

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201923Orig1s000**

**SUMMARY REVIEW**

Summary Review #3 for Regulatory Action  
(fourth review cycle)

<b>Date</b>	See electronic stamp date
<b>From</b>	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
<b>Subject</b>	Division Director Summary Review #3
<b>NDA Number</b>	NDA 201923
<b>Related IND</b>	IND 72,056
<b>Applicant Name</b>	Alimera Sciences, Inc.
<b>Date of Original Submission</b>	June 30, 2010 (priority review)
<b>Complete Response Letter #1</b>	December 22, 2010
<b>Date of Resubmission, Class II</b>	May 12, 2011
<b>Complete Response Letter #2</b>	November 10, 2011
<b>Date of Resubmission, Class II</b>	April 17, 2013
<b>Complete Response letter #3</b>	October 17, 2013
<b>Date of Resubmission Class II</b>	March 26, 2014
<b>PDUFA Goal Date</b>	September 26, 2014
<b>Application Type</b>	505(b)(1)
<b>Proprietary Name / Established (USAN) Name</b>	Iluvien Fluocinolone acetonide intravitreal insert
<b>Formulation</b>	Intravitreal Insert (non-biodegradable/non-bioerodable)
<b>Dose</b>	0.19 mg
<b>Proposed Indication(s)</b>	Treatment of diabetic macular edema
<b>Action for Application</b>	<i>Approval</i>

<b>Material Reviewed/ Consulted for this or previous actions:</b>	<b>Names of discipline reviewers</b>
Medical Officer Review	Martin Nevitt, Bill Boyd 12/20/2010, 9/13/2011, 9/9/2013, 8/22/2014
CDTL Review	Bill Boyd 12/22/2010, 10/27/2011, 10/17/2013, 9/18/2014, 9/23/2014
Deputy Director	Wiley Chambers 12/22/2010, 10/19/2011, 10/17/2013, 9/16/2014
Statistical Review	Rima Izem, Yan Wang 11/30/2010, 8/1/2011, 6/20/2012 Dongliang Zhuang, Daphne Lin 9/27/2013 Abel Eshete, Yan Wang 9/2/2014
Clinical Pharmacology Review	Yongheng Zhang, Charles Bonapace 11/18/2010, Yongheng Zhang, Philip Colangelo, 6/28/2011, 10/07/2013
Pharmacology/Toxicology Review	Conrad Chen, Wendelyn Schmidt 11/17/2010 Lori Kotch 7/28/2014
OC/OMPQ/DGMPA	Juandria Williams, Tara Goen 10/15/2013, 10/17/2013
ONDQA/DNDQA II, Branch V Review	Lin Qi, Rapti Madurawe 7/22/2011, 9/30/2011 Lin Qi, Balajee Shanmugan 9/24/2013, 10/15/2013, Lin Qi, Balajee Shanmugan, Rapti Madurawe 8/6/2014
EA	Dorota Matecka, Stephen Miller 12/1/2010
ONDQA Biopharmaceutics	Tapash Ghosh, Patrick Marroum 6/27/2011 Tapash Ghosh, John Duan 9/23/2013
Product Quality Microbiology Review	Steven Fong, John Metcalfe 12/8/2010, 2/9/2011, 7/25/2011
OSI/DGCPC	Kassa Ayalew, Tejashri Purohit-Sheth 12/1/2010
OSE/DMEPA Proprietary Name	Denise Toyer 10/13/2010 (tentatively acceptable) Rachna Kapoor,, Yelena Maslov 8/1/2014 Kellie Taylor 8/6/2014
DMEPA Labeling Review	Rachna Kapoor, Yelena Maslov 8/5/2014 Rachna Kapoor, Lubna Merchant 8/28/2014
OPDP Labeling Review	Christine Corser 8/13/2014
CDRH Consult	Nikhil Thakur
Project Manager	Diana Willard

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

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## 1. Summary and Recommendations

### Product:

ILUVIEN is a non-bioerodable intravitreal implant, light brown in color, measuring 3.5 mm x 0.37 mm, containing 0.19 mg (190 mcg) of the active ingredient fluocinolone acetonide and the following inactive ingredients: polyimide tube, polyvinyl alcohol, silicone adhesive and water for injection. Fluocinolone acetonide is a synthetic corticosteroid, a white or almost white, microcrystalline powder, practically insoluble in water, soluble in methanol, ethanol, chloroform and acetone, and sparingly soluble in ether.

ILUVIEN is preloaded into a single-use applicator to facilitate injection of the implant directly into the vitreous, and designed to release fluocinolone acetonide at an initial rate of 0.25 µg/day for up to 36 months. It is supplied in a sterile single use preloaded applicator with a 25-gauge needle, packaged in a tray sealed with a lid inside a carton.

