from [redacted] from Study 10123, at what time points these samples were collected. This needs to be clarified. In addition, 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 Tables 2 and 3 needs to be submitted.

4. No final concurrence can be made regarding Release Rates Specification without data and clarification as requested in Comment #2 above. However, the proposed range [redacted] 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 needs to be described. The release rate specifications should [redacted]

5. We have reviewed the information regarding the sterilization validation you provided in your original submission (June 28, 2010) and Amendments 9 (August 12, 2010), 17 (November 11, 2010), and 22 (May 12, 2011). Your validation reports state that your validation was conducted per the [redacted] method described [redacted] However, your product specifications (provided in theoriginal Submission, Section 3.2.P.5.1, and in subsequent Amendments) state that your validation was performed per [redacted]. Therefore, please clarify which documents were used for your validation, and provide a rationale on how your sterilization validation meets the recommendations stated within [redacted]

6. No updated stability data were submitted in the resubmission.

7. You have not provided the polymorph testing method done at [redacted] (b) (4) the polymorph testing site proposed in this NDA.

   a. Provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ([redacted] (b) (4) method if applicable), operation procedures, and quantitative analysis.

   b. Provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA.

8. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

9. Because the resubmission dated May 12, 2011 provided updated analytical procedures and method validation reports for the drug product, provide the following updates and information:

   a. List under specified impurities, each degradant reported in the drug product specification identified by its name or relative retention tim [redacted] (b) (4)

   b. Specify how impurities [redacted] (b) (4) are to be "combined reported" in the drug product specification.

   c. The method transfer report-08202 recommends [redacted] (b) (4)

   d. Explain the [redacted] (b) (4) RSD results observed on accuracy, precision, and intermediate precision for assay in the validation report (DP2006-156) compared to those in the method transfer report (08202).

   e. For the in-vitro drug release test, we recommend you maintain a record of the visual checks being performed as part of the protocol.

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

/s/

WILLIAM M BOYD
10/27/2011

WILEY A CHAMBERS
10/27/2011

Deputy Division Director Review of NDA 201923

Date	October 11, 2011
From	Wiley A. Chambers, M.D.
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Amendment to first action letter	May 12, 2011
Type of Application	505(b)(1)
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Proposed Action:	Complete Response

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant.

There is no previous marketing experience with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg as this product is not commercially available.

There are no approved drug therapies for the treatment of diabetic macular edema (DME).

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) and has been developed for the treatment of Diabetic Macular Edema (DME). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.

The safety and efficacy seen with this product are class effects related to ophthalmic steroids. Use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

2. Background

Diabetic macular edema (DME), a chronic, debilitating disease, is a cause of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008. The Division expressed concern that the benefits might not outweigh the risks if Illuvien demonstrated a safety profile which was similar to other corticosteroids. The applicant stated that they did not expect to see the development of cataracts or elevated intraocular pressure due to the low release rate.

A Pre-NDA meeting was held for IND 72,056 on March 4, 2010.

The NDA was submitted on June 30, 2010. The Agency issued a Complete Response letter on December 22, 2010, citing a lack of substantial evidence to support the efficacy, facilities that were not in compliance with cGMPs and a lack of methods, facility and controls to assure identity, strength, quality, purity and stability.

3. CMC

Many of the Chemistry/Manufacturing deficiencies identified during the original submission have been resolved, but not all and some new deficiencies have been introduced with the resubmission. The CMC reviewer does not recommend approval and has cited the following items as deficiencies.

1. The proposed *in-vitro* release rate range (b) (4) It is not clear from the data submitted in your May 12, 2011, submission, specifically "*Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured at* (b) (4) " and "*Table 3: Release Rates from* (b) (4) *from Study 10123*," at what time points these samples were collected. This needs to be clarified. In addition, 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 Tables 2 and 3 is needed to support any range. Without the release rate data of batches that were tested in the clinical studies, we cannot accept the proposed specification range for the *in-vitro* release rate. The proposed release rate specification range should (b) (4)

2. The polymorph testing method done at (b) (4) has not been provided. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. The proposed acceptance criterion for polymorph testing should take into consideration

commercial and clinical batch data as well as the effect of polymorphic form on solubility.

a. The applicant should provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ((b) (4) method if applicable), operation procedures, and quantitative analysis.

b. The applicant should provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA.

3. Because the resubmission dated May 12, 2011 provided updated analytical procedures and method validation reports for the drug product, the following updates and information are needed:

a. A list of specified impurities with each degradant reported in the drug product specification identified by its name or relative retention tim (b) (4)

b. Information on how impurities (b) (4) are to be "combined reported" in the drug product specification.

c. Details from the method transfer report-08202 which recommends (b) (4)

d. An explanation of the (b) (4) RSD results observed on accuracy, precision, and intermediate precision for assay in the validation report (DP2006-156) compared to those in the method transfer report (08202).

e. A record of the visual checks for in-vitro drug release test results being performed as part of the protocol.

4. The stability data were not updated in the May 12, 2011, resubmission. All available stability data should have been submitted.

4. Nonclinical Pharmacology/Toxicology

Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. Orally administered PVA is relatively harmless, with LD_{50} in the range of 15-20 g/kg. The content of PVA in a 0.19 mg Iluvien is (b) (4) The sponsor also conducted several biocompatibility studies with polyimide tubing and extracts of stainless steel injection needles. The results were negative.

The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber. Continuous exposures of ocular tissues for both toxicity studies were achieved via one or two injections of the insert into the eye. There appeared to be no definable toxicity associated with the administration of 0.2 µg/day FA. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations.

The panel of genotoxicity tests performed by the Sponsor included the bacterial mutation test, mammalian cell mutation test and a mouse micronucleus test. Fluocinolone acetonide did not show any evidence of genotoxic activity in these tests when tested in accordance with regulatory guidelines.

No carcinogenicity studies were conducted for Iluvien. Reproductive and developmental toxicity studies with Iluvien were not conducted. During a communication from the FDA to sponsor on 02/03/10, FDA requested the human PK data be submitted for the evaluation of carcinogenicity waiver. Since human systemic exposure to FA after Iluvien is below LLOQ, the waiver of carcinogenicity study was granted.

5. Clinical Pharmacology/Biopharmaceutics

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 (manufactured by (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)

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. However, the assessment on FA exposure in aqueous humor and any conclusions thus derived will not be used to support any regulatory decisions because the analytical method was not validated.

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 a full development and validation report for the *in-vitro* release methodology.

6. Sterility Assurance

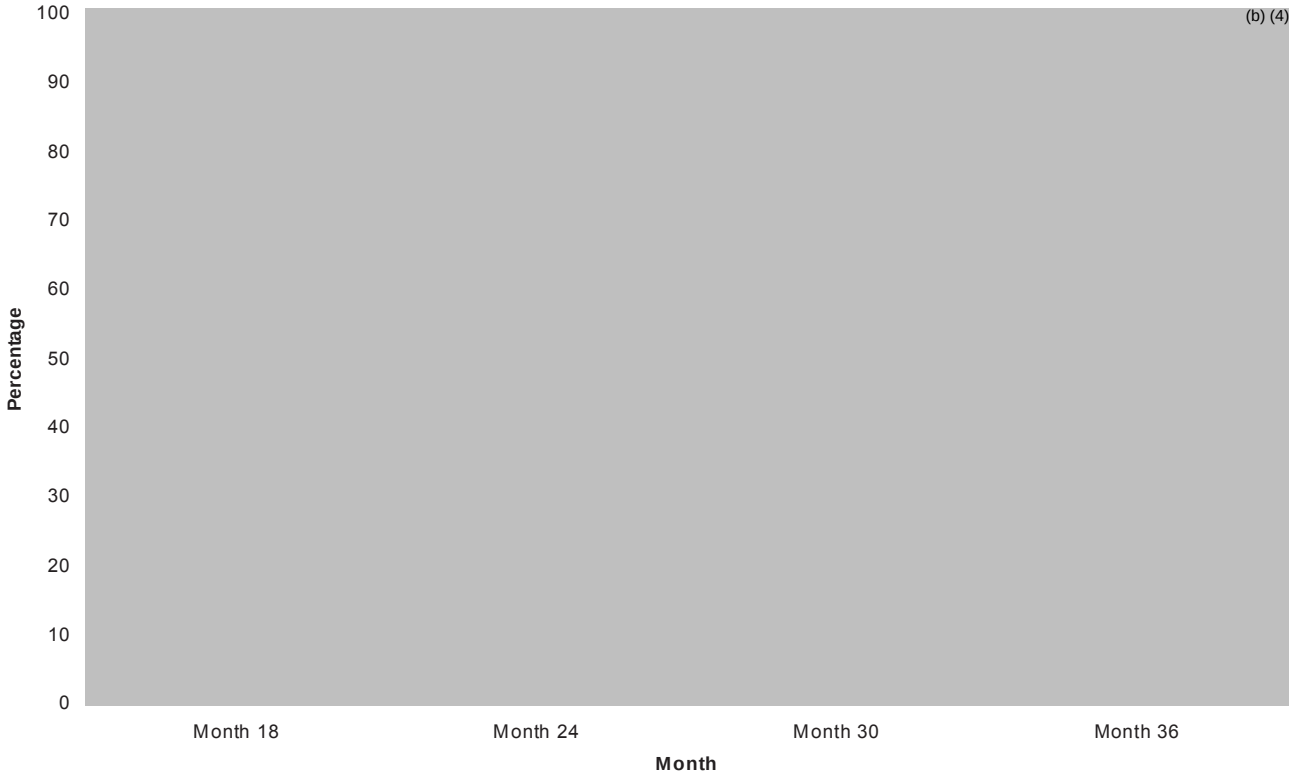
As noted in the Product Quality Microbiology Review, the product quality microbiology deficiencies were addressed and there are no remaining issues concerning sterility assurance.

7. Clinical/Statistical - Efficacy

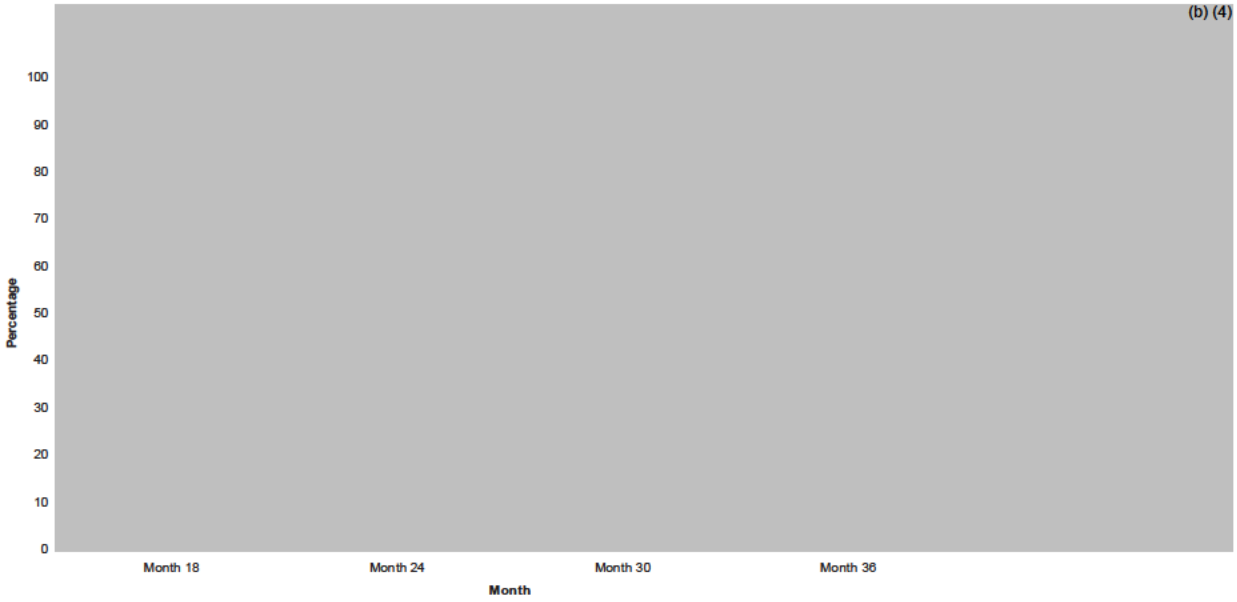
The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The 24-month data was confounded by the development of cataracts.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 μg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

Originally, the primary endpoint was for either dose (0.2 μg/day or 0.5 μg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline; the current Complete Response modified the endpoint to be evaluated at Month 36, instead of Month 24, compared to baseline.



None of the differences are statistically significant at Month 36.



(b) (4)

It is not clear how patients were identified as having DME (b) (4) since DME has a variable course.

Fame A and B studies did not demonstrate statistically or clinically significant results at 36 months for the original primary endpoint. The newly proposed primary endpoint, i.e., Number (%) of Subjects with a ≥ 15-Letter Increase from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye by Duration of Diabetic Macular Edema (DME) (b) (4) was not adequately defined. Efficacy of this drug product has not been satisfactorily demonstrated for either the proposed original or the proposed revised indications.

The proposed new subgroup, (b) (4) had multiple issues:

1. The analysis of the proposed subgroup lacked a statistical adjustment for multiplicity.

2. The newly proposed endpoint was not pre-specified as a primary or secondary endpoint or listed as an exploratory variable. The statistical plan should have included statistical adjustments for the multiplicity introduced with any secondary, exploratory or additionally added endpoint.

3. Diabetic macular edema (DME) is a disease that can wax and wane over the course of many years with varying degrees of macular involvement. Given the variable course of DME over time, the proposed subgroup "Duration of DME (b) (4)" was not specifically defined in terms of objective observations nor was it documented that the subjects had DME (b) (4)

8. Safety

The results from two Fame studies (Fame A and FAME B) form the basis for the safety evaluation. The 2 FAME studies were performed under one protocol and enrolled subjects during the same time period. The only significant difference between the studies was geographical location of the study sites. FAME A was conducted at 49 sites in 7 countries (US, Canada, 4 countries in the European Union [EU], and India). FAME B was conducted at 52 sites in 5 countries (US, India, and 3 countries in the EU). When the 2 studies enrolled subjects in the same countries, FAME A enrolled subjects in the northern portions of the countries involved, and FAME B enrolled subjects in the southern portions of the countries. The demographics of the 2 study populations were essentially the same.

The exposure of subjects was adequate. A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the Fame studies. The total number of treatments administered during the studies was 252, 488, and 534 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for the 0.2 µg/day group and 1.4 for the sham and 0.5 µg/day groups.

The completion rate was poor.

Dropouts and/or Discontinuations through Month 36 for Fame A&B

Disposition	Sham	0.2 µg/day FA	0.5 µg/day FA
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated[1]	185	375	393
Total completed (n, %)	126 (68.1)	272 (72.9)	279 (70.6)
Total discontinued (n,%):	59 (31.9)	102 (27.1)	116 (29.4)
Adverse events	5 (2.7)	4 (1.1)	15 (3.8)
Unsatisfactory therapeutic effect	3 (1.6)	0	1 (0.3)
Protocol violation	2 (1.1)	2 (0.5)	5 (1.3)
Subject withdrew consent	14 (7.6)	31 (8.2)	27 (6.8)
Lost to follow-up	24 (13.0)	37 (9.8)	37 (9.4)
Death	11 (5.9)	27 (7.2)	31 (7.8)
Unknown	0	1 (0.3)	0

The rate of cataract development was high.

Cataract Rate in study eye only

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)	61 (50.4)	192 (81.7)	235 (88.7)
Cataract operation	33 (27.3)	188 (80.0)	231(87.2)

Cataract formation (any type in Phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operations occurred in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. The drug's potential benefits do not overcome this significant risk in the phakic population.

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Cataract	53 (28.6)	171 (45.6)	213 (54.2)
Cataract operation	33 (17.8)	188 (50.1)	132 (58.8)
Cataract subcapsular	8 (4.3)	28 (7.5)	24 (6.1)
Conjunctival haemorrhage	20 (10.8)	43 (11.5)	50 (12.7)
Dry eye	11 (5.9)	23 (6.1)	22 (5.6)
Eye irritation	9 (4.9)	27 (7.2)	22 (5.6)
Eye pain	22 (11.9)	51 (13.6)	65 (16.5)
Glaucoma	4 (2.2)	19 (5.1)	18 (4.6)
IOP increased	21 (11.4)	132 (35.2)	170 (43.3)
Maculopathy	16 (8.6)	23 (6.1)	34 (8.7)
Myodepsia	13 (7.0)	67 (17.9)	68 (17.3)
Posterior capsule opacification	6 (3.2)	32 (8.5)	25 (6.4)
Retinal hemorrhage	11 (5.9)	9 (2.4)	17 (4.3)
Trabeculectomy	0	10 (2.7)	22 (5.6)
Vision blurred	13 (7.0)	28 (7.5)	20 (5.1)
Visual acuity reduced	17 (9.2)	39 (10.4)	35 (8.9)
Visual impairment	7 (3.8)	13 (3.5)	31 (7.9)
Vitrectomy	16 (8.6)	19 (5.1)	23 (5.9)
Vitreous detachment	12 (6.5)	26 (6.9)	20 (5.1)
Vitreous Hemorrhage	28 (15.1)	41 (10.9)	48 (12.2)

The rate of IOP elevation and glaucoma is unacceptable. The risk of increased intraocular pressure (IOP) is nearly three times higher in the drug treatment groups compared to the Sham (control) group in the 36-month data. The drug's potential benefits do not overcome this significant risk.

The inserter used in the preclinical and clinical trials was modified; use of the proposed (b) (4) inserter was 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 have been submitted to the application.

While a protocol to enroll 100 eyes in an open label extension study with subjects from Fame A and B studies was submitted, there was no clinical data provided from this protocol in the May 12, 2011, submission. It was expected that results be submitted of a clinical comparative trial with at least 100 enrolled eyes using the (b) (4) inserter versus at least 50 enrolled eyes using the inserter configuration from the original clinical trials. It was expected that at least 100 eyes would have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval.

9. Advisory Committee Meeting

No Advisory Committee Meeting was scheduled because 36 month data did not support the approval for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg and the safety profile suggested that the observed benefits did not outweigh the risks of the product.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population. This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. The DSI Clinical Inspection Summary was finalized on 12/1/10.

Two sites were selected for inspection, one domestic and one foreign, due to enrollment of large numbers of study subjects, high number of INDs and lack of previous inspectional history.

The preliminary classification of Clinical Investigator inspections of Drs. Blackburn (Kentucky) and Garg (India) are Voluntary Action Indicated (VAI). Although regulatory violations were noted at both of these sites, given the nature of the findings, DSI considered it unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

Dr. Blackburn (Study C-01-05-001B /Site 001/17) failed to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Dr. Garg (Study C-01-05-001A /Site 016/ 45) failed to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided.

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable.

DMEPA again reviewed the name Iluvien for the NDA application. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable.

DDMAC
The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle.

BIOSTATISTICS
The Statistical review found that the applicant did not demonstrate (b) (4)

In conclusion, the reviewer defer to the clinical review to weigh the benefit against the risk of this drug in the general population or in the subgroup of DME (b) (4) but the drug harms a significantly higher proportion of subjects compared to sham. The two main harms considered here are IOP elevation or cataract surgery. (b) (4) However, this subgroup was determined post-hoc so any results should be considered with caution. The statistical review cannot weigh the benefit of BCVA gain versus the risk of cataract surgery or elevated IOP and we defer to the clinical review team to weigh these outcomes against each other.

12. Labeling

A formal labeling review is deferred until additional data is submitted to support the application for Iluvien.

13. Regulatory Action

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended to be approved for the treatment diabetic macular edema based on the information submitted to date. The deficiencies include:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

a. Fame A and B studies did not demonstrate statistically or clinically significant results at 36 months for your original primary endpoint. The newly proposed primary endpoint, i.e., Number (%) of Subjects with a ≥ 15-Letter Increase from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye by Duration of Diabetic Macular Edema (DME) (b) (4) was not adequately defined. Efficacy of this drug product has not been satisfactorily demonstrated for either the proposed original or the proposed revised indications.

b. The proposed new subgroup, (b) (4) has multiple issues and concerns:

   i. The analysis of the proposed subgroup lacked a statistical adjustment for multiplicity.

   ii. The newly proposed endpoint was not pre-specified as a primary or secondary endpoint or listed as an exploratory variable. The statistical plan should have included statistical adjustments for the multiplicity introduced with any secondary, exploratory or additionally added endpoint.

   iii. Diabetic macular edema (DME) is a disease that can wax and wane over the course of many years with varying degrees of macular involvement. Given the variable course of DME over time, the proposed subgroup "Duration of DME (b) (4) " was not specifically defined in terms of objective observations nor was it documented that the subjects had DME (b) (4)

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.

   While a protocol to enroll 100 eyes in an open label extension study with subjects from Fame A and B studies was submitted, there was no clinical data provided from this protocol in the May 12, 2011, submission. It was expected that results be submitted of a clinical comparative trial with at least 100 enrolled eyes using the (b) (4) inserter versus at least 50 enrolled eyes using the inserter configuration from the original clinical trials. It was expected that at least 100 eyes would have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval.

2. The results of tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Specifically,

a. The risk of increased intraocular pressure (IOP) was nearly three times higher in the drug treatment groups compared to the Sham (control) group in the 36-month data. The drug's potential benefits do not overcome this significant risk.

b. Cataract formation (any type in Phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operations occurred in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. The drug's potential benefits do not overcome this significant risk in the phakic population.

3. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to preserve its identity, strength, quality, purity, and stability. Specifically,

a. The proposed *in-vitro* release rate range (b) (4) It is not clear from the data submitted in your May 12, 2011, submission, specifically "*Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured at* (b) (4) " and "*Table 3: Release Rates from* (b) (4) *from Study 10123*," at what time points these samples were collected. This needs to be clarified. In addition, 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 Tables 2 and 3 is needed to support any range. Without the release rate data of batches that were tested in the clinical studies, we cannot accept the proposed specification range for the *in-vitro* release rate. The proposed release rate specification range should (b) (4)

b. The applicant did not provided the polymorph testing method done at (b) (4) the polymorph testing site proposed in this NDA. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

c. The applicant should be asked to provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ((b) (4) method if applicable), operation procedures, and quantitative analysis.

d. The applicant should be asked to provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA.

4. New, but incomplete information on the analytical procedures and method validation was submitted in the resubmission dated May 12, 2011. The following additional information should be provided:

   a. List under specified impurities, each degradant reported in the drug product specification identified by its name or relative retention tim [redacted] (b) (4)

   b. Specify how impurities [redacted] (b) (4) are to be "combined reported" in the drug product specification.

   c. The method transfer report-08202 recommends [redacted] (b) (4)

   d. Explain the [redacted] (b) (4) RSD results observed on accuracy, precision, and intermediate precision for assay in the validation report (DP2006-156) compared to those in the method transfer report (08202).

   e. For the in-vitro drug release test, we recommend you maintain a record of the visual checks being performed as part of the protocol.

5. No updated stability data were submitted in the May 12, 2011, resubmission. All available stability data should have been submitted.

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

/s/

WILEY A CHAMBERS
10/19/2011

Medical Officer Review - NDA 20193

Date	July 12, 2011
From	Martin P. Nevitt, M.P.H., M.D.
Subject	Medical Officer Review of Complete Response
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	May 12, 2011
PDUFA Goal Date	November 12, 2011
Type of Application	NDA
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Recommended:	Not Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant. There is no previous marketing experience with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg as this product is not commercially available.

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) and has been developed for the treatment of Diabetic Macular Edema (DME). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter. The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

2. Background

Diabetic macular edema (DME), a serious, chronic, debilitating disease, is one of the causes of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008. The Division expressed concern that the benefits might not outweigh the risks if Illuvien demonstrated a safety profile which was similar to other corticosteroids. The applicant stated that they did not expect to see the development of cataracts or elevated intraocular pressure due to the low release rate.

A Pre-NDA meeting was held for IND 72,056 on March 4, 2010.

NDA 201923 was submitted June 30, 2010 as a Priority review and a PDUFA goal date of December 30, 2010. A Complete Response action was taken December 22, 2010 outlining that the application could not be approved in its present form. A summary of the clinical reasons for this action are described below:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

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.

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.

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.

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.

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.

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.

On February 2, 2011 a Type A Guidance meeting was held to discuss with the Division the steps necessary for the application approval. Specifically, the following clinical issues were reiterated:

1. Alimera must demonstrate a "win" where the benefits outweigh the risks of using the drug product. Carving out a subset is suggested when the subsets can be identified prior to starting the study. 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. Demonstration of safety and efficacy to support approval of an NDA will require that at least 2 adequate and well-controlled, multi-center trials show that the benefits of the drug product outweigh its risks. To demonstrate a "win" would require statistical significance (p value ≤ 0.05) in at least two trials for the primary endpoint (the primary endpoint in the trials was defined as the proportion of subjects with a ≥ 15 letter increase in BCVA on the ETDRS eye chart at Month 24. (Given the timing of the confounding effect of cataract formation and extraction the primary endpoint would be at Month 36 and the data would be re-submitted with this time point.)

2. 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). The Division stated that the final configuration of the inserter used in the trials was required before submitting the NDA. As presented in the NDA submission, it was not clear that the final product was going to be used in the way it was actually used during the trials. When those trials are completed, Alimera can submit the results to the NDA. The trials should be conducted in the indication intended for use.

On May 12, 2011 the applicant submitted its response to the Complete Response action taken on December 22, 2010, which included 36 Month data.

3. CMC

INSERTER:
During the development phase of this drug produc [redacted] (b) (4)

(b) (4)

(b) (4)

This was the packaging configuration used for all the preclinical and clinical studies.

During the clinical studies, feedback was solicited from the investigators on the inserter device. Feedback was also obtained from retinal specialists who were not part of the clinical study.

Figure 4: Iluvien Inserter Device

The FAVOR study, C-01-08-006, entitled "A randomized, double-masked, pilot study of the safety and efficacy of 0.5 µg/day and 0.2 µg/day Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg in subjects with macular edema secondary to retinal vein occlusion", is an ongoing study (b) (4) The study utilizes the new (b) (4) inserter and collects information from the treating physician on the performance of the inserter. As of the sponsor's May 12, 2011, complete response submission the FAVOR trial is ongoing and has enrolled and treated 8 subjects as of December 31, 2010. In the FAVOR study no adverse events were reported related to the insertion procedure.

There is currently no clinical data to support the use of the new (b) (4) inserter for the Iluvien drug product. The modifications to the inserter are so significant that clinical data is necessary to bridge the two different inserter configurations.

On March 2, 2011, IND 72,056 SDN 110 the following protocol was submitted titled, "An Open Label, Multi-center Extension Study of the Safety and Utility of the New Inserter of ILUVIEN (Fluocinolone Acetonide Intravitreal Insert) 0.19 mg and the Safety of ILUVIEN in Subjects

with Diabetic Macular Edema." This study is to assess the safety and utility of the new Inserter for the administration of ILUVIEN in subjects with diabetic macular edema who have previously received either dose of Fluocinolone Acetonide (FA) Intravitreal Insert in the phase 3 FAME studies. This extension trial will be an open label retreatment study enrolling 100 subjects at 40 – 50 centers.

Reviewer's comments:

1) The trial as proposed will not satisfy the Agency's deficiency from the 12/22/2010 Complete Response letter for NDA 201923:

> *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.*

It is expected that the clinical trial be 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 clinical trials supporting safety and efficacy. It is expected that at least 100 eyes will have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval.*

2) The Inclusion Criteria as proposed are not acceptable. Criterion #2 (In the judgment of the Investigator, the subject will benefit from retreatment with ILUVIEN) is too vague. The protocol should specify exactly what inclusion parameters identify subjects as candidates for retreatment.

DRUG SUBSTANCE:

From the applicant's submission dated 11/11/10:

Table 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4)	CTM-200500
Related Substances		
(b) (4)	Not more than (b) (4)	CTM-200500
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Test	Acceptance Criteria	Analytical Method
(b) (4)	Not more than (b) (4)	
	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	Not more than (b) (4)	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4)	Not less than (b) (4)	(b) (4) MGR051FLU011
Particle	Not less than	
Particle	Not less than	
Polymorphism		
(b) (4)	Not less than (b) (4)	Contract Laboratory[c] High Resolution X-Ray Powder Diffraction and/or Differential Scanning Calorimety
Microbial Limits		
Total Aerobic Count	Not more than (b) (4)	Current USP/NF <61> MTM-200155
Yeast/Mold Count	Not more than	
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
(b) (4)		

DRUG PRODUCT:

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)			

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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)

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

Table 1: Quality Control Specifications

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Specified Identified and Unidentified Individual Impurity		
Release	Not more than (b) (4)	CTM-200501
Stability	Not more than	
Unspecified Individual Impurity		
Release	Not more than (b) (4)	
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4)	CTM-200502
Endotoxin		MTM-200033
Sterility		
Release	(b) (4	(b) (4)
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

From CMC's review 7/22/2011:

From the ONDQA viewpoint, NDA 201-923 is not recommended for approval. There are outstanding CMC and biopharmaceutic deficiencies.

4. Nonclinical Pharmacology/Toxicology

The original Pharmacology Toxicology Review finalized 11/17/10 recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 11/18/2010:

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.

6. Sterility Assurance

Per the original Product Quality Microbiology review completed on 12/8/10:

The applicant should:

(1) include a [redacted] (b) (4) and impose [redacted] (b) (4) bioburden alert and action limits;
(2) describe the bioburden and endotoxin testing procedures used [redacted] (b) (4)
(3) describe [redacted] (b) (4) the procedure [redacted] (b) (4)
(4) provide the procedures, acceptance criteria and data sets [redacted] (b) (4)
(5) provide the procedures for bioburden determination, sterility testing, and bacteriostasis-fungistasis testing carried out [redacted] (b) (4)
(6) modify the endotoxin limit value so that it is based on a per drug rod [redacted] (b) (4)
(7) provide a description of the FA endotoxin testing procedure.

Failure to address the product quality microbiology deficiencies could result in an increased risk of product contamination.

7. Clinical/Statistical - Efficacy

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness $\geq$ 250 microns.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

Originally, the primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a $\geq$ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline; the current Complete Response modified the endpoint to be evaluated at Month 36, instead of Month 24, compared to baseline.

Primary Efficacy at 36 Months

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

Time Point	FAME Study A			FAME Study B		
	Treatment Group			Treatment Group		
	Sham	0.2 µg/day FA	0.5 µg/day FA	Sham	0.2 µg/day FA	0.5 µg/day FA
	N=95	N=190	N=196	N=90	N=186	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 (%)						
Difference[1]						
P-value[2]						

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 stratified by baseline VA.

Reviewer's comments:

Fame A and B studies do not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05).

Primary Efficacy at 36 Months in a Post-Hoc Subgroup Analysis

The applicant subsequently performed multiple analyses and determined that the following subgroup (b) (4) at Month 36:

(b) (4)

(b) (4)

(b) (4)

The analyses for this subgroup follows:

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, Full Analysis Population = ITT with LOCF)

(b) (4)

Reviewer's comments:

(b) (4)

Efficacy Summary Statement

Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05) for the applicant's original primary endpoint. The newly proposed primary endpoint was not adequately defined. Efficacy of this drug product has not been satisfactorily demonstrated for the original or the revised indications.

The applicant's proposed new subgroup, (b) (4) has multiple issues and concerns:

1. The a priori primary efficacy endpoint for either dose (0.2 µg/day or 0.5 µg/day) of the FA intravitreal insert was for it to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24, or Month 36, compared to baseline.

Reviewer's comments:

Fame A and B studies did not demonstrate statistically significant results for the original primary endpoint at either dose at 36 months (p values all > 0.05).

2. Subsequently to failing the primary endpoint, the sponsor proposed the new primary endpoint:

Number (%) of Subjects with a ≥ 15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4)

Reviewer's comments:

The analysis of the proposed subgroup lacks a statistical adjustment for multiplicity.

This newly proposed endpoint was not a pre-specified primary or secondary endpoint or listed as an exploratory variable. Even for planned secondary / exploratory variables no statistical adjustment was taken, as noted in the applicant's complete response submission of May 12, 2011:

(b) (4)

[The sponsor did make the following adjustments:

(b) (4)

(b) (4)

3. The endpoint was changed to the following criteria: subjects with "duration of DME (b) (4) "

Reviewer's comments:

The duration of DME was defined by the applicant as follows:

(b) (4)

Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time. Given DME can wax and wane over time the proposed subgroup "Duration of DME (b) (4) " is not defined well nor is it documented that the subjects had DME (b) (4)

The Definition of duration of DME was not adequately assessed as a study inclusion criterion given DME can wax and wane over time.

4. Fame A and B studies were not performed with the final drug configuration ((b) (4) Inserter).

In addition to the eight eyes treated in the FAVOR study, the applicant has submitted results from a questionnaire completed by 31 physicians from a wet lab demonstration and has also submitted a protocol to enroll 100 eyes in an open label extension study with subjects from Fame A and B studies. There is no clinical data provided from this new protocol in this May 12, 2011, submission.

Reviewer's comments:

Prior to approval of a drug, it is recommended that at least one clinical study include treatment of patients with the proposed final market formulation. Neither Fame A or Fame B were performed with the final drug/dispenser configuration ((b) (4) Inserter). Per the sponsor's complete reponse of May 12, 2011, as of December 31, 2010, there have been eight eyes treated with the final drug/dispenser configuration in another of the sponsor's studies – the retinal vein occlusion study (FAVOR).

It is recommended that at least a minimum of 100 eyes be treated with the final drug/dispenser formulation,

5. The applicant has proposed the following revised indicaton [redacted] (b) (4)

[redacted] (b) (4)

Reviewer's comments:

Because [redacted] (b) (4) *the drug can not be labelled as suggested by the applicant.*

6. Clinical results when comparing similar groups for Primary Efficacy at 36 Months:

i. Lens Status: Phakic at Baseline and Pseudophakic at Month 36
ii. Lens Status: Phakic at Baseline and Month 36
iii. Lens Status: Pseudophakic at Baseline and Month 36
iv. An integrated analysis of FAME A and B in a subgroup of subjects with no confounding variables

Primary Efficacy at 36 Months when comparing similar subgroups

i. Lens Status: Phakic at Baseline and Pseudophakic at Month 36

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye by Duration of DME [redacted] (b) (4) **at Month 36 by Treatment Group (Fame A and Fame B, with LOCF)**

[redacted] (b) (4)

ii. Lens Status: Phakic at Baseline and Month 36

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) at Month 36 by Treatment Group (Fame A and Fame B, with LOCF)

(b) (4)

iii. Lens Status: Pseudophakic at Baseline and Month 36

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) at Month 36 by Treatment Group (Fame A and Fame B, with LOCF)

(b) (4)

CI = confidence interval

Reviewer's Comments:

When comparing similar subgroups for those with DME (b) (4) duration: Tables 6. i. (Lens Status: Phakic at Baseline and Pseudophakic at Month 36); 6. ii. (Lens Status: Phakic at Baseline and Month 36); and 6. iii.(Lens Status: Pseudophakic at Baseline and Month 36) , none of these subgroups demonstrated a statistically significant difference for the clinically meaningful endpoint of the gain of 15 or more letters at 36 months although it is recognized that the subsets have relatively few patients.

iv. Efficacy in Pseudophakes Treated Only with Iluvien for the Subjects with Duration of DME (b) (4)

To examine the duration of therapeutic effect of a single dose of FA insert without the confounding effects of cataracts, additional laser treatments and disallowed therapies, the applicant performed the additional subgroup analysis for the percentage of subjects with ≥15 letter improvement from baseline in the subgroup of subjects who were pseudophakic at baseline and received 1 study treatment and no laser or disallowed therapies during the study.

Percent of Pseudophakic Subjects with ≥15 Letter Improvement with One Treatment, No Laser or Disallowed Therapies (Integrated FAME Studies, Observed Cases)

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
Month 18	(b) (4)					
Difference[1]						
P–value[2]						
Month 24	8	1 (12.5)	41	15 (36.6)	44	17 (38.6)
Difference[1]			-24.1		-26.1	
P–value[2]			0.208		0.154	
Month 30	(b) (4)					
Difference[1]						
P–value[2]						
Month 36						
Difference[1]						
P–value[2]						

(b) (4)

.

Reviewer's comments:

The applicant acknowledged the numerous confounding variables within the data set and did the above combined analyses of the FAME A and B studies of the pseudophakic subjects without the confounding effects of cataracts, additional laser treatments and disallowed therapies, etc.

When controlling for the confounding effects of cataracts, additional laser treatments and disallowed therapies the integrated analysis of the Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (nor at any of the time points listed at 18 months or more), (p values all > 0.05).

Again, a statistically significant difference for the clinically meaningful endpoint of the gain of 15 or more letters at 36 months was not demonstrated in the additional subgroup of "Pseudophakic subjects with One Treatment and NO Laser or Disallowed Therapies."

8. Safety

The 36 Month results from the two Fame studies (Fame A and Fame B) form the basis for the safety evaluation. The 2 Fame studies were performed under one protocol and enrolled subjects during the same time period. The only significant difference between the studies was geographical location of the study sites. Fame A was conducted at 49 sites in 7 countries (US, Canada, 4 countries in the European Union [EU], and India). Fame B was conducted at 52 sites in 5 countries (US, India, and 3 countries in the EU). When the 2 studies enrolled subjects in the same countries, Fame A enrolled subjects in the northern portions of the countries involved, and Fame B enrolled subjects in the southern portions of the countries. The demographics of the 2 study populations were essentially the same.

Exposure in Study Treatments:
36 Month Integrated Fame A and B Studies (Total n = 953)

Study Treatments	Sham (N=185)	0.2 µg/day FA (N=375)	0.5 µg/day FA (N=393)
Number of Treatments Completed			
Number of Treatments	252	488	534
Number of Subjects Receiving at Least 1 Treatment	185	375	393
Mean (SD)	1.4 (0.7)	1.3 (0.6)	1.4 (0.6)
Median	1.0	1.0	1.0
Minimum, Maximum	(1.0, 6.0)	(1.0, 4.0)	(1.0, 4.0)
Number of Treatments Completed by Frequency, n (%)			
1 Treatment	132 (71.4)	279 (74.4)	278 (70.7)
2 Treatments	4 (23.8)	81 (21.6)	91 (23.2)
3 Treatments	6 (3.3)	13 (3.5)	22 (5.6)

4 Treatments	2 (1.1)	2 (0.5)	2 (0.5)
> 4 Treatments	1 (0.5)	0	0

A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the Fame studies. The total number of treatments administered during the studies was 252, 488, and 534 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for the 0.2 µg/day group and 1.4 for the sham and 0.5 µg/day groups.

Dropouts and/or Discontinuations
36 Month Integrated Studies (Fame A and B)

Disposition	**Sham**	**0.2 µg/day FA**	**0.5 µg/day FA**
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated[1]	185	375	393
Total completed (n, %)	126 (68.1)	272 (72.9)	279 (70.6)
Total discontinued (n,%):	59 (31.9)	102 (27.1)	116 (29.4)
Adverse events	5 (2.7)	4 (1.1)	15 (3.8)
Unsatisfactory therapeutic effect	3 (1.6)	0	1 (0.3)
Protocol violation	2 (1.1)	2 (0.5)	5 (1.3)
Subject withdrew consent	14 (7.6)	31 (8.2)	27 (6.8)
Lost to follow-up	24 (13.0)	37 (9.8)	37 (9.4)
Death	11 (5.9)	27 (7.2)	31 (7.8)
Unknown	0	1 (0.3)	0

1. This represents the set of subjects included in the safety population.

Overall, 277 (29%) subjects discontinued the trial, primarily due to loss to follow-up (10%). withdrawn consent (8%), or death (7%).Of the 277 subjects who discontinued the study, 43 (16%) subjects discontinued during the first 12 months of the study, and 97 (35%) subjects discontinued during the second year of the study. Overall, discontinuations rates were similar throughout the three treatment groups.

Ocular Adverse Events Leading to Discontinuation
Integrated Studies (Fame A and B)

Treatment Group	**Subject No.**	**Adverse Event**
Sham	102404	Vision loss (OU)
0.2 µg/day FA	100403	Chemical eye injury
0.2 µg/day FA	101634	Endophthalmitis
0.2 µg/day FA	105645	Eye infection fungal
0.5 µg/day FA	100313	Intraocular pressure increased
0.5 µg/day FA	10221	Trabeculectomy
0.5 µg/day FA	104921	Cataract
0.5 µg/day FA	109406	Glaucoma, Trabeculectomy, Iris incarceration
0.5 µg/day FA	109502	Retinal detachment

In the Integrated Analysis at 36 Months by dose in the Fame A and B studies, 621 (77%) of the 953 subjects who received drug therapy were phakic at baseline and at risk for primary cataract formation.

Cataract-Related Events in Phakic Subjects
36 Month Integrated Studies (Fame A and B)
Study eye only

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)	61 (50.4)	192 (81.7)	235 (88.7)
Cataract operation	33 (27.3)	188 (80.0)	231(87.2)

The percentage of phakic subjects who developed a cataract or had a cataract operation was lower in the sham group compared to the 0.2 µg/day FA and 0.5 µg/day FA groups. Fifty percent of the sham group compared with 82% of the 0.2 µg/day FA and 89% of the 0.5 µg/day FA had a cataract with 27% of the sham group compared to 80% of the 0.2 µg/day and 87% of the FA 0.2 µg/day FA groups requiring a cataract operation during the 36 month study period.

The risks of cataract formation and cataract operation are significant by 36 months after the drug treatment and this risk appears to be dose and time dependent.

Common (≥ 5%) Ocular Adverse Events by Treatment Group: 36 Month Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Cataract	53 (28.6)	171 (45.6)	213 (54.2)
Cataract operation	33 (17.8)	188 (50.1)	132 (58.8)
Cataract subcapsular	8 (4.3)	28 (7.5)	24 (6.1)
Conjunctival haemorrhage	20 (10.8)	43 (11.5)	50 (12.7)
Dry eye	11 (5.9)	23 (6.1)	22 (5.6)
Eye irritation	9 (4.9)	27 (7.2)	22 (5.6)
Eye pain	22 (11.9)	51 (13.6)	65 (16.5)
Glaucoma	4 (2.2)	19 (5.1)	18 (4.6)
IOP increased	21 (11.4)	132 (35.2)	170 (43.3)
Maculopathy	16 (8.6)	23 (6.1)	34 (8.7)
Myodepsia	13 (7.0)	67 (17.9)	68 (17.3)
Posterior capsule opacification	6 (3.2)	32 (8.5)	25 (6.4)
Retinal hemorrhage	11 (5.9)	9 (2.4)	17 (4.3)
Trabeculectomy	0	10 (2.7)	22 (5.6)
Vision blurred	13 (7.0)	28 (7.5)	20 (5.1)
Visual acuity reduced	17 (9.2)	39 (10.4)	35 (8.9)
Visual impairment	7 (3.8)	13 (3.5)	31 (7.9)
Vitrectomy	16 (8.6)	19 (5.1)	23 (5.9)
Vitreous detachment	12 (6.5)	26 (6.9)	20 (5.1)
Vitreous Hemorrhage	28 (15.1)	41 (10.9)	48 (12.2)

Overall, the most common ocular adverse events were cataract operation (47%), cataract (46%), increased intraocular pressure (34%) and myodesopsia (16%). Several events had a lower incidence in the sham group with the most notable observed differences being for cataract operation (18%, sham; 50%, 0.2 µg/day FA; 59%, 0.5 µg/day FA); cataract (29%, sham; 46%, 0.2 µg/day FA; 54%, 0.5 µg/day FA); and increased intraocular pressure (11%, sham; 35%, 0.2 µg/day FA; 43%, 0.5 µg/day FA). Similar trends were observed for myodesopsia (7%, sham; 18%, 0.2 µg/day FA; 17%, 0.5 µg/day FA), posterior capsular opacification (3%, sham; 9%, 0.2 µg/day FA; 6%, 0.5 µg/day FA,) and glaucoma (2%, sham; 5%, 0.2 µg/day FA; 5%, 0.5 µg/day FA). The only cases of trabeculectomy occurred in the active treatment groups (3%, 0.2 µg/day FA; 6%, 0.5 µg/day FA).

POSTMARKETING EXPERIENCE
Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not marketed in any country.

Safety Summary Statement

At 36 months the risk of cataract formation, cataract operation, and increased IOP are adverse events that continue to occur at significantly high rates in the drug group when compared to the Sham group.

Cataract formation (any type in Phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes.

Increased IOP occurs in 11% of the Sham group versus 35% in the 0.2 µg/day FA. The risk of increased IOP is three times the rate in the 0.2 µg/day FA drug group.

Safety Summary Statement

At 36 Months the risk of cataract formation, cataract operation, and increased IOP are adverse events that occur at significantly high rates in the drug group when compared to the Sham group.

9. Advisory Committee Meeting

No Advisory Committee Meeting has been scheduled. There are no outstanding clinical issues which are believed to benefit from an advisory committee discussion at this time.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

BIOSTATISTICS

Per the statistical review: The main review issue with the results of this submission is the same as with the original NDA, that is weighing the benefit of Iluvien treatment on improving Best Corrected Visual Acuity (BCVA) against its risks of causing elevated Intra Ocular Pressure (IOP) and cataract formation and surgery.

We defer to the clinical review to weigh the benefit against the risk of this drug in the general population or in the subgroup of DME (b) (4) but the drug harms a significantly higher proportion of subjects compared to sham. The two main harms considered here are IOP elevation or cataract surgery. (b) (4) However, this subgroup was determined post-hoc so any results should be considered with caution. The statistical review cannot weigh the benefit of BCVA gain versus the risk of cataract surgery or elevated IOP and we defer for the clinical review team to weigh these outcomes against each other.

12. Labeling

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment of diabetic macular edema.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment diabetic macular edema.

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

1) Fame A and B, the confirmatory clinical trials, failed their original primary endpoint (p values > 0.05).
2) When evaluating for the newly proposed primary endpoint there was a lack of statistical adjustment for multiplicity.
3) The newly proposed primary endpoint's definition of duration DME was not adequately assessed as a study inclusion criterion.
4) There were not results from patients treated with the proposed final market formulation (drug/dispenser) in a minimum of 100 treated eyes.
5) The drug can not be labeled as proposed by the applicant.
6) When evaluating for the newly proposed primary endpoint analysis based on similar pre/post op groups no statistically significant results (based on a p value of 0.5) at 36 Months were demonstrated.

RISK BENEFIT ASSESSMENT:

1) There is not substantial evidence to demonstrate that the benefits of the drug outweigh its risks for either the low dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.25 μg/day) or the high dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.5 μg/day). The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema. This recommendation is based on the results from the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) studies submitted with 36 month data for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 μg/day.

   Fame A and B studies did not demonstrate statistically significant results at either dose at 36 months (p values all > 0.05) for the sponsor's original primary endpoint and the newly proposed primary endpoint was not adequately defined as a group.

   At 36 months follow-up cataract formation occurs in 50% of the Sham group study eyes versus 82% in the 0.2 μg/day FA study eyes. Cataract operation occurs in 27% of the Sham group study eyes versus 80% in the 0.2 μg/day FA study eyes and Increased IOP occurs in 11% of the Sham group study eyes versus 35% in the 0.2 μg/day FA study eyes. The risk of increased IOP is three times the rate in the 0.2 μg/day FA drug group.

2) On March 2, 2011 IND 72,056 SDN 110 the following protocol was submitted titled, "An Open Label, Multi-center Extension Study of the Safety and Utility of the New Inserter of ILUVIEN (Fluocinolone Acetonide Intravitreal Insert) 0.19 mg and the Safety of ILUVIEN in Subjects with Diabetic Macular Edema."

   The trial as proposed will not satisfy the Agency's deficiency from the 12/22/2010 Complete Response letter for NDA 201923:

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.

It is expected that the clinical trial be 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 clinical trials supporting safety and efficacy. It is expected that at least 100 eyes will have been treated with the drug in its proposed formulation with the New Inserter prior to NDA approval.

The Inclusion Criteria for this trial as proposed are not acceptable. Criterion #2 (In the judgment of the Investigator, the subject will benefit from retreatment with ILUVIEN) is too vague. The protocol should specify exactly what inclusion parameters identify subjects as candidates for retreatment.

Conclusion:

Based on the risk/benefit of this drug, NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg, is not recommended for approval for the treatment of diabetic macular edema.

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/s/

MARTIN P NEVITT
09/13/2011

WILLIAM M BOYD
09/13/2011

Cross-Discipline Team Leader Review

Date	December 14, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	June 30, 2010
PDUFA Goal Date	December 30, 2010
Type of Application	505(b)(1)
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Recommended:	Not Recommended for Approval

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant.

There is no previous marketing experience with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg as this product is not commercially available.

There are no approved drug therapies for the treatment of diabetic macular edema (DME).

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) and has been developed for the treatment of Diabetic Macular Edema (DME). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.
The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

Use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

2. Background

Diabetic macular edema (DME), a serious, chronic, debilitating disease, is the primary cause of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

A conference call on 01/10/07 documented FDA's agreement to accept the NDA submission with efficacy data at 24 month's follow-up with additional safety and efficacy data provided at 36 months. In order to accept efficacy data at 24 months a two time point comparison with "wins" on both comparisons might be considered for a demonstration of efficacy. The first comparison was recommended to be between the original baseline and a time point that is at 24 months or longer. It was recommended that a clinically and statistically superior difference be demonstrated between the selected timepoint and the original baseline. The second comparison was recommended to be between the 18 month time point and the time point at 24 months or longer; this comparison was recommended to be numerically noninferior using the 18 month time point as a baseline.

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008. The Division expressed concern that the benefits might not outweigh the risks if Illuvien demonstrated a safety profile which was similar to other corticosteroids. The applicant stated that they did not expect to see the development of cataracts or elevated intraocular pressure due to the low release rate.

A Pre-NDA meeting was held for IND 72,056 on March 4, 2010.

3. CMC

INSERTER:
During the development phase of this drug produc [redacted] (b) (4)

(b) (4)

(b) (4)

This was the packaging configuration used for all the preclinical and clinical studies.

During the clinical studies, feedback was solicited from the investigators on the inserter device. Feedback was also obtained from retinal specialists who were not part of the clinical study.

(b) (4) designed an inserter incorporating the feedback received. Modifications included:

(b) (4)

Figure 4: Iluvien Inserter Device

Study C-01-08-006, entitled "A randomized, double-masked, pilot study of the safety and efficacy of 0.5 µg/day and 0.2 µg/day Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg in subjects with macular edema secondary to retinal vein occlusion", is an ongoing study (b) (4) The study utilizes the new inserter and collects information from the treating physician on the performance of the inserter. The trial is ongoing, and no study report was submitted with the application. The study is not presented in Module 5 of the NDA submission; it was not included in the 120-day Safety Update.

There is currently no clinical data to support the use of the new (b) (4) inserter for the Iluvien drug product. The modifications to the inserter are so significant that clinical data is necessary to bridge the two different inserter configurations.

From the CMC Review dated 12/1/10:

DRUG SUBSTANCE:
Fluocinolone acetonide (FA), which is the only active pharmaceutical ingredient used in Iluvien is a member of a class of fluorinated synthetic corticosteroids that include dexamethasone, triamcinolone, and fluocinolone. It has been used extensively as an anti-inflammatory in various products including dermal ointments and creams, shampoos, ear drops, eye drops, nasal sprays and suppositories in the United States, Canada and Europe. It is a monographed drug substance listed in both the USP and Ph. Eur.

In the development program for Iluvien, two versions were designed to deliver fluocinolone acetonide at different rates - the high dose and the low dose with targeted initial release rates of 0.5 µg/day and 0.25 µg/day, respectively. The two versions are identical in composition (b) (4)

From the applicant's submission dated 11/11/10:

Table 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
Identification by HPLC	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4)	CTM-200500
Related Substances		
(b) (4)	Not more than (b) (4)	CTM-200500
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Test	Acceptance Criteria	Analytical Method
(b) (4)	Not more than (b) (4)	
	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	Not more than (b) (4)	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4)	Not less than (b) (4)	(b) (4) MGR051FLU011
Particle	Not less than	
Particle	Not less than	
Polymorphism		
(b) (4)	Not less than (b) (4)	Contract Laboratory[c] High Resolution X-Ray Powder Diffraction and/or Differential Scanning Calorimety
Microbial Limits		
Total Aerobic Count	Not more than (b) (4)	Current USP/NF <61> MTM-200155
Yeast/Mold Count	Not more than	
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
(b) (4)		

DRUG PRODUCT:

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a nonbiodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to conveniently insert it into the ocular vitreous chamber.

The inserter is placed into a tray, sealed with a (b) (4) lid and placed into a carton (b) (4) The inserter has a 25 gauge extra-thin wall needle attached, which allows the physician to place the insert through the sclera into the vitreous.

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)

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

From the applicant's submission dated 11/11/10:

Table 1: Quality Control Specifications

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Specified Identified and Unidentified Individual Impurity		
Release	Not more than (b) (4)	CTM-200501
Stability	Not more than	
Unspecified Individual Impurity		
Release	Not more than (b) (4)	
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4)	CTM-200502
Endotoxin		MTM-200033
Sterility		
Release	(b) (4)	(b) (4)
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

As of the date of this review, Compliance recommends withholding approval of the application based on facility inspections. The (b) (4) facility and (b) (4) are not in compliance with cGMPs.

The CMC reviewer does not recommend approval and has cited deficiencies regarding a lack of information for the facilities conducting the polymorph testing (b) (4)

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology Toxicology Review finalized 11/17/10:

Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. Orally administered PVA is relatively harmless, with LD_{50} in the range of 15-20 g/kg. The content of PVA in a 0.19 mg Iluvien is [redacted] (b) (4) The sponsor also conducted several biocompatibility studies with polyimide tubing and extracts of stainless steel injection needles. The results were negative.

The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber. Continuous exposures of ocular tissues for both toxicity studies were achieved via one or two injections of the insert into the eye. There appeared to be no definable toxicity associated with the administration of 0.2 µg/day FA. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations.

The panel of genotoxicity tests performed by the Sponsor included the bacterial mutation test, mammalian cell mutation test and a mouse micronucleus test. Fluocinolone acetonide did not show any evidence of genotoxic activity in these tests when tested in accordance with regulatory guidelines.

No carcinogenicity studies were conducted for Iluvien. Reproductive and developmental toxicity studies with Iluvien were not conducted. During a communication from the FDA to sponsor on 02/03/10, FDA requested the human PK data be submitted for the evaluation of carcinogenicity waiver. Since human systemic exposure to FA after Iluvien is below LLOQ, the waiver of carcinogenicity study was granted.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 11/18/2010:

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 (manufactured by [redacted] (b) (4)) contains 0.19 mg FA versus the clinical development product (manufactured at pSivida, Inc.) that averaged [redacted] (b) (4) mg. [redacted] (b) (4)

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

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. However, the assessment on FA exposure in aqueous humor and any conclusions thus derived will not be used to support any regulatory decisions because the analytical method was not validated.

From the ONDQA (Biopharmaceutics) Review finalized 12/1/10:

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 a full development and validation report for the *in-vitro* release methodology.

6. Sterility Assurance

Per the original Product Quality Microbiology review completed on 12/8/10:

The applicant should:

(1) include (b) (4) and impose (b) (4) bioburden alert and action limits;
(2) describe the bioburden and endotoxin testing procedures used (b) (4)
(3) describe (b) (4) the procedure (b) (4)
(4) provide the procedures, acceptance criteria and data sets (b) (4)
(5) provide the procedures for bioburden determination, sterility testing, and bacteriostasis-fungistasis testing carried out (b) (4)
(6) modify the endotoxin limit value so that it is based on a per drug rod (b) (4)
(7) provide a description of the FA endotoxin testing procedure.

Failure to address the product quality microbiology deficiencies could result in an increased risk of product contamination.

7. Clinical/Statistical - Efficacy

From the Medical Officer Review finalized 12/20/2010:

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness ≥ 250 microns.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline.

In studies FAME A and B when comparing ≥ 15-letter Increase from Baseline in BCVA at 18 and 24 months for both doses of FA the trend for BCVA demonstrates improvement of visual acuity with time. Given this improvement in visual acuity between these two time points, data at 24 months is acceptable for the Primary Efficacy Analysis [see Medical Officer's Review, Section 6.1.4, regarding the two point comparison at 18 and 24 months].

Primary Efficacy at 24 Months

FAME A
Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 24	95	14 (14.7)	190	51 (26.8)	(b) (4)	
Difference (95% CI)[1]			-12.1 (-21.6, -2.6)			
P-value[2]			0.029			
Per Protocol Population (observed data only)						
Month 24	46	7 (15.2)	112	33 (29.5)	(b) (4)	
Difference (95% CI)[1]			-14.2 (-27.6, -0.9)			
P-value[2]			0.112			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

For the All Treated with LOCF, the difference between the 0.2 µg/day FA group and the sham group was −12.1% (95% CI: −21.6%, −2.6%; p=0.029), and the difference between the 0.5 µg/day FA group and the sham group was −11.4% (95% CI: −15.2%, −1.9%; p=0.032). Based on the PP observed data only, the 0.2 µg/day FA group (p=0.112) was not statistically significantly different from the sham group.

Corrections for the multiple interim looks (9) have not been made in the values reported above.

FAME B
Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 24	90	16 (17.8)	185	57 (30.8)	(b) (4)	
Difference (95% CI)[1]			-13.0 (-23.4, -2.7)			
P-value[2]			0.028			
Per Protocol Population (observed data only)						
Month 24	40	6 (15.0)	125	45 (36.0)	(b) (4)	
Difference (95% CI)[1]			-21.0 (-34.9, -7.1)			
P-value[2]			0.023			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

For the All Treated with LOCF and PP observed data only at Month 24 marginal statistical significance was demonstrated for both treatment groups.

Corrections for the multiple interim looks (9) have not been made in the values reported above.

Efficacy Summary Statement

The results from the PP observed data only are likely confounded by cataract formation during the 24 month period which resulted in the PP observed data only population failing the primary endpoint, p = 0.112, in FAME A.

FAME A is considered a failed trial due to the PP observed data only having a p value > 0.0491 at 24 months (p = 0.112). Additionally, 18 month data for Fame A failed the test of a p value of 0.05 or better. For the All Treated with LOCF and PP observed data only groups the p values were 0.466 and 0.941, respectively [see Medical Officer's Review, Section 6.1.4, regarding the two point comparison at 18 and 24 months]. The overall results at 18 and 24 months do not provide additional support for Fame A being a successful clinical trial.

FAME B results for the PP observed data only are considered marginal due to 0.5 µg dose demonstrating a p value > 0.0491.

At least two replicated trials are recommended to demonstrate robustness of the results for this indication. The applicant did not demonstrate success in two replicated trials.

8. Safety

From the Medical Officer Review finalized 12/20/2010:

The results from two Fame studies (Fame A and FAME B) form the basis for the safety evaluation. The 2 FAME studies were performed under one protocol and enrolled subjects during the same time period. The only significant difference between the studies was geographical location of the study sites. FAME A was conducted at 49 sites in 7 countries (US, Canada, 4 countries in the European Union [EU], and India). FAME B was conducted at 52 sites in 5 countries (US, India, and 3 countries in the EU). When the 2 studies enrolled subjects in the same countries, FAME A enrolled subjects in the northern portions of the countries involved, and FAME B enrolled subjects in the southern portions of the countries. The demographics of the 2 study populations were essentially the same.

Exposure in Study Treatments:
Integrated Fame A and B Studies (Total n = 953)

Study Treatments	**Sham (N=185)**	**0.2 µg/day FA (N=375)**	**0.5 µg/day FA (N=393)**
Number of Treatments Completed			
Number of Treatments	240	472	505
Number of Subjects Receiving at Least 1 Treatment	185	375	393
Mean (SD)	1.3 (0.6)	1.3 (0.5)	1.3 (0.5)
Median	1.0	1.0	1.0
Minimum, Maximum	(1.0, 4.0)	(1.0, 4.0)	(1.0, 4.0)
Number of Treatments Completed by Frequency, n (%)			
1 Treatment	141 (76.2)	287 (76.5)	293 (74.6)
2 Treatment	36 (19.5)	80 (21.3)	89 (22.6)
3 Treatment	5 (2.7)	7 (1.9)	10 (2.5)
4 Treatment	3 (1.6)	1 (0.3)	1 (0.3)
Time on Study	**N (%)**	**N (%)**	**N (%)**
Month 6	183 (98.6)	367 (97.9)	391 (98.7)
Month 9	178 (96.2)	365 (97.3)	383 (97.5)
Month 12	178 (96.2)	354 (94.4)	378 (96.2)
Month 18	165 (89.2)	333 (88.8)	358 (91.1)
Month 24	150 (81.1)	310 (82.7)	318 (80.9)
Month 30	66 (35.7)	130 (34.7)	148 (37.7)

A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the FAME studies. The total number of treatments administered during the studies was 240, 472, and 393 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for all 3 treatment groups.

Dropouts and/or Discontinuations
Integrated Studies (Fame A and B)

Disposition	Sham	0.2 µg/day FA	0.5 µg/day FA
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated	185	375	393
Total discontinued (n,%):	42 (22.7)	75 (19.9)	75 (19.0)
Adverse events	3 (1.6)	4 (1.1)	11 (2.8)
Unsatisfactory therapeutic effect	1 (0.5)	0	1 (0.3)
Protocol violation	0	0	3 (0.8)
Subject withdrew consent	14 (7.6)	25 (6.6)	21 (5.3)
Lost to follow-up	17 (9.2)	21 (5.6)	16 (4.1)
Death	8 (4.3)	25 (6.7)	23 (5.9)
Unknown	0	1 (0.3)	0

Overall, 192 (20%) subjects discontinued the trial, primarily due to withdrawn consent (6%), death (6%), or loss to follow-up (6%). Of the 192 subjects who discontinued the study, 43 (22%) subjects discontinued during the first 12 months of the study, and 132 (69%) subjects discontinued during the second year of the study. Overall, discontinuations rates were similar throughout the three treatment groups.

Ocular Adverse Events Leading to Discontinuation
Integrated Studies (Fame A and B)

Treatment Group	Subject No.	Adverse Event
Sham	102404	Vision loss (OU)
0.2 µg/day FA	100403	Chemical eye injury
0.2 µg/day FA	101634	Endophthalmitis
0.2 µg/day FA	105645	Eye infection fungal
0.5 µg/day FA	100313	Intraocular pressure increased
0.5 µg/day FA	10221	Trabeculectomy
0.5 µg/day FA	104921	Cataract
0.5 µg/day FA	109406	Glaucoma, Trabeculectomy, Iris incarceration
0.5 µg/day FA	109502	Retinal detachment

In the Integrated Analysis by dose in the Fame A and B studies, 621 (77%) of the 953 subjects who received drug therapy were phakic at baseline and at risk for primary cataract formation.

Cataract-Related Events in Phakic Subjects
Integrated Studies (Fame A and B)
Study eye only

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)	56 (46.3)	188 (80.0)	232 (87.5)
Cataract operation	28 (23.1)	176 (74.9)	224(84.5)

The percentage of phakic subjects who developed a cataract and a cataract operation was lower in the sham group compared to the 0.2 µg/day FA and 0.5 µg/day FA groups. Forty-six percent of the sham group compared with 80% of the 0.2 µg/day FA and 88% of the 0.5 µg/day FA had a cataract with 28% of the sham group compared to 75% of the 0.2 µg/day and 85% of the FA 0.2 µg/day FA groups requiring a cataract operation during the 24 month study period.

Using the subjects Non-study eye as a comparison to the Study-eye (the drug treatment is an intravitreal implant into the study-eye with no systemic absorption) further demonstrates the significant risk of cataract formation and cataract operation in the study eye resulting from exposure to the drug.

Cataract-Related Events in Phakic Subjects
Integrated Studies (Fame A and B)
Study eye compared to Non-study eye

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)			
Study eye	56 (46.3)	188 (80.0)	232 (87.5)
Non-study eye	43 (35.5)	94 (40.0)	108 (40.8)
Cataract operation			
Study eye	28 (23.1)	176 (74.9)	224(84.5)
Non-study eye	26 (21.5)	64 (27.2)	68 (25.7)

For the 0.2 µg/day FA and 0.5 µg/day FA groups when comparing the Non-study eye to the Study eye, cataract formation and cataract operation continue to demonstrate the increased risk of cataract formation and cataract operation resulting from the localized (intravitreal) drug treatment.

The risks of cataract formation and cataract operation are significant by 24 months after the drug treatment. This risks appears to be dose and time dependent.

Common (≥ 1%) Ocular Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Abnormal sensation in eye	2 (1.1)	5 (1.3)	5 (1.3)
Anterior chamber cell	1 (0.5)	6 (1.6)	3 (0.8)
Blepharitis	3 (1.6)	7 (1.9)	7 (1.8)
Cataract	58 (31.4)	189 (50.4)	222 (56.5)
Cataract nuclear	6 (3.2)	9 (2.4)	13 (3.3)
Cataract operation	36 (19.5)	193 (51.5)	236 (60.1)
Cataract subcapsular	11 (5.9)	33 (8.8)	26 (6.6)
Conjunctival haemorrhage	22 (11.9)	48 (12.8)	48 (12.2)
Conjunctival hyperemia	6 (3.2)	5 (1.3)	5 (1.3)
Conjunctivitis	5 (2.7)	12 (3.2)	9 (2.3)
Corneal abrasion	5 (2.7)	4 (1.1)	10 (2.5)
Corneal epithelial defect	0	4 (1.1)	6 (1.5)
Corneal edema	4 (2.2)	11 (2.9)	15 (3.8)
Diabetic retinal edema	1 (0.5)	4 (1.1)	6 (1.5)
Diabetic retinopathy	4 (2.2)	6 (1.6)	14 (3.6)
Diplopia	2 (1.1)	6 (1.6)	2 (0.5)
Dry eye	10 (5.4)	23 (6.1)	17 (4.3)
Eye discharge	1 (0.5)	5 (1.3)	5 (1.3)
Eye irritation	9 (4.9)	26 (6.9)	21 (5.3)
Eye pain	25 (13.5)	50 (13.3)	65 (16.5)
Eye pruitus	2 (1 1)	10 (2.7)	12 (3.1)
Eyelid edema	2 (1.1)	4 (1.1)	4 (1.0)
Foreign body sensation	4 (2.2)	14 (3.7)	13 (3.3)
Glaucoma or open angle glaucoma[1]	5 (2.7)	21 (5.6)	24 (6.1)
Glaucoma surgery	2 (1.1)	6 (1.6)	8 (2.0)
IOP increased	24 (13.0)	132 (35.2)	173 (44.0)
Iris neovascularization	6 (3.2)	6 (1.6)	6 (1.5)
Keratoconjunctivitis sicca	1 (0.5)	6 (1.6)	4 (1.0)
Lacrimation increased	9 (4.9)	19 (5.1)	14 (3.6)
Macular edema	5 (2.7)	10 (2.7)	10 (2.5)
Maculopathy	19 (10.3)	27 (7.2)	43 (10.9)
Myodepsia	20 (10.8)	70 (18.7)	77 (19.6)
Myopia	0	6 (1.6)	5 (1.3)
Ocular hyperemia	3 (1.6)	10 (2.7)	17 (4.3)
Ocular hypertension	2 (1.1)	9 (2.4)	12 (3.1)
Optic atrophy	3 (1.6)	5 (1.3)	14 (3.6)
Photophobia	2 (1.1)	7 (1.9)	4 (1.0)
Photopsia	2 (1.1)	5 (1.3)	7 (1.8)
Posterior capsule opacification	8 (4.3)	28 (7.5)	27 (6.9)
Punctate keratitis	1 (0.5)	5 (1.3)	5 (1.3)
Retinal detachment	4 (2.2)	5 (1.3)	7 (1.8)
Retinal exudates	2 (1.1)	11 (2.9)	8 (2.0)
Retinal hemorrhage	11 (5.9)	13 (3.5)	16 (4.1)
Retinal neovascularization	11 (5.9)	16 (4.3)	15 (3.8)
Trabeculectomy	0	8 (2.1)	20 (5.1)
Trabeculoplasty	0	3 (0.8)	9 (2.3)
Vision blurred	13 (7.0)	35 (9.3)	26 (6.6)
Visual acuity reduced	20 (10.8)	45 (12.0)	40 (10.2)
Visual impairment	7 (3.8)	14 (3.7)	31 (7.9)
Vitrectomy	15 (8.1)	25 (6.7)	35 (8.9)
Vitreous detachment	10 (5.4)	28 (7.5)	25 (6.4)
Vitreous Hemorrhage	35 (18.9)	59 (15.7)	73 (18.6)
Vitreous opacities	1 (0.5)	4 (1.1)	5 (1.3)
Vitritis	3 (1.6)	3 (0.8)	4 (1.0)

1 Includes the total number of unique subjects who experienced glaucoma or open-glaucoma

Four of the most common ocular adverse events (i.e., cataract, cataract operation, increased intraocular pressure and myodesopsia) occurred more frequently in the active-treated groups compared with the sham group.

The incidence of adverse events was also higher in the 0.5 µg/day FA group than the 0.2 µg/day FA group, suggesting a dose response. The most notable differences were observed for cataract (31%, sham; 50%, 0.2 µg/day FA; 57%, 0.5 µg/day FA); cataract operation (20%, sham; 52%, 0.2 µg/day FA; 60%, 0.5 µg/day FA); increased intraocular pressure (13%, sham; 35%, 0.2 µg/day FA; 44%, 0.5 µg/day FA); and myodesopsia (11%, sham; 19%, 0.2 µg/day FA; 20%, 0.5 µg/day FA).

Common (≥ 5%) Systemic Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Anemia	6 (3.2)	26 (6.9)	34 (8.7)
Cardiac failure congestive	9 (4.9)	12 (3.2)	20 (5.1)
Constipation	3 (1.6)	12 (3.2)	21 (5.3)
Nausea	13 (7.0)	23 (6.1)	22 (5.6)
Vomiting	10 (5.4)	13 (3.5)	4 (1.0)
Nasopharyngitis	11 (5.9)	20 (5.3)	22 (5.6)
Pneumonia	3 (1.6)	19 (5.1)	14 (3.6)
Sinusitis	7 (3.8)	12 (3.2)	20 (5.1)
Hypercholesterolemia	11 (5.9)	17 (4.5)	19 (4.8)
Headache	10 (5.4)	26 (6.9)	20 (5.1)
Renal failure	9 (4.9)	23 (6.1)	25 (6.4)
Hypertension	25 (13.5)	35 (9.3)	38 (9.7)

POSTMARKETING EXPERIENCE
Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not marketed in any country.

Safety Summary Statement

The risk of cataract formation, cataract operation, and increased IOP are adverse events that occur at extraordinary high rates in the drug group when compared to the Sham group.

Cataract formation occurs in 46% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 23% of the Sham group study eyes versus 75% in the 0.2 µg/day FA study eyes. Increased IOP occurs in 13% of the Sham group study eyes versus 35% in the 0.2 µg/day FA study eyes. The risk of increased IOP is nearly three times the rate in the 0.2 µg/day FA drug group.

9. Advisory Committee Meeting

No Advisory Committee Meeting will be scheduled until the 36 month data is available for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. The DSI Clinical Inspection Summary was finalized on 12/1/10.

Two sites were selected for inspection, one domestic and one foreign, due to enrollment of large numbers of study subjects, high number of INDs and lack of previous inspectional history.

The preliminary classification of Clinical Investigator inspections of Drs. Blackburn (Kentucky) and Garg (India) are Voluntary Action Indicated (VAI). Although regulatory violations were noted at both of these sites, given the nature of the findings, DSI considered it unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

Dr. Blackburn (Study C-01-05-001B /Site 001/17) failed to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Dr. Garg (Study C-01-05-001A /Site 016/ 45) failed to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided.

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable.

DMEPA again reviewed the name Iluvien for the NDA application. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable.

DDMAC
The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle. .

BIOSTATISTICS
The Biostatistician considered both the FAME A and FAME B studies to be successful based on the Full Analysis = Intent-to-Treat with Last Observation Carried Forward dataset.

Table 1: Main Efficacy Results by Study and Treatment for the Full Analysis Population

Study	**FAME A**			**FAME B**			**Results**
Treatment arms	**sham N = 95**	**low dose N = 190**	**high dose N = 196**	**sham N=90**	**low dose N=186**	**high dose N=199**	**comparing low dose to sham**
Primary Endpoint							
Definition	**Proportion of subjects with a larger or equal to 15 letter increase from baseline in BCVA in the study eye at Month 24.**						
N (%)	14 (15)	51 (27)	51 (26)	16 (18)	57 (31)	62 (31)	Statistically significant effect in each study in favor of low dose.
Difference Trt-sham (95% CI)		21 (2.6, 21.6)	11.3 (1.9, 20.7)		12.9 (2.6, 23.2)	13.4 (3.2, 23.6)	
p-value[1]		0.029	0.034		0.030	0.027	

The Medical Officer utilized the All Randomized = All Treated with LOCF dataset. The M.O. did not consider FAME A to be a successful trial because of the lack of a statistically significant treatment effect observed in FAME A for the Per Protocol observed data only populations.

Per the Biostatistician, the drug induces serious risk of cataract surgery and elevated intra-ocular pressure. The incidence of cataract surgery during the study is significantly higher in the active dose arms compared to the sham arm. The incidence of surgery due to elevated intra-ocular pressure is also higher in the active dose arms compared to the sham arm.

12. Labeling

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment diabetic macular edema.

A formal labeling review is deferred until additional data is submitted to support the application for Iluvien.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is not recommended for approval for the treatment diabetic macular edema.

Clinical Issues:

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

1) The development of cataracts in eyes which were phakic at baseline creates difficulty in interpreting visual acuity during months 12 to 24. Visual acuity data from the post-operative period of study subjects 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, 36-month clinical trial data will need to be evaluated. Thirty-six month clinical trial data should be submitted to the application.

2) 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.

3) 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 C-01-08-006, should be submitted to the application.

4) 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.

5) Efficacy rates are low. [redacted] 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.

6) 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.

7) The product causes clinically significant decreases in visual acuity, which may or may not be related to the development of cataracts.

8) Primary effect is in the first 6 months. It is not clear that there is any additional benefit beyond the first six months.

9) Difference between groups with respect to mean visual acuity is minimal.

10) Number of patients "withdrawing consent" is relatively high.

Quality Microbiology Issues:

1) The currently proposed limit [redacted] 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. Modify the endotoxin limit value so that it is based on a per drug rod or per mg [redacted]

2) 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 and the proposed post-approval stability protocol are not acceptable without an adequate description of the endotoxin testing procedure and appropriate acceptance criteria. 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.

Chemistry/Manufacturing Issues:

1) There is insufficient information for the facilities [redacted] Provide information regarding the [redacted] facility if a site that is different from the drug substance manufacturer facility [redacted] of your drug substance.

2) There is insufficient information for the facilities conducting the polymorph testing. Provide a method description to be used for the testing of the polymorph content in the fluocinolone acetonide drug substance. Also, provide, once identified, the name, address and contact information for the facility which will be conducting the polymorph testing.

3) Manufacturing facilities for the drug product are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved. Please amend the application with facilities that are in compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.

RISK BENEFIT ASSESSMENT:
There is not substantial evidence to demonstrate that the benefits of the drug outweigh its risks for either the low dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.25 μg/day) or the high dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.5 μg/day). The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema. This recommendation is based on the results from the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) studies submitted with 24 month data for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 μg/day.

FAME A is considered a failed trial due to the PP observed data only having a p value > 0.05 at 24 months (p = 0.112). Additionally, 18 month data for Fame A failed the test of a p value of 0.05 or better. For the All Treated with LOCF and PP observed data only groups the p values were 0.466 and 0.941, respectively [see Medical Officer's Review, Section 6.1.4, regarding the two point comparison at 18 and 24 months]. The overall results at 18 and 24 months do not provide additional support for Fame A being a successful clinical trial. FAME B is considered marginally statistically significant.

Cataract formation occurs in 46% of the Sham group study eyes versus 80% in the 0.2 μg/day FA study eyes. Cataract operation occurs in 23% of the Sham group study eyes versus 75% in the 0.2 μg/day FA study eyes. Increased IOP occurs in 13% of the Sham group study eyes versus 35% in the 0.2 μg/day FA study eyes. The risk of increased IOP is nearly three times the rate in the 0.2 μg/day FA drug group.

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/s/

WILLIAM M BOYD
12/21/2010

WILEY A CHAMBERS
12/22/2010

Division Director Review of NDA 201923

Date	December 21, 2010
From	Wiley A. Chambers, M.D.
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	June 30, 2010
Type of Application	505(b)(1)
Name	Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg
Dosage forms / Strength	Intravitreal insert
Proposed Indication(s)	Treatment of diabetic macula edema
Action:	Complete Response

1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant.

There is no previous marketing experience with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg as this product is not commercially available.

There are no approved drug therapies for the treatment of diabetic macular edema (DME).

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) and has been developed for the treatment of Diabetic Macular Edema (DME). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.

The safety and efficacy seen with this product are class effects related to ophthalmic steroids. Use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

2. Background

Diabetic macular edema (DME), a chronic, debilitating disease, is a cause of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

An End-of-Phase 2 meeting was held for IND 72,056 on September 2, 2008. The Division expressed concern that the benefits might not outweigh the risks if Illuvien demonstrated a safety profile which was similar to other corticosteroids. The applicant stated that they did not expect to see the development of cataracts or elevated intraocular pressure due to the low release rate.

A Pre-NDA meeting was held for IND 72,056 on March 4, 2010.

3. CMC

INSERTER:

During the development phase of this drug product (b) (4)

(b) (4)

(b) (4)

This was the packaging configuration used for all the preclinical and clinical studies.

During the clinical studies, feedback was solicited from the investigators on the inserter device. Feedback was also obtained from retinal specialists who were not part of the clinical study.

(b) (4) designed an inserter incorporating the feedback received. Modifications included:

(b) (4)

(b) (4)

Figure 4: Iluvien Inserter Device

Study C-01-08-006, entitled "A randomized, double-masked, pilot study of the safety and efficacy of 0.5 µg/day and 0.2 µg/day Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg in subjects with macular edema secondary to retinal vein occlusion", is an ongoing study (b) (4) The study utilizes the new inserter and collects information from the treating physician on the performance of the inserter. The trial is ongoing, and no study report was submitted with the application. The study is not presented in Module 5 of the NDA submission; it was not included in the 120-day Safety Update.

There is currently no clinical data to support the use of the new (b) (4) inserter for the Iluvien drug product. The modifications to the inserter are so significant that clinical data is necessary to bridge the two different inserter configurations.

DRUG SUBSTANCE:
Fluocinolone acetonide (FA), which is the active pharmaceutical ingredient used in Iluvien is a member of a class of fluorinated synthetic corticosteroids that include dexamethasone, triamcinolone, and fluocinolone. It is a monographed drug substance listed in both the USP and Ph. Eur.

In the development program for Iluvien, two versions were designed to deliver fluocinolone acetonide at different rates - the high dose and the low dose with targeted initial release rates of 0.5 µg/day and 0.25 µg/day, respectively. The two versions are identical in composition (b) (4)

Table 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4)	CTM-200500
Related Substances		
(b) (4)	Not more than (b) (4)	CTM-200500
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Test	Acceptance Criteria	Analytical Method
(b) (4)	Not more than (b) (4)	
	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	Not more than (b) (4)	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4)	Not less than (b) (4)	(b) (4)
Particle	Not less than	MGR051FLU011
Particle	Not less than	
Polymorphism		
(b) (4)	Not less than (b) (4)	Contract Laboratory[c] High Resolution X-Ray Powder Diffraction and/or Differential Scanning Calorimety
Microbial Limits		
Total Aerobic Count	Not more than (b) (4)	Current USP/NF <61>
Yeast/Mold Count	Not more than	MTM-200155
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
		(b) (4)

DRUG PRODUCT:
Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg, is a sterile, drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a nonbiodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg.

The inserter is placed into a tray, sealed with a (b) (4) lid and placed into a carton (b) (4) The inserter has a 25 gauge extra-thin wall needle attached, which allows the physician to place the insert through the sclera into the vitreous.

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)

(b) (4)

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

Table 1: Quality Control Specifications

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Specified Identified and Unidentified Individual Impurity		
Release	Not more than (b) (4)	CTM-200501
Stability	Not more than	
Unspecified Individual Impurity		
Release	Not more than (b) (4)	
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4)	CTM-200502
Endotoxin		MTM-200033
Sterility		
Release	(b) (4)	
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

As of the date of this review, Compliance recommends withholding approval of the application based on facility inspections. The (b) (4) facility and (b) (4) are not in compliance with cGMPs.

The CMC reviewer does not recommend approval and has cited deficiencies regarding a lack of information for the facilities conducting the polymorph testing (b) (4)

4. Nonclinical Pharmacology/Toxicology

Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. Orally administered PVA is relatively harmless, with LD_{50} in the range of 15-20 g/kg. The content of PVA in a 0.19 mg Iluvien is (b) (4) The sponsor also

conducted several biocompatibility studies with polyimide tubing and extracts of stainless steel injection needles. The results were negative.

The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber. Continuous exposures of ocular tissues for both toxicity studies were achieved via one or two injections of the insert into the eye. There appeared to be no definable toxicity associated with the administration of 0.2 µg/day FA. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations.

The panel of genotoxicity tests performed by the Sponsor included the bacterial mutation test, mammalian cell mutation test and a mouse micronucleus test. Fluocinolone acetonide did not show any evidence of genotoxic activity in these tests when tested in accordance with regulatory guidelines.

No carcinogenicity studies were conducted for Iluvien. Reproductive and developmental toxicity studies with Iluvien were not conducted. During a communication from the FDA to sponsor on 02/03/10, FDA requested the human PK data be submitted for the evaluation of carcinogenicity waiver. Since human systemic exposure to FA after Iluvien is below LLOQ, the waiver of carcinogenicity study was granted.

5. Clinical Pharmacology/Biopharmaceutics

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 (manufactured by (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)

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. However, the assessment on FA exposure in aqueous humor and any conclusions thus derived will not be used to support any regulatory decisions because the analytical method was not validated.

The sponsor proposes *in-vitro* release specification (b) (4) While the sponsor's justification to use *in-vitro* release specification as an in-process control appears reasonable, Report 10066

could not be reviewed without a full development and validation report for the *in-vitro* release methodology.

6. Sterility Assurance

As noted in the Product Quality Microbiology Review, failure to address the product quality microbiology deficiencies could result in an increased risk of product contamination. The Product Quality Microbiology Reviewer recommends that the application:
(1) include (b) (4) and impose (b) (4) bioburden alert and action limits;
(2) describe the bioburden and endotoxin testing procedures used (b) (4)
(3) describe (b) (4) the procedure (b) (4)
(4) provide the procedures, acceptance criteria and data sets (b) (4)
(5) provide the procedures for bioburden determination, sterility testing, and bacteriostasis-fungistasis testing carried out (b) (4)
(6) modify the endotoxin limit value so that it is based on a per drug rod (b) (4)
(7) provide a description of the FA endotoxin testing procedure.

7. Clinical/Statistical - Efficacy

The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period, although only Month 24 data has been submitted. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness ≥ 250 microns.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline.

Primary Efficacy at 24 Months

FAME A

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 24	95	14 (14.7)	190	51 (26.8)	(b) (4)	
Difference (95% CI)[1]			-12.1 (-21.6, -2.6)			
P-value[2]			0.029			
Per Protocol Population (observed data only)						
Month 24	46	7 (15.2)	112	33 (29.5)	(b) (4)	
Difference (95% CI)[1]			-14.2 (-27.6, -0.9)			
P-value[2]			0.112			

FAME B

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 24	90	16 (17.8)	185	57 (30.8)	(b) (4)	
Difference (95% CI)[1]			-13.0 (-23.4, -2.7)			
P-value[2]			0.028			
Per Protocol Population (observed data only)						
Month 24	40	6 (15.0)	125	45 (36.0)	(b) (4)	
Difference (95% CI)[1]			-21.0 (-34.9, -7.1)			
P-value[2]			0.023			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

Corrections for the multiple interim looks (9) have not been made in the values reported above.

The results from the PP observed data only are likely confounded by cataract formation during the 24 month period which resulted in the PP observed data only population failing the primary endpoint, p = 0.112, in FAME A and being marginally statistically significant in FAME B.

FAME A is considered a failed trial due to the PP observed data only having a p value > 0.0491 at 24 months (p = 0.112). Additionally, 18 month data for Fame A failed the test of a p value of 0.05 or better. For the All Treated with LOCF and PP observed data only groups the p values were 0.466 and 0.941, respectively. The overall results at 18 and 24 months do not provide additional support for Fame A being a successful clinical trial. FAME B results for the PP observed data only are considered marginal due to 0.5 µg dose demonstrating a p value > 0.0491.

At least two replicated trials are recommended to demonstrate robustness of the results for this indication. The applicant did not demonstrate success in two replicated trials.

8. Safety

The results from two Fame studies (Fame A and FAME B) form the basis for the safety evaluation. The 2 FAME studies were performed under one protocol and enrolled subjects during the same time period. The only significant difference between the studies was geographical location of the study sites. FAME A was conducted at 49 sites in 7 countries (US, Canada, 4 countries in the European Union [EU], and India). FAME B was conducted at 52 sites in 5 countries (US, India, and 3 countries in the EU). When the 2 studies enrolled subjects in the same countries, FAME A enrolled subjects in the northern portions of the countries involved, and FAME B enrolled subjects in the southern portions of the countries. The demographics of the 2 study populations were essentially the same.

Exposure in Study Treatments:
Integrated Fame A and B Studies (Total n = 953)

Study Treatments	**Sham (N=185)**	**0.2 µg/day FA (N=375)**	**0.5 µg/day FA (N=393)**
Number of Treatments Completed			
Number of Treatments	240	472	505
Number of Subjects Receiving at Least 1 Treatment	185	375	393
Mean (SD)	1.3 (0.6)	1.3 (0.5)	1.3 (0.5)
Median	1.0	1.0	1.0
Minimum, Maximum	(1.0, 4.0)	(1.0, 4.0)	(1.0, 4.0)
Number of Treatments Completed by Frequency, n (%)			
1 Treatment	141 (76.2)	287 (76.5)	293 (74.6)
2 Treatment	36 (19.5)	80 (21.3)	89 (22.6)
3 Treatment	5 (2.7)	7 (1.9)	10 (2.5)
4 Treatment	3 (1.6)	1 (0.3)	1 (0.3)
Time on Study	**N (%)**	**N (%)**	**N (%)**
Month 6	183 (98.6)	367 (97.9)	391 (98.7)
Month 9	178 (96.2)	365 (97.3)	383 (97.5)
Month 12	178 (96.2)	354 (94.4)	378 (96.2)
Month 18	165 (89.2)	333 (88.8)	358 (91.1)
Month 24	150 (81.1)	310 (82.7)	318 (80.9)
Month 30	66 (35.7)	130 (34.7)	148 (37.7)

A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the FAME studies. The total number of treatments administered during the studies was 240, 472, and 393 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for all 3 treatment groups.

Dropouts and/or Discontinuations
Integrated Studies (Fame A and B)

Disposition	Sham	0.2 µg/day FA	0.5 µg/day FA
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated	185	375	393
Total discontinued (n,%):	42 (22.7)	75 (19.9)	75 (19.0)
Adverse events	3 (1.6)	4 (1.1)	11 (2.8)
Unsatisfactory therapeutic effect	1 (0.5)	0	1 (0.3)
Protocol violation	0	0	3 (0.8)
Subject withdrew consent	14 (7.6)	25 (6.6)	21 (5.3)
Lost to follow-up	17 (9.2)	21 (5.6)	16 (4.1)
Death	8 (4.3)	25 (6.7)	23 (5.9)
Unknown	0	1 (0.3)	0

Overall, 192 (20%) subjects discontinued the trial, primarily due to withdrawn consent (6%), death (6%), or loss to follow-up (6%). Of the 192 subjects who discontinued the study, 43 (22%) subjects discontinued during the first 12 months of the study, and 132 (69%) subjects discontinued during the second year of the study. Overall, discontinuations rates were similar throughout the three treatment groups.

In the Integrated Analysis by dose in the Fame A and B studies, 621 (77%) of the 953 subjects who received drug therapy were phakic at baseline and at risk for primary cataract formation.

Cataract-Related Events in Phakic Subjects Integrated Studies (Fame A and B)

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)			
Study eye	56 (46.3)	188 (80.0)	232 (87.5)
Non-study eye	43 (35.5)	94 (40.0)	108 (40.8)
Cataract operation			
Study eye	28 (23.1)	176 (74.9)	224(84.5)
Non-study eye	26 (21.5)	64 (27.2)	68 (25.7)

For the 0.2 µg/day FA and 0.5 µg/day FA groups when comparing the Non-study eye to the Study eye, cataract formation and cataract operation continue to demonstrate the increased risk of cataract formation and cataract operation resulting from the localized (intravitreal) drug treatment.

The risks of cataract formation and cataract operation are significant by 24 months after the drug treatment. This risks appears to be dose and time dependent.

Common (≥ 1%) Ocular Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Abnormal sensation in eye	2 (1.1)	5 (1.3)	5 (1.3)
Anterior chamber cell	1 (0.5)	6 (1.6)	3 (0.8)
Blepharitis	3 (1.6)	7 (1.9)	7 (1.8)
Cataract	58 (31.4)	189 (50.4)	222 (56.5)
Cataract nuclear	6 (3.2)	9 (2.4)	13 (3.3)
Cataract operation	36 (19.5)	193 (51.5)	236 (60.1)
Cataract subcapsular	11 (5.9)	33 (8.8)	26 (6.6)
Conjunctival haemorrhage	22 (11.9)	48 (12.8)	48 (12.2)
Conjunctival hyperemia	6 (3.2)	5 (1.3)	5 (1.3)
Conjunctivitis	5 (2.7)	12 (3.2)	9 (2.3)
Corneal abrasion	5 (2.7)	4 (1.1)	10 (2.5)
Corneal epithelial defect	0	4 (1.1)	6 (1.5)
Corneal edema	4 (2.2)	11 (2.9)	15 (3.8)
Diabetic retinal edema	1 (0.5)	4 (1.1)	6 (1.5)
Diabetic retinopathy	4 (2.2)	6 (1.6)	14 (3.6)
Diplopia	2 (1.1)	6 (1.6)	2 (0.5)
Dry eye	10 (5.4)	23 (6.1)	17 (4.3)
Eye discharge	1 (0.5)	5 (1.3)	5 (1.3)
Eye irritation	9 (4.9)	26 (6.9)	21 (5.3)
Eye pain	25 (13.5)	50 (13.3)	65 (16.5)
Eye pruitus	2 (1 1)	10 (2.7)	12 (3.1)
Eyelid edema	2 (1.1)	4 (1.1)	4 (1.0)
Foreign body sensation	4 (2.2)	14 (3.7)	13 (3.3)
Glaucoma or open angle glaucoma[1]	5 (2.7)	21 (5.6)	24 (6.1)
Glaucoma surgery	2 (1.1)	6 (1.6)	8 (2.0)
IOP increased	24 (13.0)	132 (35.2)	173 (44.0)
Iris neovascularization	6 (3.2)	6 (1.6)	6 (1.5)
Keratoconjunctivitis sicca	1 (0.5)	6 (1.6)	4 (1.0)
Lacrimation increased	9 (4.9)	19 (5.1)	14 (3.6)
Macular edema	5 (2.7)	10 (2.7)	10 (2.5)
Maculopathy	19 (10.3)	27 (7.2)	43 (10.9)
Myodepsia	20 (10.8)	70 (18.7)	77 (19.6)
Myopia	0	6 (1.6)	5 (1.3)
Ocular hyperemia	3 (1.6)	10 (2.7)	17 (4.3)
Ocular hypertension	2 (1.1)	9 (2.4)	12 (3.1)
Optic atrophy	3 (1.6)	5 (1.3)	14 (3.6)
Photophobia	2 (1 1)	7 (1.9)	4 (1.0)
Photopsia	2 (1.1)	5 (1.3)	7 (1.8)
Posterior capsule opacification	8 (4.3)	28 (7.5)	27 (6.9)
Punctate keratitis	1 (0.5)	5 (1.3)	5 (1.3)
Retinal detachment	4 (2.2)	5 (1.3)	7 (1.8)
Retinal exudates	2 (1.1)	11 (2.9)	8 (2.0)
Retinal hemorrhage	11 (5.9)	13 (3.5)	16 (4.1)
Retinal neovascularization	11 (5.9)	16 (4.3)	15 (3.8)
Trabeculectomy	0	8 (2.1)	20 (5.1)
Trabeculoplasty	0	3 (0.8)	9 (2.3)
Vision blurred	13 (7.0)	35 (9.3)	26 (6.6)
Visual acuity reduced	20 (10.8)	45 (12.0)	40 (10.2)
Visual impairment	7 (3.8)	14 (3.7)	31 (7.9)
Vitrectomy	15 (8.1)	25 (6.7)	35 (8.9)
Vitreous detachment	10 (5.4)	28 (7.5)	25 (6.4)
Vitreous Hemorrhage	35 (18.9)	59 (15.7)	73 (18.6)
Vitreous opacities	1 (0.5)	4 (1.1)	5 (1.3)
Vitritis	3 (1.6)	3 (0.8)	4 (1.0)

1 Includes the total number of unique subjects who experienced glaucoma or open-glaucoma

Four of the most common ocular adverse events (i.e., cataract, cataract operation, increased intraocular pressure and myodesopsia) occurred more frequently in the active-treated groups compared with the sham group.

Common (≥ 5%) Systemic Adverse Events by Treatment Group: Integrated Studies

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Anemia	6 (3.2)	26 (6.9)	34 (8.7)
Cardiac failure congestive	9 (4.9)	12 (3.2)	20 (5.1)
Constipation	3 (1.6)	12 (3.2)	21 (5.3)
Nausea	13 (7.0)	23 (6.1)	22 (5.6)
Vomiting	10 (5.4)	13 (3.5)	4 (1.0)
Nasopharyngitis	11 (5.9)	20 (5.3)	22 (5.6)
Pneumonia	3 (1.6)	19 (5.1)	14 (3.6)
Sinusitis	7 (3.8)	12 (3.2)	20 (5.1)
Hypercholesterolemia	11 (5.9)	17 (4.5)	19 (4.8)
Headache	10 (5.4)	26 (6.9)	20 (5.1)
Renal failure	9 (4.9)	23 (6.1)	25 (6.4)
Hypertension	25 (13.5)	35 (9.3)	38 (9.7)

Safety Summary

The risk of cataract formation, cataract operation, and increased IOP are adverse events that occur at high rates in the drug group when compared to the Sham group.

Cataract formation occurs in 46% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 23% of the Sham group study eyes versus 75% in the 0.2 µg/day FA study eyes. Increased IOP occurs in 13% of the Sham group study eyes versus 35% in the 0.2 µg/day FA study eyes. The risk of increased IOP is nearly three times the rate in the 0.2 µg/day FA drug group.

9. Advisory Committee Meeting

No Advisory Committee Meeting will be scheduled until the 36 month data is available for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

10. Pediatrics

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population. This application went before the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed that a full waiver in pediatric patients should be granted.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. The DSI Clinical Inspection Summary was finalized on 12/1/10.

Two sites were selected for inspection, one domestic and one foreign, due to enrollment of large numbers of study subjects, high number of INDs and lack of previous inspectional history.

The preliminary classification of Clinical Investigator inspections of Drs. Blackburn (Kentucky) and Garg (India) are Voluntary Action Indicated (VAI). Although regulatory violations were noted at both of these sites, given the nature of the findings, DSI considered it unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

Dr. Blackburn (Study C-01-05-001B /Site 001/17) failed to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Dr. Garg (Study C-01-05-001A /Site 016/ 45) failed to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

FINANCIAL DISCLOSURE
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided.

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable.

DMEPA again reviewed the name Iluvien for the NDA application. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable.

DDMAC
The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle. .

BIOSTATISTICS
The Biostatistician considered both the FAME A and FAME B studies to be successful based on the Full Analysis = Intent-to-Treat with Last Observation Carried Forward dataset.

The Medical Officer utilized the All Randomized = All Treated with LOCF dataset. The M.O. did not consider FAME A to be a successful trial because of the lack of a statistically significant treatment effect observed in FAME A for the Per Protocol observed data only populations.

Per the Biostatistician, the drug induces serious risk of cataract surgery and elevated intra-ocular pressure. The incidence of cataract surgery during the study is significantly higher in the active dose arms compared to the sham arm. The incidence of surgery due to elevated intra-ocular pressure is also higher in the active dose arms compared to the sham arm.

12. Labeling

A formal labeling review is deferred until additional data is submitted to support the application for Iluvien.

13. Regulatory Action

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg will not be approved for the treatment diabetic macular edema based on the information submitted to date. The deficiencies include:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,

    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.

    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.

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

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.

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.

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.

2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to preserve its identity, strength, quality, purity, and stability. Specifically,

a. The currently proposed limit of (b) (4) that 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 and the proposed post-approval stability protocol are not acceptable without an adequate description of the endotoxin testing procedure and appropriate acceptance criteria. 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.

c. There is insufficient information for the facilities (b) (4)

d. There is insufficient information for the facilities conducting the polymorph testing.

e. Identification tests (e.g., IR) in the specification for each of the inactive components of the drug product, polyvinyl alcohol, (b) (4)%, polyimide tubes, and silicone adhesive have not been included.

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

g. The proposed release rate specification (b) (4) is (b) (4)

h. Excessive bioburden in the fluocinolone acetonide (FA) rods could contaminate the product with microbial toxins, debris, and metabolites. These contaminants (b) (4) should be controlled for. The manufacturing process should be modified to include (b) (4) product bioburden testing, and the (b) (4) quality control parameters should be amended to include product bioburden alert and action levels.

i. The proposed hold period is not acceptable. Presentation of study results without including the details of how they were performed is not acceptable.

j. The description of the (b) (4) procedure is not complete.

k. The (b) (4) studies should be conducted under the conditions to be used for (b) (4).

l. The descriptions of the procedures for bioburden determination, sterility testing and bacteriostasis-fungistasis testing are not complete.

3. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. During a recent inspection of the (b) (4) manufacturing facilities for this application, our field investigators conveyed deficiencies to the representative of the facilities. All facilities and controls will need to comply with the cGMP regulations.

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

/s/

WILEY A CHAMBERS
12/22/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201923
Priority or Standard	P
Submit Date(s)	June 30, 2010
Received Date(s)	June 30, 2010
PDUFA Goal Date	December 30, 2010
Division / Office	DAIOP
Reviewer Name(s)	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	December 9, 2010
Established Name	fluocinolone acetonide intravitreal insert, 0.19 mg
(Proposed) Trade Name	Iluvien
Therapeutic Class	Corticosteroid
Applicant	Alimera Sciences, Inc.
Formulation(s)	Intravitreal insert
Dosing Regimen	One insert per ey (b) (4)
Indication(s)	Treatment of diabetic macula edema
Intended Population(s)	Patients with diabetic macular edema

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 201923 not be approved for the treatment of diabetic macular edema based on this submission of 24 month data.

There is not substantial evidence to demonstrate that the benefits of the drug outweigh its risks for either the low dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.25 µg/day) or the high dose version of Iluvien 0.19 mg (designed to have an initial release rate of 0.5 µg/day).

1.2 Risk Benefit Assessment

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of fluocinolone acetonide (FA) in the anterior segment would provide a better safety profile while maintaining efficacy.

Iluvien (0.19 mg) has been studied based on the initial release rates of 0.2 or 0.5 µg/day. Iluvien was designed to have initial release rates of 0.25 µg/day (which is still the target) (b) (4).

Reviewer's comments:

Throughout this review, the release rate of 0.2 µg/day and 0.25 µg/day are used interchangeably. This reviewer considers these release rates to be sufficiently the same.

The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema. This recommendation is based on the results from the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) studies submitted with 24 month data for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day.

Benefit

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group for Fame A and Fame B Studies

Visit	Treatment Group							
	Fame A				Fame B			
	Sham		0.25 µg/day		Sham		0.25 µg/day	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF								
Month 24	95	14 (14.7)	190	51 (26.8)	90	16 (17.8)	185	57 (30.8)
P-value[1]			0.029				0.028	
Per Protocol Population (observed cases only)								
Month 24	46	7 (15.2)	112	33 (29.5)	40	6 (15.0)	125	45 (36.0)
P-value[1]			0.112				0.023	

1 P-value is based on Fischer's exact test.

Reviewer's comments:

Fame A failed its endpoint at 24 months for the PP observed data only Population (p value > 0.05), while Fame B demonstrated statistical significance (p value ≤ 0.05).

Risks

Cataract-Related Events (Phakic Subjects only)
Dose (0.2 µg/day FA)
Integrated Studies (Fame A and B)

Term	Sham (N=121) N (%)	0.2 µg/day FA (N=235) N (%)
Cataract (any type)		
Study eye	56 (46.3)	188 (80.0)
Non-study eye	43 (35.5)	94 (40.0)
Cataract operation		
Study eye	28 (23.1)	176 (74.9)
Non-study eye	26 (21.5)	64 (27.2)

Increased IOP
Dose (0.2 µg/day FA)
Integrated Studies (Fame A and B)

Term	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)
IOP increased	24 (13.0)	132 (35.2)

Reviewer's comments:

The risk of cataract formation, cataract operation, and increased IOP are adverse events that occur at extraordinary high rates in the drug group when compared to the Sham group.

Cataract formation occurs in 46% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Additional support for the significantly increased risk of cataract formation in the drug group (0.2 µg/day FA) is observed when using the patient's other eye as an additional control. The 0.2 µg/day FA group has a cataract formation rate in the non-study eye of 40% versus 80% in the study eye. Whichever comparison is used, the risk of cataract formation is nearly twice the rate in the 0.2 µg/day FA drug group.

Cataract operation occurs in 23% of the Sham group study eyes versus 75% in the 0.2 µg/day FA study eyes. Additional support for the significantly increased risk of cataract operation in the drug group (0.2 µg/day FA) is observed when using the patient's other eye as an additional control. The 0.2 µg/day FA group has a cataract operation rate in the non-study eye of 22% versus 75% in the study eye. Whichever comparison is used, the risk of cataract operation is nearly thrice (3 x) the rate in the 0.2 µg/day FA drug group.

Increased IOP occurs in 13% of the Sham group study eyes versus 35% in the 0.2 µg/day FA study eyes. The risk of increased IOP is nearly thrice (3 x) the rate in the 0.2 µg/day FA drug group.

Reviewer's Conclusion:

Given the risk of cataract formation, cataract operation, and increased IOP is two to three times higher in the drug group compared to the Sham group, and only one study, FAME B, demonstrated a statistically significant result (p value ≤ 0.05) while the other study (FAME A) did not demonstrate a statistically significant result in the PP population (p value > 0.05), the risks of this drug greatly exceed its potential benefit through the 24 month exam. The benefits of using this drug product do not outweigh the risks for the treatment of diabetic macular edema.

For these reasons, the drug is not recommended for approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no proposed risk management actions.

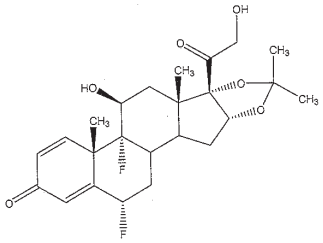
1.4 Recommendations for Postmarket Requirements and Commitments

There are no Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Chemical Structure



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

Contains:

Active: fluocinolone acetonide 0.19 mg

Inactives: (b)(4)% polyvinyl alcohol and water for injection

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved drug therapies for the treatment of diabetic macular edema (DME).

2.3 Availability of Proposed Active Ingredient in the United States

Fluocinolone acetonide, a synthetic glucocorticoid, is a well established active ingredient currently marketed as topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant.

There is no previous marketing experience with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg as this product is not commercially available.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

Use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On June 28, 2010 Alimera Sciences, Inc. requested Priority Review for Iluvien in accordance with the provisions of Section 112 of the Food and Drug Administration Modernization Act of 1997 (P.L. 105-115) which amended the FFDCA by adding section 506 (21 U.S.C. 356) authorizing FDA to direct overall attention and resources to the evaluation of applications for drugs that are intended to treat serious or life-threatening conditions or offer major advances in treatment where no adequate therapy exists.

Diabetic macular edema (DME), a serious, chronic, debilitating disease, is the primary cause of vision loss associated with diabetic retinopathy. There are currently no approved drug therapies for the treatment of DME.

A conference call on 01/10/07 documented FDA's agreement to accept the NDA submission with efficacy data at 24 month's follow-up with additional safety and efficacy data provided at 36 months.

Reviewer's comments:

For the indication of diabetic macular edema (and diabetic retinopathy) it is recommended that clinical trials be continued for at least 36 months.

Efficacy data for the primary endpoint can be accepted at 24 months or more.

The 36-month minimum has been suggested because past trials have demonstrated that earlier findings in diseases such as diabetic retinopathy and diabetic macular edema are not necessarily predictive of later findings (i.e., a drug product has shown different results at 6, 12, 24 months versus 36 months and longer).

In order to accept efficacy data at 24 months a two time point comparison with "wins" on both comparisons might be considered for a demonstration of efficacy. The first

comparison is recommended to be between the original baseline and a time point that is at 24 months or longer. It is recommended that a clinically and statistically superior difference be demonstrated between the selected timepoint and the original baseline. The second comparison is recommended to be between the 18 month time point and the time point at 24 months or longer; this comparison is recommended to be numerically noninferior using the 18 month time point as a baseline.

It is recommended that the trials continue to collect safety and efficacy information for at least 3 full years.

2.6 Other Relevant Background Information

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) and has been developed for the treatment of Diabetic Macular Edema (DME). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 µg/day. Based on *in vitro* and *in vivo* data, FA is released at gradually decreasing levels over (b) (4) 36 months depending on the dose. The Sponsor is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.

Reviewer's comments:

The applicant's goal is to develop a lower dose exposure of FA in the anterior segment to provide a better safety profile while maintaining efficacy.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested. Refer to the DSI review for additional information.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies, nor did any one single investigator or site enroll a significant number of subjects.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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.

Iluvien is manufactured (b) (4) The inserter is placed into a tray, sealed with a (b) (4) lid and placed into a (b) (4). The insert is inserted through the sclera into the vitreous of the eye by a physician.

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)

The insert will be placed into a one-time use inserter which has a 25 gauge extra-thin wall needle attached. See Table 3 for the inserter components.

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Long-term animal studies have not been conducted with Iluvien to determine the carcinogenic potential or the effect on fertility of fluocinolone acetonide.

Fluocinolone acetonide was not genotoxic *in vitro* in the Ames test (*S. typhimurium* and *E. coli*) and the mouse lymphoma TK assay, or *in vivo* in the mouse bone marrow micronucleus assay.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Corticosteroids inhibit the inflammatory response to a variety of inciting agents. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

Corticosteroids are thought to act by the inhibition of phospholipase A_2 via induction of 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 the common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

4.4.2 Pharmacodynamics

The phase 3 studies demonstrated that the efficacy of the 0.2 µg/day dose and that of the 0.5 µg/day dose are essentially the same. Based on the *in vitro* release profiles, FA is released from the low dose at quantifiable levels for a longer period of time. This is supported by the finding that slightly fewer subjects who were treated with the low dose were retreated through Month 21 than those treated with the high dose (0.2 µg/day, 16% [59/376]; (0.5 µg/day, 18% [73/395]). The safety profile of the low dose is also better than the high dose with regard to the incidence of increased IOP and cataracts. As a result, the low dose is proposed for the marketed product.

Reviewer's comments:

*The applicant is proposing to market the low dose release of FA (*0.2 µg/day).

*The data presented throughout the review will include data from the control group (sham treatment), from the low dose release of FA (*0.2 µg/day) *and from the high dose release of FA (0.5 µg/day).*

4.4.3 Pharmacokinetics

In a human pharmacokinetic study (C-01-06-002, the FAMOUS Study) fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all time points from Day 1 through Month 18 indicating negligible systemic exposure. The maximal aqueous humor fluocinolone acetonide concentrations were observed on Day 7 for most of the subjects. Aqueous humor fluocinolone acetonide concentrations decreased over the first 3−6 months and remained essentially the same through Month 18 for subjects who were not retreated.

Subjects who were retreated experienced a second fluocinolone acetonide peak concentration similar to that following the initial dose. After retreatment, aqueous humor concentrations of fluocinolone acetonide returned to levels approximately similar to those observed at the time of first treatment.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Type of Study	**Study Identifier**	**Study Objectives**	**Study Design and Type of Control**	**Test Product(s);** **Dosage regimen;** **Route of Administration**	**Number of Subjects**	**Duration of Treatment** **Study Status;** **Report**
Phase 3	C-01-05-001A (Study A)	Efficacy: Proportion of subjects with a ≥ 15 letter increase from baseline in BCVA at Month 24 Safety: AEs, IOP and other assessments	Prospective, randomized, double masked, multi-center comparison of 0.2 µg/day FA. 0.5 µg/day FA and sham in subjects with DME	Iluvien insert 0.2 and 0.5 µg/day FA or sham injection administered at baseline and any time after Month 12 if subject experienced vision loss or retinal thickening; Intravitreal Route	481 randomized (276 males, 205 females)	36 months Ongoing; Final study report for Month 24 (primary endpoint)
Phase 3	C-01-05-001B (FAMOUS Study)	Efficacy: Proportion of subjects with a ≥ 15 letter increase from baseline in BCVA at Month 24 Safety: AEs, IOP and other assessments	Prospective, randomized, double masked, multi-center comparison of 0.2 µg/day FA. 0.5 µg/day FA and sham in subjects with DME	Iluvien insert 0.2 and 0.5 µg/day FA or sham injection administered at baseline and any time after Month 12 if subject experienced vision loss or retinal thickening; Intravitreal Route	475 randomized (292 males, 183 females)	36 months Ongoing; Final study report for Month 24 (primary endpoint

Type of Study	Study Identifier	Study Objectives	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Administration	Number of Subjects	Duration of Treatment Study Status; Report
Phase 2b	C-01-06-002 (Study A)	Pharmacokinetics: FA in plasma and aqueous Efficacy: Change from baseline in retinal thickness by OCT.	Randomized, open label, parallel-group, multi-center PK and efficacy study in subjects with DME	Iluvien insert 0.2 and 0.5 µg/day FA; administered at baseline and any time after Month 12 if subject experienced vision loss or retinal thickening; Intravitreal Route	37 randomized (21 males, 16 females)	36 months Ongoing; Final study report for Month 18

5.2 Review Strategy

5.3 Discussion of Individual Studies/Clinical Trials

The two phase 3 studies were conducted at 101 sites in North America, Europe, and India. All sites in the FAME (A and B) studies used the same protocol (C-01-005-001A and C-01-005-001B) and performed the studies in accordance with current Good Clinical Practices and local requirements.

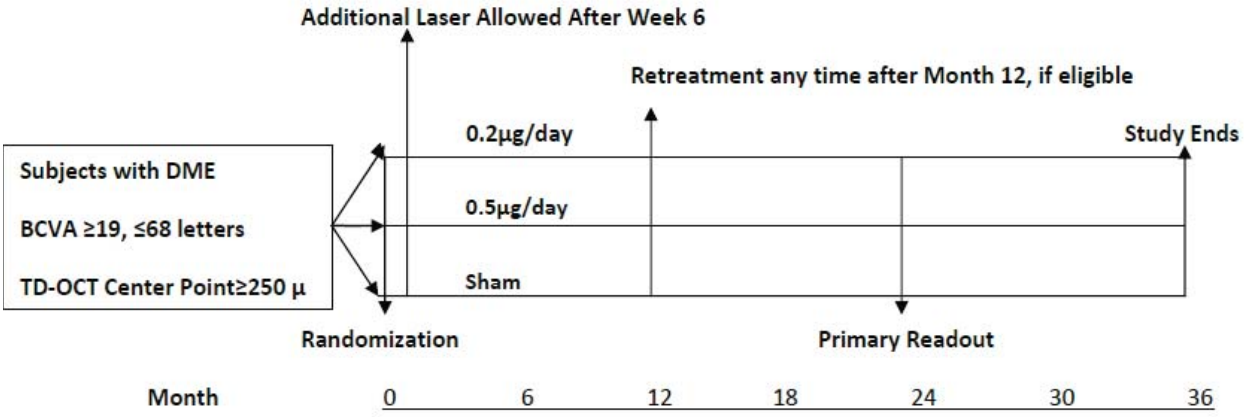
The FAME studies A and B were randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies conducted over a 36-month period. The inclusion/exclusion criteria were selected to recruit patients with DME who had received prior laser photocoagulation with retinal thickness ≥ 250 microns.

The studies were randomized and double-masked to eliminate bias. To preserve masking, 2 investigators were used. One investigator performed the treatments and the other performed all assessments. A sham injection control was selected because injection of a placebo insert, while viewed as the best control, was not ethically acceptable to the investigators and IECs/IRBs. The primary variable (15-letter improvement in BCVA) was assessed by masked, certified assessors and not by either of the investigators.

An important consideration in evaluating the design of the phase 3 studies is that subjects (including those who received active drug) were allowed to have additional laser treatments at the discretion of the investigator. This was viewed as necessary

because the duration of the studies (3 years) was too long to deny treatment to any subject who did not respond to treatment. Subjects were not to receive any non-approved treatments in the study eye for DME or systemic treatments for DME. However, a small percentage of subjects did receive these therapies.

A final important issue with the design is that subjects were eligible for retreatment any time after the Month 12 assessments if they experienced vision loss or retinal thickening per optical coherence tomography (OCT). As a result, subjects received various numbers of treatments (1−4) during the studies.



The primary endpoint (percent of subjects with ≥ 15-letter improvement in BCVA at Month 24) was chosen based on input from regulatory authorities to represent a clinically relevant change in vision. The Month 36 follow-up will be reported in the future to confirm the durability of the drug effectiveness and safety.

Study C-01-005-001 (FAME A) and C-01-005-001 (FAME B)

A randomized, double-masked, parallel group, multi-center, dose-finding comparison of the safety and efficacy of 0.5 µg/day and 0.2 µg/day fluocinolone acetonide intravitreal inserts (0.19 mg) to sham injection in subjects with diabetic macular edema

Inclusion Criteria

A subject must have fulfilled all of the following criteria:
1. Males and non-pregnant females at least 18 years of age.
2. BCVA of ≥ 19 and ≤ 68 letters (20/50 or worse but at least 20/400) in the study eye by an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. BCVA of the non-study eye must have been no worse than 20/400.
3. Diagnosis of diabetes mellitus (type 1 or type 2). Any 1 of the following were

considered sufficient evidence that diabetes was present:

a. Use of insulin for the treatment of diabetes for at least the 3 months before screening.

b. Use of oral antihyperglycemia agents for the treatment of diabetes for at least the 3 months before screening.

4. At least 1 macular laser treatment more than 12 weeks before the screening visit. Per the protocol, initially all subjects were required to have had prior macular laser; however, in an attempt to increase enrollment the protocol was amended to permit subjects with no prior laser into the study.
5. DME based on investigator's clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and OCT.
6. Mean foveal thickness of at least 250 μm by OCT in the study eye.
7. Ability and willingness to comply with the treatment and follow up procedures.
8. Ability to understand and sign the ICF. No expectation that subject was moving out of the area of the clinical center to an area not covered by another clinical center during the next 36 months.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:
1. Pregnant, lactating females or females of childbearing potential (unless using reliable contraception, i.e., double barrier, surgical sterilization, oral contraceptives, Norplant, intrauterine device.
2. Laser treatment for DME within 12 weeks of screening or judged to be necessary within 6 weeks following enrollment.
3. Any ocular surgery in the study eye within 12 weeks of screening.
4. Yag capsulotomy in the study eye within 15 days of screening.
5. Prior intravitreal, sub-Tenon, or periocular steroid therapy within 3 months before enrollment (e.g., triamcinolone) or prior treatment with intravitreal anti-VEGF treatment within 2 months of enrollment (Lucentis®, Avastin®, Macugen®.) Systemic treatment with Avastin was also not allowed within 3 months before screening.
6. Any change in systemic steroidal therapy within 3 months of screening.
7. Glaucoma, ocular hypertension, intraocular pressure (IOP) >21 mmHg or concurrent therapy at screening with IOP-lowering agents in the study eye.
8. Retinal or choroidal neovascularization due to ocular conditions other than DR (e.g., presumed ocular histoplasmosis, high myopia [spherical equivalent >8 diopters], macular degeneration).
9. Any active viral, fungal or bacterial disease of the cornea or conjunctiva or any history of a potentially recurrent infection which could have been activated by treatment with a steroid, (e.g., ocular herpes simplex virus).
10. Known or suspected hypersensitivity to any of the ingredients of the investigational product or to other corticosteroids.
11. History of vitrectomy in the study eye.
12. History of uncontrolled IOP elevation with steroid use that did not respond to topical

therapy.
13. History or presence of any disease or condition (malignancy) that in the investigator's opinion would preclude study treatment or follow-up.
14. Any lens opacity which impairs visualization of the posterior pole or significantly impairs vision, in the opinion of the investigator.
15. Peripheral retinal detachment in prospective area of insertion.
16. Participation in another clinical trial within 12 weeks before the screening visit or during the study.
17. Resting systolic blood pressure (BP) of greater than 180 mmHg or diastolic BP greater than 105 mmHg at the screening visit.

Exams

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Retreatment Visits		
Week / Month				W 1	W 3	W 6	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 33	M 36	After M12	Trt + 1	Trt +7
Med./Ophth. Hx	X																				
Preg. Test	X																	X	X		
Vital Signs	X													X				X			
Clinical labs		X												X				X			
Pharmacogenetic sample		X																			
QOL survey	X													X				X			
Specular Microscopy		X												X				X			
Ophth. Exam.[a]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Fundus Photography	X							X		X		X		X				X	X		
OCT	X			X		X	X	X	X	X		X		X		X		X	X		
Fluoreseein Angiography	X						X			X		X		X				X	X		
Contrast Sensitivity	X													X				X	X		
Enrollment		X																	X		
Day 1 post –op call			X																	X	
Post-treatment Medications		X	X	X															X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Treatments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion form																		X			

[a] Ophthalmic exam includes BCVA, IOP, slit-lamp exam, and dilated ophthalmoscopy

Primary Objective

The primary objective was to determine if either dose level of FA intravitreal insert is superior to the control group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) at Month 24 compared to baseline.

Reviewer's comments:

The applicant's primary endpoint analysis: a statistically significant difference between groups in the percentage of patients with 15 letters or more increase in BCVA on the ETDRS eye chart is acceptable.

Subjects Enrolled by Site and Treatment Group

FAME A

Principal Investigator Name & Address	Site Number	Number of Subjects Enrolled		
		Sham	0.2 µg/day	0.5 µg/day
Campochiaro, M.D. Wilmer Eye Baltimore, MD	003	4	9	8
George Sharuk, M.D. Joslin Diabetes Center Boston, MA	005	1	0	0
Seenu Hariprasad, M.D. U. Chicago Dept. Ophthalmology Chicago, IL	008	2	4	4
Miguel Busquets, MD Assoc. Ophthalmology West Mifflin, PA	011	0	1	2
Prema Abraham, M.D. Black Hills Eye Inst. Rapid City, SD	014	1	3	2
Sat P Garg, M.D. All India Inst. Ansari Nagar New Dehli, India	016	9	18	18
Ken Carnevale, MD Ophthalmic Consultants Lynbrook, NY	020	1	0	0
Thomas Ciulla, MD Midwest Eye Inst. Indianapolis, IN	022	5	8	8
Trexler Topping, M.D. Ophthalmic Consultants of Boston Boston, MA	025	0	2	1
Steven Madreperla, M.D. Retina Associates of NJ Teaneck, NJ	026	5	12	11
Jay Prensky, M.D. Pennsylvania Retina Specialists Camp Hill, PA	029	1	1	3
Robert Equi, M.D. Retina Consultants Sacramento, CA	031	2	4	5
Doug Dehning, M.D. Discover Vision Centers Independence, MO	036	3	8	8
Brian Joondeph, M.D. Retinal Alliance Denver, CO	038	1	3	2
Elias Reichel, MD New England Eye Boston, MA	039	1	3	3
Frank Holz, MD Dept. Ophthalmology Bonn, Germany	040	1	2	3
Carol Schwartz, MD Sunnybrook Health Sci. Toronto, Canada	043	0	1	2
David DiLoreto, Jr., MD Flaum Eye Inst.	044	1	1	1

Rochester, NJ				
Anselm Kampik, M.D. Muchen, Germany	045	1	1	0
Deborah Hoffert, M.D. Maine Vitreoretinal Consultants Bangor, ME	046	5	9	8
Louis Glazer, M.D. Vitreo-Retinal Consultants Grand Rapids, MI	049	5	8	8
Robert Frank, M.D. Kresge Eye Inst. Detroit, MI	050	4	7	7
Hugo Quiroz-Mercado, M.D. Denver Health Denver, CO	051	1	3	3
Uday Desai, MD Henry Ford Detroit, MI	054	1	4	2
Jeffrey Marx. M.D. Lahey Clinic Peabody, MA	055	2	4	4
Amod Gupta, M.D. Chandigarh, India	056	9	18	20
Carl Regillo, M.D. Mid Atlantic Retina Philadelphia, PA	057	0	2	0
Gisele Soubrane, M.D. Cretel, France	058	0	1	0
Brian Kim, MD Fletcher Allen Health Care Burlington, VT	059	0	2	0
Michel Weber, MD Ophthalmology Unit Nantes, France	061	0	1	2
Richard Chace, M.D. Eyesight Ophthalmic Services Portsmouth NH	062	3	5	4
Claire Bailey, M.D. Bristol, United Kingdom	067	1	4	4
Yit Yang, M.D. New Cross Hospital Wolverhamptom, UK	070	1	0	1
Himadri Datta, M.D. Medical College Ko kata, India	074	1	3	3
Howard Lazarus, M.D. John-Kenyon American Eye Inst. New Albant, IN	078	2	2	4
Ewa Herba, M.D. Bytom, Poland	080	2	2	2
Robert Devenyi, MD Toronto Western Hospital Toronto, Canada	081	0	1	1
John Galic, MD Royal Victoria Hospital Montreal, Canada	083	0	1	2
Nauman Chaudhry, M.D. New England Retina Associates New London, CT	086	1	3	2
Maria Forminsa-Kapuscik, M.D.	089	2	4	4

Katowice, Poland				
Jack Cohen, M.D. Rush U. Medical Center Chicago, IL	091	0	0	1
John Gonder, M.D. Ivey Inst. London, Ontario	092	5	6	8
W. McLaughlin, Jr. D.O. Eye Care Specialist Kingston, PA	093	1	0	2
William Rosenthal, M.D. Mid-America Retina Kansas City, MO	094	2	4	4
Michael Rivers, M.D. Retina Group of Washington Fairfax, VA	095	1	1	3
Vladimir Kozousek, M.D. Capital Health Halifax, Canada	103	2	4	4
Bruce Garretson, M.D. Associated Retinal Consultants Royal Oaks, MI	104	2	5	5
Nelson Sabates, M.D. UMKC Vision Research Center Kansas City, MO	105	2	4	6
Andrew Lotery, MD Southampton General Hospital Southamptom, UK	108	1	1	1

FAME B

Principal Investigator Name & Address	**Site Number**	**Number of Subjects Enrolled**		
		Sham	**0.2 µg/day**	**0.5 µg/day**
Peter Blackburn, MD U. Kentucky Lexington, KY	001	3	7	7
David Boyer, MD Retina Vitreous Associates Beverly Hills, CA	002	3	6	7
Glen Jaffe, M.D. DUMC Durham, NC	004	2	4	5
Joseph Walker, M.D. National Ophthalmic Research Fort Myers, FL	006	0	1	1
Carl Baker, M.D. Paducah, KY	007	3	4	4
Randy Katz, M.D. Florida Eye Boynton Beach, FL	009	1	2	3
Lawrence Halperin, MD Retina Group of FL Fort Lauderdale, FL	010	2	5	5
G. Baker Hubbard, M.D. Emory Clinic Atlanta, GA	012	3	5	4
Rafael Alemany, MD Barcelona, Spain	013	1	1	2

Peter Pavan, M.D. U. South Florida Eye Inst. Tampa, FL	015	1	4	3
Sami Uwaydat, MD Jones Eye Inst. Little Rock, AZ	017	1	1	2
Jose Ruiz-Moreno, MD Alicante, Spain	018	2	5	5
Andrew Antosyk, M.D. Charlotte EENT Charlotte, NC	019	2	3	4
Jose Iribarren, M.D. Bi bao, Spain	021	0	1	1
Jeffrey Gross, M.D. Carolina Retina Center Columbia, SC	023	1	1	3
V. Narendram, M.D. Aravind Eye Hospital Coimbatore, India	024	7	15	15
Liliaane Durate, M.D. Coimbra, Portugal	027	3	7	6
John Mason III, M.D. Retinal Consultants Birmingham, AL	028	2	5	4
Ugo Menchini, MD Florence, Italy	030	1	3	3
Daniel Alfaro III, M.D. Retina Consultants Charleston, SC	032	1	3	3
Professor Traverso, M.D. Genova, Italy	033	0	2	3
Nazimul Hussain, M.D. L.V. Prasad Eye Inst. Andhra Pradesh, India	034	1	0	0
Clement Chan, M.D. Southern California Desert Retina Palm Desert, CA	035	0	3	1
Baruch Kuppermann, M.D. U. California Irvine Irvine, CA	041	0	0	2
Ravilla Ravindran, M.D. Aravind Eye Hospital Tamil Nadu, India	042	5	11	11
Robert Wang, MD Texas Retina Inst. Dallas, TX	047	0	0	1
Kevin Blinder, MD Barnes Retina Inst. St. Louis, MO	048	1	3	2
Allen Thach, MD Retina Consultants Las Vegas, NV	052	0	0	1
Gisele Soubrane, M.D. Cretel, France	058	0	1	0
Michael Antworth, M.D. Retina Consultants Greenville, SC	060	1	1	2
Richard Chace, M.D. Eyesight Ophthalmic Services Portsmouth NH	062	0	0	1
Steven Sanislo, M.D. California Vitreoretinal Research Center	063	1	2	2

Menlo Park, CA				
Tauran Sharma, MD Bhagwan Mahavir Vitreo Retinal Services Chennai, India	064	3	7	8
Joseph Gunn, M.D. Southeast Retina Associates Kingsport, TN	065	2	6	5
Claire Bailey, M.D. Bristol, United Kingdom	067	0	1	1
Dennis Marcus, M.D. Southeast Retina Center Augusta, GA	068	2	2	5
George Mincey, MD Carolina Eye Associates Southern Pines, NC	069	1	1	0
Yit Yang, M.D. New Cross Hospital Wolverhamptom, UK	070	0	0	1
Michael Tolentino, M.D. Center for Retina and Macular Disease Winter Haven, FL	071	5	10	8
Melvin Chen, M.D. Sarasota Retina Inst. Sarasota, FL	072	0	0	3
Alvaro Fernandez-Vega, MD Oviedo, Spain	073	0	0	1
Himadri Datta, M.D. Medical College Ko kata, India	074	0	1	0
David Brown, M.D. Retinal Consultants Houston, TX	075	5	10	10
Sanford Chen, M.D. Orange County Retina Santa Ana, CA	076	3	6	6
Howard Lazarus, M.D. John-Kenyon American Eye Inst. New Albant, IN	078	1	0	1
Sunil Patel, M.D. Retina Research Abilene, TX	079	3	6	7
Ewa Herba, M.D. Bytom, Poland	080	0	0	1
R. Ramakrishnan, M.D. Aravind Eye Hospital Tamil Nadu, India	082	4	8	7
Stephen Feman, M.D. St. louis Univ. St. Louis, MO	084	1	1	2
Nauman Chaudhry, M.D. New England Retina Associates New London, CT	086	1	2	0
Michael Rauser Loma Linda Loma Linda, CA	087	1	2	2
Michael Varenhorst, M.D. Vitreo-retinal Consultants Wichita, KS	088	0	3	4
Maria Forminsa-Kapuscik,	089	1	2	0

M.D. Katowice, Poland				
Brian Berger, M.D. Retina Research Center Austin, TX	090	2	4	4
Jack Cohen, M.D. Rush U. Medical Center Chicago, IL	091	0	0	1
John Gonder, M.D. Ivey Inst. London, Ontario	092	0	1	2
William Rosenthal, M.D. Mid-America Retina Kansas City, MO	094	2	3	3
Michael Rivers, M.D. Retina Group of Washington Fairfax, VA	095	0	1	1
Victor Gonzalez. M.D. Valley etina Inst. McAllen, TX	098	2	4	1
Mark Levitan, M.D. Austin Retina Austin, TX	100	1	0	3
X. Kathryn Sun, MD St. Joe's Clinic Springfield, MO	102	0	0	1
Vladimir Kozousek, M.D. Capital Health Halifax, Canada	103	0	1	0
Bruce Garretson, M.D. Associated Retinal Consultants Royal Oaks, MI	104	0	1	0
Nelson Sabates, M.D. UMKC Vision Research Center Kansas City, MO	105	0	1	0
John Olson, M.D. Central FL Retina Orlando, FL	106	1	2	2
Steven Bloom, MD Eye Centers of Louisville Louisville, KY	107	2	4	4
Fernando Falcao-Reis, MD Porto, Portugal	109	1	2	1

Reviewer's comments:

No site enrolled a majority of the subjects. Enrollment was dispersed about all the sites.

Secondary Variables

Secondary efficacy variables included mean change from baseline in BCVA, mean change from baseline in the excess average foveal thickness, and the proportion of subjects with ≥ 3-step worsening in the study eye compared to baseline in the ETDRS visual acuity eye chart.

Reviewer's comments:

OCT (measurement of foveal thickness) has not been correlated to visual function. For OCT to be considered as an acceptable endpoint a clinical trial would be required to validate retinal (foveal) thickness to visual function. The applicant has not validated OCT data to visual function; therefore OCT data has not been included in this review.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the treatment of diabetic macular edema.

6.1.1 Methods

The support for efficacy for fluocinolone acetonide intravitreal insert, 0.19 mg comes from two studies, the FAME studies: C-01-005-001 A (FAME A) and C-01-005-001 B (FAME B).

The populations used in the analysis of efficacy in the individual FAME trials are defined below. All primary and secondary efficacy variables were analyzed using the Full Analysis, All Randomized, ITT and PP datasets.

Reviewer's comments:

The applicant uses analysis terms that are slightly different than those defined by the agency. The agency would define the applicant's treatment groups as follows:

Full Analysis = Intent-to-Treat with Last Observation Carried Forward (ITT with LOCF)
All Randomized = All Treated with LOCF
Intent-to-Treat (ITT) = All Treated – Interventions with LOCF
Per-Protocol (PP) = PP observed data only

This review will focus on the agency's defined treatment groups: 1) All Treated with LOCF, and 2) PP observed data only.

Full Analysis (*Intent-to-Treat with Last Observation Carried Forward (ITT with LOCF)*): The Full Analysis dataset included all randomized subjects. The method of last observation carried forward (LOCF) was used to impute values for all missing data.

All Randomized *(All Treated with LOCF)*: The All Randomized dataset included the data from all randomized subjects who received any study drug. The method of LOCF was used to impute values for all missing data.

Intent-to-Treat (ITT) (*All Treated – Interventions with LOCF*): The ITT dataset was created from the All Randomized dataset. Subjects treated with non-laser therapy outside of the protocol which had potential confounding effects on their DME, (e.g., Avastin®, intravitreal triamcinolone, vitrectomy), had all efficacy data collected after the date of treatment set to missing. The method of LOCF was used to impute values for all missing data.

Reviewer's comments:

The applicant's Intent-to-Treat (ITT), which the agency refers to as All Treated – Interventions with LOCF, is not an appropriate analysis. Intervention(s) should be treated as treatment failures.

Per-Protocol (PP) (*PP observed data only)*: The PP dataset included all available data from subjects who followed the protocol without significant deviation. Data were not imputed for missing values. Data excluded from the PP population were determined before database lock and unmasking of the treatment codes, and were assessed per subject or per visit. Potential reasons for the exclusion of subjects included:
• No qualifying DME.
• Administration of non-laser therapy for DR outside of the protocol.
This list is not exhaustive and other reasons were added before unmasking of the treatment codes.

Reviewer's comments:

In study FAME A, All subjects (N=481) were included in the ITT with LOCF population (95, sham; 190, 0.2 µg/day FA; 196, 0.5 µg/day FA), and all but 1 subject was included in the All Treated – Interventions with LOCF, and All Treated with LOCF populations (95, sham; 190, 0.2 µg/day FA; 195, 0.5 µg/day FA).

In study FAME B, All subjects (N=475) were included in the ITT with LOCF population (90, sham; 186, 0.2 µg/day FA; 199, 0.5 µg/day FA), and all but 2 subjects were included in the All Treated – Interventions with LOCF and All Treated with LOCF populations (90, sham; 185, 0.2 µg/day FA; 198, 0.5 µg/day FA).

6.1.2 Demographics

FAME A study (C-01-05-001A) had a total of 481 subjects and FAME B (C-01-05-001B) a total of 475 subjects randomized to sham injection, 0.2 µg/day FA intravitreal insert, or 0.5 µg/day FA intravitreal insert. For the treatment groups studied (sham, 0.2 µg/day FA and 0.5 µg/day FA) the demographics were similar (refer to the following Table).

Demographics by Treatment Group: Integrated FAME Studies

Demographics by Treatment Group: Integrated FAME Studies

Demographics	Treatment Group			
	Sham (N=185)	0.2 µg/day FA (N=375)	0.5 µg/day FA (N=393)	Total (N=953)*
Gender, n (%)				
Male	108 (58.4)	215 (57.3)	243 (61.8)	566 (59.4)
Female	77 (41.6)	160 (42.7)	150 (38.2)	387 (40.6)
Age (yrs)				
Mean (SD)	61.9 (9.6)	63.0 (9.3)	62.2 (9.3)	62.5 (9.4)
Ethnicity, n (%)				
Hispanic or Latino	25 (13.5)	36 (9.6)	47 (12.0)	108 (11.3)
Not Hispanic or Latino	160 (86.5)	339 (90.4)	346 (88.0)	845 (88.7)
Race, n (%)				
White	132 (71.4)	264 (70.4)	269 (68.4)	665 (69.8)
Black/African American	11 (5.9)	22 (5.9)	32 (8.1)	65 (6.8)
Asian	40 (21.6)	85 (22.7)	87 (22.1)	212 (22.2)
American Indian/ Alaskan Native	0	1 (0.3)	0	1 (0.1)
Other	2 (1.1)	3 (0.8)	5 (1.3)	10 (1.0)
Iris Color, n (%)				
Black	10 (5.4)	25 (6.7)	26 (6.6)	61 (6.4)
Brown	97 (52.4)	194 (51.7)	200 (50.9)	491 (51.5)
Hazel	24 (13.0)	39 (10.4)	45 (11.5)	108 (11.3)
Green	9 (4.9)	18 (4.8)	21 (5.3)	48 (5.0)
Blue	39 (21.1)	88 (23.5)	88 (22.4)	215 (22.6)
Gray	5 (2.7)	9 (2.4)	11 (2.8)	25 (2.6)
Other	1 (0.5)	2 (0.5)	2 (0.5)	5 (0.5)
General Iris Color, n (%)				
Light	77 (41.6)	154 (41.1)	165 (42.0)	396 (41.6)
Dark	107 (57.8)	219 (58.4)	226 (57.5)	552 (57.9)
Other/Missing	1 (0.5)	2 (0.5)	2 (0.5)	5 (0.5)

* 3 subjects were randomized but not treated and are not included in the above.

Overall, most of the subjects were White (70%) and non-Hispanic/Latino in origin (89%). More than half of the subjects were male (59%). Mean age was 62.5 years. The most common iris colors were brown (52%) and blue (23%). Race and ethnicity were well balanced among the treatment groups; however, the representation of blacks was relatively small (7%). The distribution of iris colors was also balanced between the groups, with the majority having dark irides (58%).

Reviewer's comments:

Age, gender, race and iris color had nearly equal distribution across all treatment groups.

6.1.3 Subject Disposition

Patient Discontinuations from C-01-05-001A

Patient ID #	Treatment	Reason for Discontinuation
100307	Sham	Subject withdrew consent
100808	Sham	Subject withdrew consent – hip fracture
101614	Sham	Lost to follow-up
101628	Sham	Death – renal failure
101638	Sham	Death – multiple organ failure
104402	Sham	Death – bladder cancer
104502	Sham	Death -internal bleeding
104906	Sham	Death - CVA
104913	Sham	Dementia – unable to examine
105003	Sham	Lost to follow-up – unable to contact
105106	Sham	Left town without contact information
105501	Sham	Subject withdrew consent – not satisfied with therapeutic effect
105602	Sham	Lost to follow-up
107803	Sham	Lost to follow-up
108603	Sham	Lost to follow-up
108902	Sham	Subject withdrew consent
109404	Sham	Subject withdrew consent – site closed, did not want to transfer
109407	Sham	Subject withdrew consent - site closed, did not want to transfer
100301	0.2 µg/day	Subject withdrew consent
100312	0.2 µg/day	Subject withdrew consent
100315	0.2 µg/day	Subject withdrew consent
100317	0.2 µg/day	Lost to follow-up
100803	0.2 µg/day	Subject withdrew consent – after vitrectomy refused to continue study
101405	0.2 µg/day	Subject withdrew consent – after diagnosed with terminal cancer

101602	0.2 µg/day	Death – renal failure
101634	0.2 µg/day	Adverse event - endopthalmitis
102215	0.2 µg/day	Lost to follow-up – does not respond to calls
102502	0.2 µg/day	Lost to follow-up
102613	0.2 µg/day	Subject withdrew consent
103804	0.2 µg/day	Death - sepsis
104605	0.2 µg/day	Death – cardiogenic shock
104608	0.2 µg/day	Subject withdrew consent
104615	0.2 µg/day	Subject withdrew consent
104902	0.2 µg/day	Subject withdrew consent
105018	0.2 µg/day	Subject withdrew consent – moved out of state
105505	0.2 µg/day	Lost to follow-up
105632	0.2 µg/day	Death – cardiac arrest
105645	0.2 µg/day	Adverse event
105702	0.2 µg/day	Subject withdrew consent
105801	0.2 µg/day	Withdrawn by investigator due to patient's medical condition
106706	0.2 µg/day	Death – cardiac failure
107404	0.2 µg/day	Death – cardiorespiratory failure
108602	0.2 µg/day	Lost to follow-up – admitted to long term care facility
108606	0.2 µg/day	Death – septic arthritis
108906	0.2 µg/day	Subject withdrew consent
108909	0.2 µg/day	Subject withdrew consent
109203	0.2 µg/day	Lost to follow-up – moved out of area
109403	0.2 µg/day	Lost to follow-up – did not respond to calls or letters
109408	0.2 µg/day	Subject withdrew consent - site closed, did not want to transfer
109410	0.2 µg/day	Subject withdrew consent - site closed, did not want to transfer
109405	0.2 µg/day	Death – ischemic cardiomyopathy
110304	0.2 µg/day	Death – liver cancer
110407	0.2 µg/day	Death – cardiac arrhythmia
110504	0.2 µg/day	Subject withdrew consent due to transportation issues
100305	0.5 µg/day	Subject withdrew consent
100310	0.5 µg/day	Lost to follow-up
100313	0.5 µg/day	Adverse event
100320	0.5 µg/day	Subject withdrew consent
100809	0.5 µg/day	Death - MI
101605	0.5 µg/day	Death - MI
101612	0.5 µg/day	Death – multiple organ failure
101620	0.5 µg/day	Lost to follow-up
101629	0.5 µg/day	Death – bone cancer
101630	0.5 µg/day	Death – lung infection
102203	0.5 µg/day	Subject withdrew consent – no

		longer wanted to participate
102206	0.5 µg/day	Adverse event
102218	0.5 µg/day	Subject withdrew consent – transportation problems
102221	0.5 µg/day	Adverse event – developed glaucoma, surgery, investigator withdrew from study
102503	0.5 µg/day	Adverse event
102605	0.5 µg/day	Adverse event – SAE amputation subject in rehab
103101	0.5 µg/day	Lost to follow-up
103608	0.5 µg/day	Death – lung cancer
104604	0.5 µg/day	Death - suicide
104901	0.5 µg/day	Death - gangrene
104903	0.5 µg/day	Death – insulin reaction
104917	0.5 µg/day	Adverse event
104921	0.5 µg/day	Adverse event – dense cataract
105001	0.5 µg/day	Lost to follow-up – patient went elsewhere care
105004	0.5 µg/day	Lost to follow-up – moved out of state
105009	0.5 µg/day	Subject withdrew consent – too ill to come in for exams
105101	0.5 µg/day	Protocol violation – unable to sign informed consent due to mental incapacity
105102	0.5 µg/day	Protocol violation – vitrectomy implant removed
105606	0.5 µg/day	Lost to follow-up
105618	0.5 µg/day	Death - MI
105633	0.5 µg/day	Death - MI
106210	0.5 µg/day	Death – renal failure
106702	0.5 µg/day	Subject withdrew consent
107001	0.5 µg/day	Unsatisfied with therapeutic effect
107805	0.5 µg/day	Death – acute mesenteric ischemia
108001	0.5 µg/day	Death – respiratory / circulatory insufficiency
109101	0.5 µg/day	Subject withdrew consent
109214	0.5 µg/day	Adverse event – concomitant illnesses – not able to complete follow-up
109217	0.5 µg/day	Subject withdrew consent
109402	0.5 µg/day	Subject withdrew consent – site closed, did not want to transfer
109405	0.5 µg/day	Subject withdrew consent – site closed, did not want to transfer
109406	0.5 µg/day	Adverse event – related to secondary open angle closure
109502	0.5 µg/day	Tractional retinal detachment

	0.5 µg/day	
	0.5 µg/day	

Patient Discontinuations from C-01-05-001B

Patient ID #	Treatment	Reason for Discontinuation
100106	Sham	Subject withdrew consent – transportation problems
100110	Sham	Adverse event - MI
100114	Sham	Lost to follow-up – not compliant with fool-up visits
100210	Sham	Lost to follow-up
100904	Sham	Unsatisfactory therapeutic effect
101007	Sham	Lost to follow-up
101205	Sham	Death – diabetic coma
101902	Sham	Death - unknown
102404	Sham	Adverse event
102705	Sham	Lost to follow-up
102710	Sham	Subject withdrew consent
103205	Sham	Subject withdrew consent
103401	Sham	Lost to follow-up – poor systemic health
106411	Sham	Lost to follow-up – poor health, had CABG
106808	Sham	Subject withdrew consent
107103	Sham	Lost to follow-up
107116	Sham	Lost to follow-up
107119	Sham	Lost to follow-up
109002	Sham	Subject withdrew consent - relocated
109010	Sham	Subject withdrew consent - Unsatisfactory therapeutic effect
109606	Sham	Subject withdrew consent
109801	Sham	Lost to follow-up
110002	Sham	Lost to follow-up – no response to certified letter
110604	Sham	Subject withdrew consent – subject felt study drug not working
100102	0.2 µg/day	Lost to follow-up
100115	0.2 µg/day	Death – intracranial hemorrhage
100203	0.2 µg/day	Lost to follow-up
100215	0.2 µg/day	Subject withdrew consent – travel became difficult
100403	0.2 µg/day	Adverse event
100404	0.2 µg/day	Subject withdrew consent – kidney failure, relocated
100701	0.2 µg/day	Lost to follow-up
100710	0.2 µg/day	Death - MI
101001	0.2 µg/day	Lost to follow-up
101003	0.2 µg/day	Lost to follow-up
101011	0.2 µg/day	Lost to follow-up

101903	0.2 µg/day	Lost to follow-up
101907	0.2 µg/day	Death – ovarian cancer
101908	0.2 µg/day	Death - MI
102402	0.2 µg/day	Death - MI
102801	0.2 µg/day	Death – multiple myeloma
103302	0.2 µg/day	Lost to follow-up
103502	0.2 µg/day	Lost to follow-up
104217	0.2 µg/day	Death – renal failure
106302	0.2 µg/day	Subject withdrew consent
106401	0.2 µg/day	Death - MI
106405	0.2 µg/day	Death – end stage kidney disease
106407	0.2 µg/day	Death - MI
106501	0.2 µg/day	Lost to follow-up
106507	0.2 µg/day	Lost to follow-up
106805	0.2 µg/day	Lost to follow-up
107106	0.2 µg/day	Death - MI
107120	0.2 µg/day	Subject withdrew consent – transportation problems
107124	0.2 µg/day	Death - CHF
107512	0.2 µg/day	Subject withdrew consent
107604	0.2 µg/day	Subject withdrew consent
107614	0.2 µg/day	Subject withdrew consent
107912	0.2 µg/day	Lost to follow-up
108219	0.2 µg/day	Death - MI
108806	0.2 µg/day	Subject withdrew consent
109001	0.2 µg/day	Lost to follow-up – lost all contact with subject
109604	0.2 µg/day	Death – end stage renal disease due to diabetes
109805	0.2 µg/day	Subject withdrew consent – distance to travel became a burden
109807	0.2 µg/day	Adverse event – developed severe back pain
100214	0.5 µg/day	Subject withdrew consent – severe problems with non-study eye, difficult to travel
100601	0.5 µg/day	Protocol violation – treatment incomplete, problem with device
101009	0.5 µg/day	Lost to follow-up
101502	0.5 µg/day	Subject withdrew consent – does not want to continue
102102	0.5 µg/day	Death – stomach cancer
102301	0.5 µg/day	Death - MI
102302	0.5 µg/day	Lost to follow-up
102409	0.5 µg/day	Lost to follow-up
102418	0.5 µg/day	Death - MI
102423	0.5 µg/day	Death - MI
102427	0.5 µg/day	Lost to follow-up
102702	0.5 µg/day	Adverse events - Alzheimer

104101	0.5 µg/day	Subject withdrew consent
104102	0.5 µg/day	Subject withdrew consent
104212	0.5 µg/day	Death – neurological problem
104215	0.5 µg/day	Lost to follow-up
106004	0.5 µg/day	Death - MI
106406	0.5 µg/day	Death - CVA
106408	0.5 µg/day	Subject withdrew consent
107110	0.5 µg/day	Lost to follow-up
107518	0.5 µg/day	Subject withdrew consent - Unsatisfactory therapeutic effect
107611	0.5 µg/day	Subject withdrew consent
107901	0.5 µg/day	Death – CAD / diabetes
107911	0.5 µg/day	Lost to follow-up
108401	0.5 µg/day	Lost to follow-up – unable to contact family
109007	0.5 µg/day	Subject withdrew consent - relocated, no study site available
109008	0.5 µg/day	Lost to follow-up – subject not compliant
109607	0.5 µg/day	Death – respiratory failure
110001	0.5 µg/day	Subject withdrew consent
110003	0.5 µg/day	Subject withdrew consent
110004	0.5 µg/day	Subject withdrew consent
110603	0.5 µg/day	Lost to follow-up, subject non-compliant with visits

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was for either dose (0.2 µg/day or 0.5 µg/day) of FA intravitreal insert to be superior to the control (sham) group with respect to the proportion of subjects with a ≥ 15-letter increase in best corrected visual acuity (BCVA) on the ETDRS eye chart at Month 24 compared to baseline.

The applicant is seeking the approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

To address the problem of multiple comparisons at the 24 month time period of analysis the Bonferroni method was applied with adjustments made for DSMB (Data Safety Monitoring Board) looks.

Reviewer's comments:

Statistically significant differences in the percentage of patients at three years with a three step (≥ 15 letters or more) change in the Early Treatment for Diabetic Retinopathy Study (ETDRS) retinopathy scale is recommended.

Alternatively, a two time point comparisons with "wins" on both comparisons might be considered for a demonstration of efficacy. The first comparison is recommended to be between the original baseline and a time point that is at 24 months or longer. It is recommended that a clinically and statistically superior difference be demonstrated between the selected timepoint and the original baseline. The second comparison is recommended to be between the 18 month time point and the time point at 24 months or longer; this comparison is recommended to be numerically noninferior using the 18 month time point as a baseline.

Two Point Comparison at 18 and 24 Months

FAME A

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Months 18 and 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 18						(b) (4)
Difference (95% CI)[1]						
P-value[2]						
Month 24	95	14 (14.7)	190	51 (26.8)		(b) (4)
Difference (95% CI)[1]			-12.1 (-21.6, -2.6)			
P-value[2]			0.029			
Per Protocol Population (observed data only)						
Month 18						(b) (4)
Difference (95% CI)[1]						
P-value[2]						
Month 24	46	7 (15.2)	112	33 (29.5)		(b) (4)
Difference (95% CI)[1]			-14.2 (-27.6, -0.9)			
P-value[2]			0.112			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

FAME B
Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Months 18 and 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 18	(b) (4)					
Difference (95% CI)[1]						
P-value[2]						
Month 24	90	16 (17.8)	185	57 (30.8)	(b) (4)	
Difference (95% CI)[1]			-13.0 (-23.4, -2.7)			
P-value[2]			0.028			
Per Protocol Population (observed data only)						
Month 18	(b) (4)					
Difference (95% CI)[1]						
P-value[2]						
Month 24	40	6 (15.0)	125	45 (36.0)	(b) (4)	
Difference (95% CI)[1]			-21.0 (-34.9, -7.1)			
P-value[2]			0.023			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

Reviewer's comments:

In studies FAME A and B when comparing ≥ 15-letter Increase from Baseline in BCVA at 18 and 24 months for both doses of FA the trend for BCVA demonstrates improvement of visual acuity with time. Given this improvement in visual acuity between these two time points, data at 24 months is acceptable for the Primary Efficacy Analysis.

Primary Efficacy Endpoints

Primary Efficacy at 24 Months

FAME A

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 24	95	14 (14.7)	190	51 (26.8)	[redacted]	(b) (4)
Difference (95% CI)[1]			-12.1 (-21.6, -2.6)			
P-value[2]			0.029			
Per Protocol Population (observed data only)						
Month 24	46	7 (15.2)	112	33 (29.5)		
Difference (95% CI)[1]			-14.2 (-27.6, -0.9)			
P-value[2]			0.112			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

For the All Treated with LOCF, the difference between the 0.2 µg/day FA group and the sham group was −12.1% (95% CI: −21.6%, −2.6%; p= (b) (4) [redacted] Based on the PP observed data only, the 0.2 µg/day FA group (p=0.112) was not statistically significantly different from the sham group.

FAME B

Number (%) of Subjects with a ≥ 15-letter Increase from Baseline in BCVA in the Study Eye at Month 24 by Treatment Group

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
All Treated with LOCF						
Month 24	90	16 (17.8)	185	57 (30.8)	[redacted]	(b) (4)
Difference (95% CI)[1]			-13.0 (-23.4, -2.7)			
P-value[2]			0.028			
Per Protocol Population (observed data only)						
Month 24	40	6 (15.0)	125	45 (36.0)		
Difference (95% CI)[1]			-21.0 (-34.9, -7.1)			
P-value[2]			0.023			

1 Difference is the sham minus the active. A negative value denotes a higher percentage of subjects in the active group who showed improvemnet in BCVA
2 P-value is based on Fischer's exact test.

For the All Treated with LOCF and PP observed data only at Month 24 statistical significance was demonstrated for both treatment groups.

Reviewer's comments:

The main difference between FAME A and FAME B studies was the lack of a statistically significant treatment effect observed in FAME A for the PP observed data only populations. The results from the PP observed data only are likely confounded by cataract formation during the 24 month period which resulted in the PP observed data only population failing the primary endpoint, p = 0.112.

FAME A is considered a failed trial due to the PP observed data only having a p value > 0.05 at 24 months (p = 0.112). Additionally, 18 month data for Fame A failed the test of a p value of 0.05 or better. For the All Treated with LOCF and PP observed data only groups the p values were 0.466 and 0.941, respectively, (Refer to Two Point Comparison data at 18 and 24 months in this section). The overall results at 18 and 24 months do not provide additional support for Fame A being a successful clinical trial.

At least two replicated trials are recommended to demonstrate robustness of the results for this indication. The applicant did not demonstrate success in two replicated trials.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy variables included mean change from baseline in BCVA, mean change from baseline in the excess average foveal thickness, and the proportion of subjects with ≥ 3-step worsening in the study eye compared to baseline in the ETDRS visual acuity eye chart.

Reviewer's comments:

OCT (measurement of foveal thickness) has not been correlated to visual function. For OCT to be considered as an acceptable endpoint a clinical trial would be required to validate retinal (foveal) thickness to visual function. Therefore, OCT results are not presented in this review.

For the Secondary endpoints this review contains only data from the Intent-to-Treat with Last Observation carried Forward (ITT with LOCF) and Per Protocol observed data only.

FAME A

Mean Change from Baseline in BCVA Letter Score in the Study Eye at Months 18 and 24 by Treatment Group

Visit	Treatment Group		
	Sham	0.2 µg/day FA	0.5 µg/day FA
ITT with LOCF			
Baseline			
N	95	190	(b) (4)
Mean (SD)	54.8 (11.36)	53.4 (13.00)	
Month 18			
Mean Change (SD)			(b) (4)
Difference (95% CI)			
p-value			
Month 24			
Mean Change (SD)	3.2 (13.07)	3.7 (18.4)	(b) (4)
Difference (95% CI)		-1.8 (-6.3, 2.8)	
p-value		0.444	
Per Protocol Population (observed data only)			
Baseline			
N	91	180	(b) (4)
Mean (SD)	54.5 (11.50)	53.0 (13.06)	
Month 18			
N			(b) (4)
Mean Change (SD)			
Difference (95% CI)			
p-value			
Month 24			
N	46	112	(b) (4)
Mean Change (SD)	5.0 (12.59)	6.5 (18.14)	
Difference (95% CI)		-0.9 (-7.0, 5.1)	
p-value		0.758	

Note: The between-treatment difference, 95% CI, and P-value are based on an analysis of variance model with treatment and baseline VA strata as fixed effects.

In the ITT with LOCF population, mean BCVA letter scores in the study eye were comparable among treatment groups at baseline (54.8, sham; 53.4, 0.2 µg/day FA; (b) (4)). Mean increases from baseline in BCVA letter scores were observed in each treatment group through Month 24. These mean increases were relatively small and ranged from 1.5 to 3.2 letters in the sham group, from 1.3 to 6.2 letters in the 0.2 µg/day FA group (b) (4) At most of the evaluations through Month 24, mean increases from baseline in BCVA letter scores were greater in each active treatment group compared with the sham group. Notable treatment differences were generally observed during the first 6 months of the study in favor of the 2 active treatment groups over the sham group, but these differences were not maintained at later time points (including Month (b) (4) 24).

Similar trends were observed in the PP observed data only population.

FAME B

Mean Change from Baseline in BCVA Letter Score in the Study Eye at Months 18 and 24 by Treatment Group

Visit	Treatment Group		
	Sham	0.2 µg/day FA	0.5 µg/day FA
ITT with LOCF			
Baseline			
N	90	186	(b) (4)
Mean (SD)	54.7 (11.23)	53.3 (12.39)	
Month 18			
Mean Change (SD)			(b) (4)
Difference (95% CI)			
p-value			
Month 24			
Mean Change (SD)	0.0 (15.62)	5.1 (17.95)	(b) (4)
Difference (95% CI)		-16.1 (-10.8, -1.4)	
p-value		0.011	
Per Protocol Population (observed data only)			
Baseline			
N	83	170	(b) (4)
Mean (SD)	54.7 (11.15)	53.4 (12.31)	
Month 18			
N	51	131	140
Mean Change (SD)			(b) (4)
Difference (95% CI)			
p-value			
Month 24			
N	40	125	(b) (4)
Mean Change (SD)	3.2 (12.66)	6.9 (18.71)	
Difference (95% CI)		-4.5 (-11.5, 2.4)	
p-value		0.200	

Note: The between-treatment difference, 95% CI, and P-value are based on an analysis of variance model with treatment and baseline VA strata as fixed effects.

In the ITT with LOCF population, mean BCVA letter scores in the study eye were comparable among treatment groups at baseline (54.7, sham; 53.3, 0.2 µg/day FA; (b) (4)). Mean increases from baseline in BCVA letter scores were observed in each active treatment group through Month 24. Mean increases from baseline in BCVA letter scores were greater in each active treatment group compared with the sham group at each time point.

Similar trends were observed in the PP observed data only population.

Reviewer's comments:

For the recommended treatment dose of 0.2 µg/day FA at 24 months for the Mean Change in BCVA from baseline in study Fame A, statistical significance was not demonstrated for either the ITT with LOCF Population or the Per Protocol observed data only Population with p-values of 0.444 and 0.758, respectively.

For the recommended treatment dose of 0.2 µg/day FA at 24 months for the Mean Change in BCVA from baseline in study Fame B, statistical significance was not demonstrated for the Per Protocol observed data only Population with a p-value of 0.20.

It should be noted that the Mean Change in BCVA from baseline obtained in both studies was relatively small. In Fame A these mean increases ranged from 1.5 to 3.2 letters in the sham group and from 1.3 to 6.2 letters in the 0.2 µg/day FA group. In Fame B these mean increases ranged from -0.7 to 2.5 letters in the sham group and from 3.1 to 6.6 letters in the 0.2 µg/day FA group.

6.1.6 Other Endpoints

There were numerous exploratory variables related to BCVA; ETDRS multi-step eye scale of diabetic retinopathy photographs; fluorescein angiography; contrast sensitivity; use of laser therapy and disallowed treatments; and retreatment. Health-Related Quality of Life (HRQOL): HRQOL was assessed using the 25-item vision function questionnaire (VFQ-25) or the VFQ-39 (at selected sites).

6.1.7 Subpopulations

Reviewer's comments:

An analysis of the impact of cataract formation and cataract extraction for subjects phakic at baseline will be provided in Section 6.1.10 Additional Efficacy Issues / Analyses.

Section 6.1.10 will also provide an analysis for pseudo-phakic subjects at baseline.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 µg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

Reviewer's comments:

This review concentrates on the risk(s) versus the benefit of the low dose drug product, the 0.2 µg/day fluocinolone acetonide (FA) intravitreal insert (0.19 mg).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Safety and efficacy data is presented out to 24 months with the trial continuing out to 36 months.

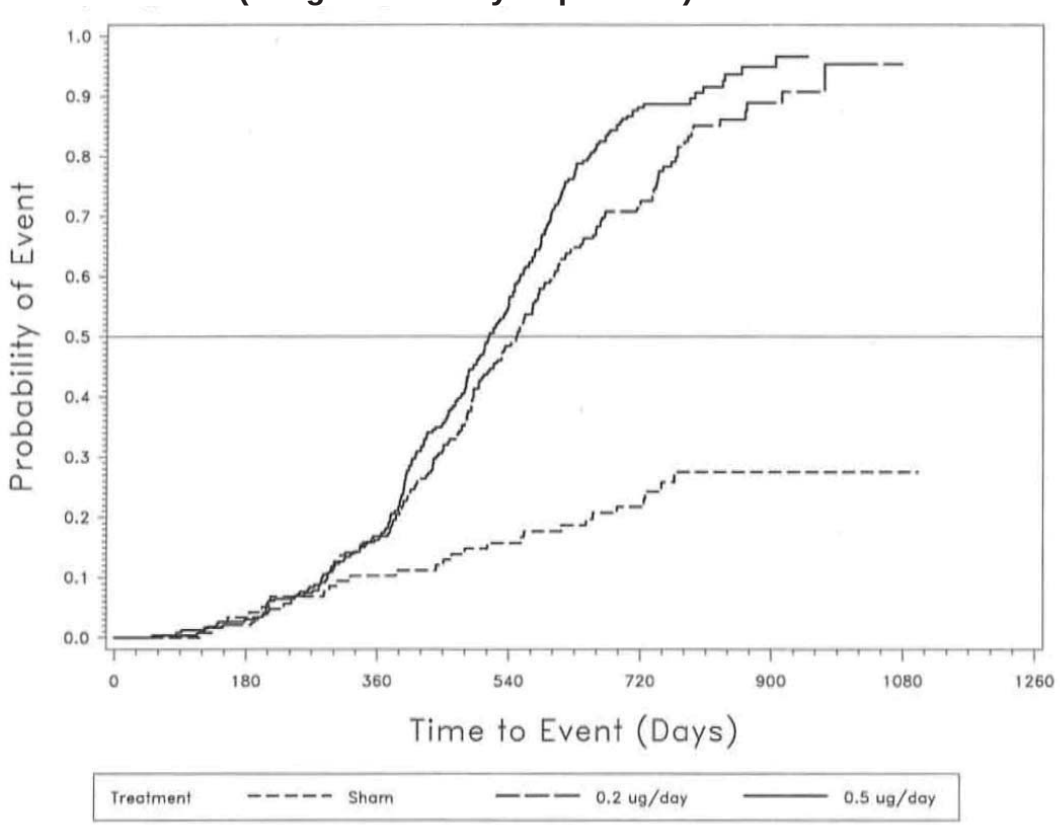
Reviewer's comments:

The majority of data submitted in this review was to 24 months.

6.1.10 Additional Efficacy Issues/Analyses

An Integrated Analysis (combined data from FAME A and FAME B studies) for cataract formation / extraction and effect on vision is presented below:

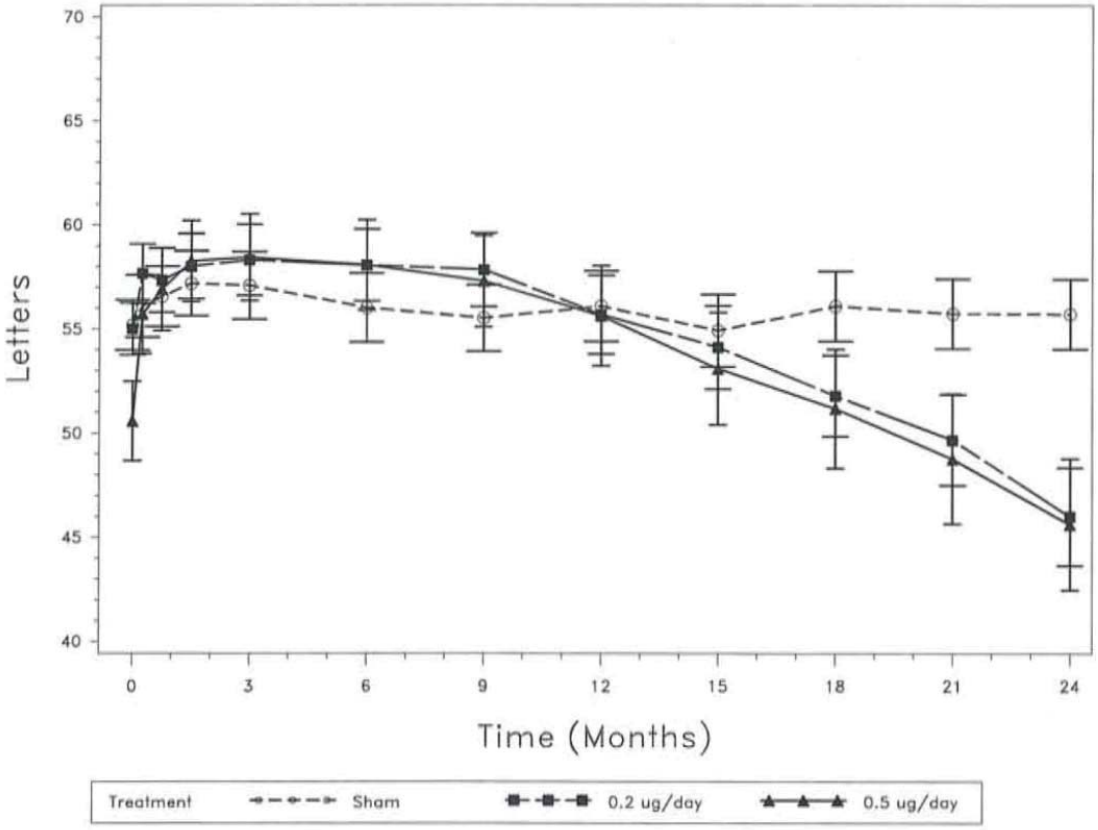
Time to Cataract Extraction in Phakic Subjects by Treatment Group (Integrated Safety Population)*



* Data combined for Fame A and B studies

Phakic at Baseline

Mean Best Corrected Visual Acuity Letter Score for Phakic Subjects by Treatment Group (Integrated Analysis for ITT with LOCF Population)*



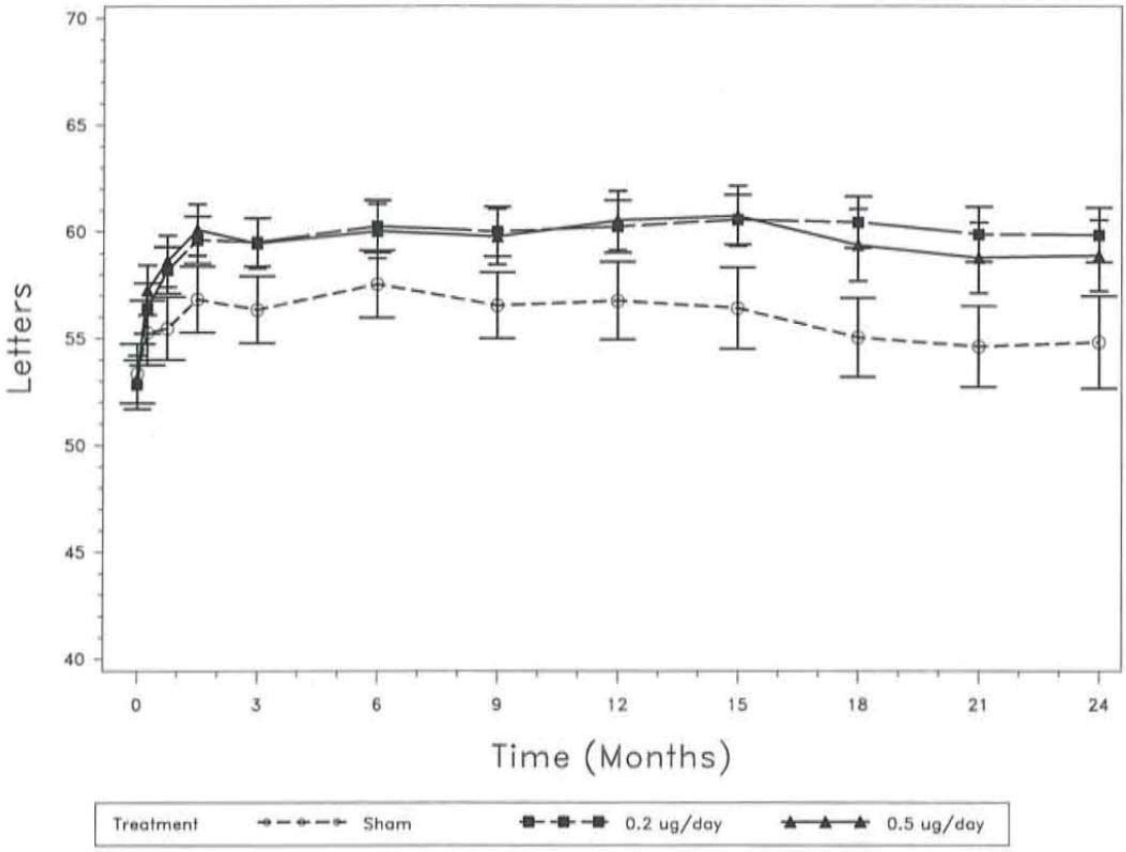
*** Data combined for Fame A and B studies**

Reviewer's comments:

From the above two graphs by 24 months nearly all subjects have developed a cataract and have had cataract extraction. The effect on visual acuity is noted by the decrease in Mean Best Corrected Visual Acuity at 24 months for the 0.2 µg/day and 0.5 µg/day dose, while little change occurs within the sham group.

Comparison to Pseudophakic at Baseline

Mean Best Corrected Visual Acuity Letter Score for Pseudophakic Subjects by Treatment Group (Integrated Analysis for ITT with LOCF Population)*



*** Data combined for Fame A and B studies**

Reviewer's comments:

For pseudophakic subjects through Month 24 by treatment group there were Mean increases from baseline in BCVA letter scores observed in each treatment group within the first few months, being greater in the active treatment groups compared with the sham group. Thereafter, the mean letter scores remained relatively stable in each group.

By 24 months cataract formation and subsequent cataract extraction are likely to be confounding the visual acuity results, especially by the 18 and 24 month time period.

It is recommended that 36 month follow up data be submitted given the confounding effects of cataract formation and subsequent cataract extraction on visual acuity results.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The results from two Fame studies (Fame A and FAME B) form the basis for the safety evaluation. The 2 FAME studies were performed under one protocol and enrolled subjects during the same time period. The only significant difference between the studies was geographical location of the study sites. FAME A was conducted at 49 sites in 7 countries (US, Canada, 4 countries in the European Union [EU], and India). FAME B was conducted at 52 sites in 5 countries (US, India, and 3 countries in the EU). When the 2 studies enrolled subjects in the same countries, FAME A enrolled subjects in the northern portions of the countries involved, and FAME B enrolled subjects in the southern portions of the countries. The demographics of the 2 study populations were essentially the same.

A total of 956 subjects were randomized into the 2 FAME studies with 1 to 47 subjects per site. One hundred and eighty-five subjects were randomized into the sham group and 771 subjects were randomized to active treatment (376, 0.2 µg/day FA; 395 0.5 µg/day FA). Of these, 3 subjects (1, 0.2 µg/day FA; 2, 0.5 µg/day FA) withdrew from the study before the investigator was able to place the insert into the subject's eye. Therefore, these subjects were randomized but not treated. These subjects are not included in the Safety Population for a total of 953 subjects.

7.1.2 Categorization of Adverse Events

The adverse events were categorized into systemic and local (ocular) events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data from the fame A and B studies is pooled into the Integrated Safety Analysis Population which is divided by treatment groups: sham versus 0.2 µg/day FA versus 0.5 µg/day FA.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

**Exposure in Study Treatments:
Integrated Fame A and B Studies (Total n = 953)**

Study Treatments	Sham (N=185)	0.2 µg/day FA (N=375)	0.5 µg/day FA (N=393)
Number of Treatments Completed			
Number of Treatments	240	472	505
Number of Subjects Receiving at Least 1 Treatment	185	375	393
Mean (SD)	1.3 (0.6)	1.3 (0.5)	1.3 (0.5)
Median	1.0	1.0	1.0
Minimum, Maximum	(1.0, 4.0)	(1.0, 4.0)	(1.0, 4.0)
Number of Treatments Completed by Frequency, n (%)			
1 Treatment	141 (76.2)	287 (76.5)	293 (74.6)
2 Treatment	36 (19.5)	80 (21.3)	89 (22.6)
3 Treatment	5 (2.7)	7 (1.9)	10 (2.5)
4 Treatment	3 (1.6)	1 (0.3)	1 (0.3)
Time on Study	**N (%)**	**N (%)**	**N (%)**
Month 6	183 (98.6)	367 (97.9)	391 (98.7)
Month 9	178 (96.2)	365 (97.3)	383 (97.5)
Month 12	178 (96.2)	354 (94.4)	378 (96.2)
Month 18	165 (89.2)	333 (88.8)	358 (91.1)
Month 24	150 (81.1)	310 (82.7)	318 (80.9)
Month 30	66 (35.7)	130 (34.7)	148 (37.7)

A total of 953 subjects (185, sham; 375, 0.2 µg/day; 393, 0.5 µg/day) received at least 1 study treatment during the FAME studies. The total number of treatments administered during the studies was 240, 472, and 393 in the sham, 0.2 µg/day, and 0.5 µg/day, respectively. The mean number of treatments administered was 1.3 for all 3 treatment groups.

In the sham group, 76% of subjects received 1 sham treatment, 20% received 2 treatments, 3% received 3 treatments, and 2% received 4 treatments. The 0.2 µg/day, and 0.5 µg/day groups received very similar numbers of intravitreal inserts (1 insert: 77% and 75%, 2 inserts: 21% and 23%, 3 inserts: 2% and 3%, and 4 inserts: <1% and <1%, respectively). As defined in the study protocol, no subjects received a second study treatment prior to the Month 12 visit.

Almost all subjects had time on study through Month 12 (96%, sham; 94% 0.2 µg/day; 96% 0.5 µg/day) and at Month 24 81%, 83%, and 81% in the sham, 0.2 µg/day and 0.5 µg/day FA groups, respectively.

Reviewer's comments:

The Fame A and B studies provide adequate exposure to assess the safety profile of this drug.

7.2.2 Explorations for Dose Response

The 0.2 µg/day and 0.5 µg/day FA groups were studied with 24 month data submitted. The FA insert is estimated to release drug into the vitreous for 24 months for the 0.5 µg/day dose and up to 30 months for the 0.2 µg/day dose.

7.2.3 Special Animal and/or In Vitro Testing

Fluocinolone acetonide was not genotoxic *in vitro* in the Ames test (*S. typhimurium* and *E. coli*) and the mouse lymphoma TK assay, or *in vivo* in the mouse bone marrow micronucleus assay.

7.2.4 Routine Clinical Testing

In a human pharmacokinetic study fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all time points from Day 1 through Month 18 indicating negligible systemic exposure. The maximal aqueous humor fluocinolone acetonide concentrations were observed on Day 7 for most of the subjects. Aqueous humor fluocinolone acetonide concentrations decreased over the first 3 − 6 months and remained essentially the same through Month 18 for subjects who were not retreated. Subjects who were retreated experienced a second fluocinolone acetonide peak concentration similar to that following the initial dose. After retreatment, aqueous humor concentrations of fluocinolone acetonide returned to levels approximately similar to those observed at the time of first treatment.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Section 7.2.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety and efficacy seen with this product are class effects related to ophthalmic steroids.

Use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the nerves, and may enhance the establishment of secondary ocular

infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

7.3 Major Safety Results

7.3.1 Deaths

Summary of Deaths by Treatment Group: Integrated Studies Fame A and B

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Acute left ventricular failure	0	1 (0.3)	0
Arthritis bacterial	0	1 (0.3)	0
Bone neoplasm malignant	0	0	1 (0.3)
Cardiac arrest	0	4 (1.1)	2 (0.5)
Cardiac failure	1 (0.5)	2 (0.5)	0
Cardiac failure congestive	0	1 (0.3)	0
Cardiopulmonary failure	0	1 (0.3)	0
Cerebrovascular accident	1 (0.5)	0	0
Completed suicide	0	0	1 (0.3)
Coronary artery disease	0	0	1 (0.3)
Death	1 (0.5)	0	0
Diabetic coma	1 (0.5)	0	0
Gangrene	0	0	1 (0.3)
Haemorrhage	1 (0.5)	0	0
Haemorrhage intracranial	0	1 (0.3)	0
Hepatic neoplasm malignant	0	1 (0.3)	0
Intestinal ischaemia	0	0	1 (0.3)
Ischaemic cardiomyopathy	0	1 (0.3)	0
Lung infection	0	0	1 (0.3)
Lung neoplasm malignant	0	0	1 (0.3)
Metastatic carcinoma of the bladder	1 (0.5)	0	0
Multi-organ failure	1 (0.5)	0	1 (0.3)
Multiple myeloma	0	1 (0.3)	0
Myocardial infarction	0	2 (0.5)	6 (1.5)
Neoplasm malignant	0	0	1 (0.3)

Neurological symptom	0	0	1 (0.3)
Ovarian cancer	0	1 (0.3)	0
Renal failure	1 (0.5)	2 (0.5)	1 (0.3)
Renal failure chronic	0	3 (0.8)	0
Respiratory failure	0	0	2 (0.5)
Sepsis	0	1 (0.3)	1 (0.3)
Shock hypoglycaemic	0	0	1 (0.3)
Small cell carcinoma	0	1 (0.3)	0
Sudden cardiac death	0	1 (0.3)	0

A total of 56 (6%) deaths occurred during the study period. Based on a sample size of 953 subjects and a Pearson's chi-square test, the difference in the proportion of subjects who died was not statistically significant between sham and low dose (p=0.2053), nor between sham and high dose (p=0.3014).

The most common outcome of death were cardiac disorders (22 subjects), neoplasms benign, malignant and unspecified including cysts and polyps (8 subjects), renal and urinary disorders (7 subjects), and infections and infestations (5 subjects). No deaths were attributed to the study drug.

Reviewer's comments:

The number of deaths is consistent with the population being studied and the studies' time frame. The subjects have a history of diabetes, a mean age of approximately 62, and the clinical trial is over two years. Narrative summaries of the deaths were submitted and are consistent with the causes of death listed.

7.3.2 Nonfatal Serious Adverse Events

Given that the subjects in the Fame A and B studies were diabetics, a high rate of systemic Adverse Events related to diabetes was expected. Adverse Events are listed in the Tables below for Systemic AE's in ≥ 3% and for Serious Ocular Adverse Events occurring in ≥ 1%.

Common (≥ 3%) Serious Systemic Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Cardiac failure congestive	6 (3.2%)	10 (2.7%)	14 (3.6%)
Myocardial Infarction	2 (1.1%)	15 (4.0%)	11 (2.8%)

Common (≥ 1%) Serious Ocular Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Glaucoma or open angle glaucoma[1]	2 (1.1)	10 (2.7)	13 (3.3)
Retinal detachment	3 (1.6)	2 (0.5)	5 (1.0)
Vitreous Haemorrhage	5 (2.7)	8 (2.1)	8 (2.0)
Intraocular pressure increased	0	12 (3.2)	17 (4.3)
Cataract operation	28 (15.1)	177 (47.2)	224 (57.0)
Glaucoma surgery	1 (0.5)	6 (1.6)	5 (1.3)
Trabeculectomy	0	8 (2.1)	20 (5.1)
Trabeculoplasty	0	3 (0.8)	9 (2.3)
Vitrectomy	11 (5.9)	12 (3.2)	19 (4.8)

1 Includes the total number of unique subjects who experienced glaucoma or open-glaucoma

Reviewer's comments:

The most common serious ocular event was cataract operation occurring in 47% in the 0.2 µg/day FA group and 57% in the 0.5 µg/day FA group.

7.3.3 Dropouts and/or Discontinuations

For a listing of subjects discontinued Refer to Section 6.1.3 Subject Disposition.

Disposition	Sham	0.2 µg/day FA	0.5 µg/day FA
Total subjects randomized	185	376	395
Randomized and not treated	0	1	2
Randomized and treated	185	375	393
Total discontinued (n,%):	42 (22.7)	75 (19.9)	75 (19.0)
Adverse events	3 (1.6)	4 (1.1)	11 (2.8)
Unsatisfactory therapeutic effect	1 (0.5)	0	1 (0.3)
Protocol violation	0	0	3 (0.8)
Subject withdrew consent	14 (7.6)	25 (6.6)	21 (5.3)
Lost to follow-up	17 (9.2)	21 (5.6)	16 (4.1)
Death	8 (4.3)	25 (6.7)	23 (5.9)
Unknown	0	1 (0.3)	0

Overall, 192 (20%) subjects discontinued the trial, primarily due to withdrawn consent (6%), death (6%), or loss to follow-up (6%). Of the 192 subjects who discontinued the

study, 43 (22%) subjects discontinued during the first 12 months of the study, and 132 (69%) subjects discontinued during the second year of the study.

Reviewer's comments:

Overall, discontinuations rates were similar throughout the three treatment groups.

7.3.4 Significant Adverse Events

Ocular Adverse Events Leading to Discontinuation
Integrated Studies (Fame A and B)

Treatment Group	Subject No.	Adverse Event
Sham	102404	Vision loss (OU)
0.2 µg/day FA	100403	Chemical eye injury
0.2 µg/day FA	101634	Endophthalmitis
0.2 µg/day FA	105645	Eye infection fungal
0.5 µg/day FA	100313	Intraocular pressure increased
0.5 µg/day FA	10221	Trabeculectomy
0.5 µg/day FA	104921	Cataract
0.5 µg/day FA	109406	Glaucoma, Trabeculectomy, Iris incarceration
0.5 µg/day FA	109502	Retinal detachment

Reviewer's comments:

As would be expected, the majority of the ocular adverse events occurred within the treatment groups.

7.3.5 Submission Specific Primary Safety Concerns

In the Integrated Analysis by dose in the Fame A and B studies, 621 (77%) of the 953 subjects who received drug therapy were phakic at baseline and at risk for primary cataract formation. The risks for cataract formation and subsequent cataract surgery in this phakic population by treatment group is presented.

Cataract-Related Events in Phakic Subjects
Integrated Studies (Fame A and B)
Study eye only

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)	56 (46.3)	188 (80.0)	232 (87.5)
Cataract operation	28 (23.1)	176 (74.9)	224(84.5)

The percentage of phakic subjects who developed a cataract and a cataract operation was lower in the sham group compared to the 0.2 µg/day FA and 0.5 µg/day FA groups. Forty-six percent of the sham group compared with 80% of the 0.2 µg/day FA and 88% of the 0.5 µg/day FA had a cataract with 28% of the sham group compared to 75% of the 0.2 µg/day and 85% of the FA 0.2 µg/day FA groups requiring a cataract operation during the 24 month study period.

Using the subjects Non-study eye as a comparison to the Study-eye (the drug treatment is an intravitreal implant into the study-eye with no systemic absorption) further demonstrates the significant risk of cataract formation and cataract operation in the study eye resulting from exposure to the drug.

Cataract-Related Events in Phakic Subjects
Integrated Studies (Fame A and B)
Study eye compared to Non-study eye

Term	Sham (N= 121) N (%)	0.2 µg/day FA (N= 235) N (%)	0.5 µg/day FA (N= 265) N (%)
Cataract (any type)			
Study eye	56 (46.3)	188 (80.0)	232 (87.5)
Non-study eye	43 (35.5)	94 (40.0)	108 (40.8)
Cataract operation			
Study eye	28 (23.1)	176 (74.9)	224(84.5)
Non-study eye	26 (21.5)	64 (27.2)	68 (25.7)

For the 0.2 µg/day FA and 0.5 µg/day FA groups when comparing the Non-study eye to the Study eye, cataract formation and cataract operation continue to demonstrate the increased risk of cataract formation and cataract operation resulting from the localized (intravitreal) drug treatment.

Reviewer's comments:

The risks of cataract formation and cataract operation are significant by 24 months after the drug treatment. This risks appears to be dose and time dependent (refer to Section 6.1.10 and Time to Cataract Extraction Graph).

The significant risk of the drug therapy needs to be weighed versus its benefit.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common (≥ 1%) Ocular Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Abnormal sensation in eye	2 (1.1)	5 (1.3)	5 (1.3)
Anterior chamber cell	1 (0.5)	6 (1.6)	3 (0.8)
Blepharitis	3 (1.6)	7 (1.9)	7 (1.8)
Cataract	58 (31.4)	189 (50.4)	222 (56.5)
Cataract nuclear	6 (3.2)	9 (2.4)	13 (3.3)
Cataract operation	36 (19.5)	193 (51.5)	236 (60.1)
Cataract subcapsular	11 (5.9)	33 (8.8)	26 (6.6)
Conjunctival haemorrhage	22 (11.9)	48 (12.8)	48 (12.2)
Conjunctival hyperemia	6 (3.2)	5 (1.3)	5 (1.3)
Conjunctivitis	5 (2.7)	12 (3.2)	9 (2.3)
Corneal abrasion	5 (2.7)	4 (1.1)	10 (2.5)
Corneal epithelial defect	0	4 (1.1)	6 (1.5)
Corneal edema	4 (2.2)	11 (2.9)	15 (3.8)
Diabetic retinal edema	1 (0.5)	4 (1.1)	6 (1.5)
Diabetic retinopathy	4 (2.2)	6 (1.6)	14 (3.6)
Diplopia	2 (1.1)	6 (1.6)	2 (0.5)
Dry eye	10 (5.4)	23 (6.1)	17 (4.3)
Eye discharge	1 (0.5)	5 (1.3)	5 (1.3)
Eye irritation	9 (4.9)	26 (6.9)	21 (5.3)
Eye pain	25 (13.5)	50 (13.3)	65 (16.5)
Eye pruitus	2 (1.1)	10 (2.7)	12 (3.1)
Eyelid edema	2 (1.1)	4 (1.1)	4 (1.0)
Foreign body sensation	4 (2.2)	14 (3.7)	13 (3.3)
Glaucoma or open angle glaucoma[1]	5 (2.7)	21 (5.6)	24 (6.1)
Glaucoma surgery	2 (1.1)	6 (1.6)	8 (2.0)
IOP increased	24 (13.0)	132 (35.2)	173 (44.0)
Iris neovascularization	6 (3.2)	6 (1.6)	6 (1.5)
Keratoconjunctivitis sicca	1 (0.5)	6 (1.6)	4 (1.0)
Lacrimation increased	9 (4.9)	19 (5.1)	14 (3.6)
Macular edema	5 (2.7)	10 (2.7)	10 (2.5)
Maculopathy	19 (10.3)	27 (7.2)	43 (10.9)
Myodepsia	20 (10.8)	70 (18.7)	77 (19.6)
Myopia	0	6 (1.6)	5 (1.3)
Ocular hyperemia	3 (1.6)	10 (2.7)	17 (4.3)
Ocular hypertension	2 (1.1)	9 (2.4)	12 (3.1)
Optic atrophy	3 (1.6)	5 (1.3)	14 (3.6)
Photophobia	2 (1.1)	7 (1.9)	4 (1.0)
Photopsia	2 (1.1)	5 (1.3)	7 (1.8)
Posterior capsule opacification	8 (4.3)	28 (7.5)	27 (6.9)
Punctate keratitis	1 (0.5)	5 (1.3)	5 (1.3)
Retinal detachment	4 (2.2)	5 (1.3)	7 (1.8)
Retinal exudates	2 (1.1)	11 (2.9)	8 (2.0)
Retinal hemorrhage	11 (5.9)	13 (3.5)	16 (4.1)
Retinal neovascularization	11 (5.9)	16 (4.3)	15 (3.8)
Trabeculectomy	0	8 (2.1)	20 (5.1)
Trabeculoplasty	0	3 (0.8)	9 (2.3)
Vision blurred	13 (7.0)	35 (9.3)	26 (6.6)
Visual acuity reduced	20 (10.8)	45 (12.0)	40 (10.2)
Visual impairment	7 (3.8)	14 (3.7)	31 (7.9)
Vitrectomy	15 (8.1)	25 (6.7)	35 (8.9)
Vitreous detachment	10 (5.4)	28 (7.5)	25 (6.4)
Vitreous Hemorrhage	35 (18.9)	59 (15.7)	73 (18.6)
Vitreous opacities	1 (0.5)	4 (1.1)	5 (1.3)
Vitritis	3 (1.6)	3 (0.8)	4 (1.0)

1 Includes the total number of unique subjects who experienced glaucoma or open-glaucoma

Four of the most common ocular adverse events (i.e., cataract, cataract operation, increased intraocular pressure and myodesopsia) occurred more frequently in the active-treated groups compared with the sham group.

The incidence of adverse events was also higher in the 0.5 µg/day FA group than the 0.2 µg/day FA group, suggesting a dose response. The most notable differences were observed for cataract (31%, sham; 50%, 0.2 µg/day FA; 57%, 0.5 µg/day FA); cataract operation (20%, sham; 52%, 0.2 µg/day FA; 60%, 0.5 µg/day FA); increased intraocular pressure (13%, sham; 35%, 0.2 µg/day FA; 44%, 0.5 µg/day FA); and myodesopsia (11%, sham; 19%, 0.2 µg/day FA; 20%, 0.5 µg/day FA).

Common (≥ 5%) Systemic Adverse Events by Treatment Group: Integrated Studies (Fame A and B)

Adverse Events	Sham (N=185) N (%)	0.2 µg/day FA (N=375) N (%)	0.5 µg/day FA (N=393) N (%)
Anemia	6 (3.2)	26 (6.9)	34 (8.7)
Cardiac failure congestive	9 (4.9)	12 (3.2)	20 (5.1)
Constipation	3 (1.6)	12 (3.2)	21 (5.3)
Nausea	13 (7.0)	23 (6.1)	22 (5.6)
Vomiting	10 (5.4)	13 (3.5)	4 (1.0)
Nasopharyngitis	11 (5.9)	20 (5.3)	22 (5.6)
Pneumonia	3 (1.6)	19 (5.1)	14 (3.6)
Sinusitis	7 (3.8)	12 (3.2)	20 (5.1)
Hypercholesterolemia	11 (5.9)	17 (4.5)	19 (4.8)
Headache	10 (5.4)	26 (6.9)	20 (5.1)
Renal failure	9 (4.9)	23 (6.1)	25 (6.4)
Hypertension	25 (13.5)	35 (9.3)	38 (9.7)

Due to the diabetic population studied, approximate mean age of 62, and many systemic common adverse events occurring at 1 % or more only those systemic common adverse events occurring in ≥ 5 % are listed.

Reviewer's comments:

Ocular adverse events (e.g. cataract, cataract operation, increased intraocular pressure and myodesopsia) were reported at higher rates in the drug treatment groups than in the sham group.

The significant risk of the drug therapy needs to be weighed versus its benefit.

7.4.2 Laboratory Findings

The systemic levels of FA are negligible; as a result, the only laboratory test performed was HbA1c.

The results confirm that treatment with FA had no effect on HbA1c values at Months 24 and 36 in the FAME studies. Mean HbA1c values were comparable among treatment groups at baseline (7.83%, sham; 7.81%, 0.2 µg/day FA; 7.71%, 0.5 µg/day FA). Mean changes from baseline in HbA1c values were small and comparable among treatment groups at Month 24, ranging from 0.17% in the sham group to 0.27% in the 0.2 µg/day FA group. In the sham and 0.2 µg/day groups, little change was observed between baseline and Month 24 in the percentage of subjects with HbA1c >11.2%. In the 0.5 µg/day group, the percentage of subjects with HbA1c >11.2% increased from 2% at baseline to 5% at Month 24. It should be noted that the percentage of subjects in the 0.5 µg/day group with HbA1c >11.2% was lower than that of the sham group at baseline and at Month 24. As a result this is not considered a significant safety signal.

7.4.3 Vital Signs

Mean systolic blood pressure (BP) values were comparable among treatment groups at baseline (139.3 mmHg, sham; 139.6 mmHg, 0.2 µg/day FA; 138.5 mmHg, 0.5 µg/day FA) Mean changes from baseline in systolic BP were small and comparable among treatment groups at Month 24, ranging from −1.6 in the 0.5 µg/day FA group to −2.9 mmHg in the 0.2 µg/day FA group.

Mean diastolic BP values were equal among treatment groups at baseline (78.3 mmHg in each group). Mean changes from baseline in diastolic BP were small and comparable among treatment groups at Month 24, ranging from −0.7 mmHg in the 0.2 µg/day FA group to −1.2 mmHg in the sham group.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed.

Reviewer's comments:

The drug is a corticosteroid; corticosteroids have a long history of use, and their effects have been widely studied. ECGs were not required.

7.4.5 Special Safety Studies/Clinical Trials

Mean Change from Baseline in Specular Microscopy and Endothelial Cell Counts in the Study Eye
Integrated Studies (Fame A and B)

Visit	Sham	0.2 µg/day FA	0.5 µg/day FA
Endothelial Cell Density (cells per mm^2)			
Baseline			
N	12	23	26
Mean Change (SD)	2392.9 (410.5)	2189.5 (434.47)	2304.0 (547.52)
Month 24			
N	10	15	15
Mean Change (SD)	-230.4 (287.38)	-302.1 (398.11)	-485.5 (375.15)

SD = Standard Deviation

At baseline, mean corneal endothelial cell density was slightly higher in the sham group (2392.9 cells/mm^2) compared with the two active treatment groups (2189.5 cells/mm^2, 0.2 µg/day FA; 2304.0 cells/mm^2, 0.5 µg/day FA). At month 24, mean decreases from baseline in corneal endothelial cell density were observed in each treatment group. These mean decreases were greater in the two active treatment groups (-302.1 cells/mm^2, 0.2 µg/day FA; -485.5 cells/mm^2, 0.5 µg/day FA) compared with the sham group (-220.4 cells/mm^2). This finding may be related to the higher rate of cataract operation among phakic subjects in the active treatment groups.

Reviewer's comments:

It is recommended that corneal endothelial measurements be performed in a minimum of 100 eyes with a minimum of six months follow-up.

7.4.6 Immunogenicity

No studies were performed given the well established profile of FA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Both the 0.2 µg/day FA and 0.5 µg/day FA inserts were associated with cataracts and increased IOP. The 0.5 µg/day FA demonstrated a higher risk than the 0.2 µg/day FA group.

7.5.2 Time Dependency for Adverse Events

The prolonged use of 0.2 µg/day FA and the 0.5 µg/day FA inserts are accompanied by an increased incidence of cataract and requirement for cataract extraction.

7.5.3 Drug-Demographic Interactions

Overall, none of the drug-demographic interactions were indicative of an appreciable safety concern for the use of intravitreal FA inserts.

7.5.4 Drug-Disease Interactions

Overall, none of the drug-disease interactions were indicative of an appreciable safety concern for the use of intravitreal FA inserts.

7.5.5 Drug-Drug Interactions

Due to the small number of subjects who concomitantly received anti-VEGF therapy, no definitive conclusions can be drawn regarding possible drug-drug interaction with this class of drugs; however, there is no indication of an interaction between anti-VEGF therapy and the use of FA inserts.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not performed given lack of systemic exposure to FA and the long history of its use in topical products.

7.6.2 Human Reproduction and Pregnancy Data

No known pregnant or lactating subjects have been treated with Iluvien. Due to known teratogenic effects of corticosteroids, use in pregnancy is not recommended.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose and drug abuse with the FA insets are not expected given its limited systemic absorption and that the drug is administered by a physician.

The need for gradual withdrawal of oral and topical corticosteroids is well established. However, because FA is inserted intravitreally directly into the vitreous cavity, the total

amount of drug delivered is small compared to other routes of corticosteroid administration, and systemic effects are unlikely.

7.7 Additional Submissions / Safety Issues

A 120 Day Safety Update was submitted in Amendment 14 on October 21, 2010. The results of the 120 Day safety Update were very similar to those previously reported. There were no substantive changes in the safety profile.

8 Postmarket Experience

Iluvien has not been previously marketed.

Appendices

9.1 Literature Review/References

Iluvien is not currently available and there are no literature reports.

9.2 Labeling Recommendations

Labeling recommendations will be made after all 36 month follow-up data has been submitted.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting will be scheduled until the 36 month data is available for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

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/s/

MARTIN P NEVITT
12/20/2010

WILLIAM M BOYD
12/20/2010