### History:

The NDA 201923 application for Iluvien by Alimera is now in its fourth review cycle for the indication of treatment of diabetic macular edema (DME). As noted in the Clinical reviews, “Diabetic macular edema (DME), a serious, chronic, debilitating disease, and one of the causes of vision loss associated with diabetic retinopathy.”

The history of this drug development program is included in the previous primary, secondary and tertiary reviews of the application. As summarized in these previous reviews, the main deficiencies identified in this application were clinical and CMC.

During the previous review cycles, the ophthalmology reviewers (Medical Officer, Team Leader and Deputy Director) unanimously concluded that the benefit of Iluvien did not outweigh the risks of cataract formation and cataract surgery, as well as the risk of increased intraocular pressure (IOP) and the need for medical and/or surgical management of increased IOP, and the Division did not recommend approval of the product for DME, and issued Complete Response letters (See Section 2 for details). Alimera did not agree with the Division’s conclusion and considered that the benefits of the product did outweigh the risks. Alimera brought ophthalmology consultants to meetings with the agency, during which the applicant and the consultants discussed their view that the cataracts and increased IOP risks could be managed medically and/or surgically and having Iluvien as a therapeutic option was needed for the management of diabetic macular edema, to maintain or improve patients’ vision. As part of the discussion, Alimera noted that they were approved in Europe and proposed to the agency limitations to the indication that would limit its use to patient subsets where the benefit would outweigh the risks. A summary of the submission dates and the proposed modification to the indications are provided in the table below:

Date of Submission	Date of Complete Response Letter	Proposed Indication	Clinical Data
Original submission 6/28/2010	CR letter 12/22/2010	<i>treatment of diabetic macular edema</i>	24-month data of two on-going 36-month phase 3 studies
First resubmission 5/12/2011	CR letter 11/10/2011		(1) 36-month data of two phase 3 studies  (2) subgroup analysis by duration of DME (b) (4)
Second resubmission 4/26/2013	CR letter 10/17/2013		No new clinical data
Third Resubmission 3/26/2014	PDUFA goal 9/26/2014		No new clinical data

Adapted from statistical review

In addition to the clinical issues, there were CMC deficiencies identified during the review cycles as well as technical problems with the Iluvien inserter. These issues were identified by the CMC team, the Office of Compliance, and the clinical team (See Section 2).

Iluvien was originally submitted in June 28, 2010 and given a priority review. Since 2010, three products have been approved for the indication of DME:

Product	Application Number	Date of Approval	Indication	Duration of clinical studies
Lucentis ranibizumab	BLA 125156/76	8/10/2012	DME	3 years
Ozurdex dexamethasone	NDA 22315/09	6/28/2014	DME*	3 years
Eylea aflibercept	BLA 125387/37	7/29/2014	DME	1 year

\*The initial approved indication for Ozurdex was diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery (the Summary Review is included as Appendix A to this review); the Division is now removing the limitation based on the reasons summarized in this review - Section 13, and NDA 22315/S10.

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, the ophthalmology reviewers unanimously 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), specifically the benefit did not outweigh the risks. Based on the review of the resubmission dated March 26, 2014, the ophthalmology reviewers unanimously concluded that Iluvien should be approved for the indication:

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated 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.

Although during the review of the three previous submissions the Division ophthalmology reviewers did not recommend approval, it appears that after considering the results from the Ozurdex studies in DME (See Appendix A), the ophthalmologists have revised their recommendations regarding the risks and benefits of Iluvien in the setting of DME (See Section 13).

The clinical reviews address the resolution of the clinical and inserter related issues, and the CMC reviews address the resolution of deficiencies in manufacturing listed in the Complete Response letter dated October 17, 2013. Labeling has been finalized, clinical site and manufacturing facility inspections have been completed and the Office of Compliance issued a recommendation of Acceptable. Therefore, there are no deficiencies to preclude approval of the application.

The application will be approved.

### **1.1 Post-Marketing Studies:**

None

### **1.2 Other Issues**

None

## **2. Background**

Corticosteroids approved for intravitreal administration 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, or diabetic macular edema. The Ozurdex insert is injected into the vitreous with an injector 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. <sup>1</sup>
- TRISENCE® (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.

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<sup>1</sup> Retisert was approved April 8, 2005 under NDA 21-737.

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

The Medical Officer 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. 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; cataract surgery can be performed and IOP lowering medications can be used in patient who have these adverse reactions. As summarized in Appendix A, similar adverse reactions findings at similar rates were reported in the application for Ozurdex for DME, NDA 22315/S-009.

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.<sup>2</sup> 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) 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.

<sup>2</sup> Since then, Lucentis, Ozurdex and Eylea have been approved for the treatment of diabetic macular edema.

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.

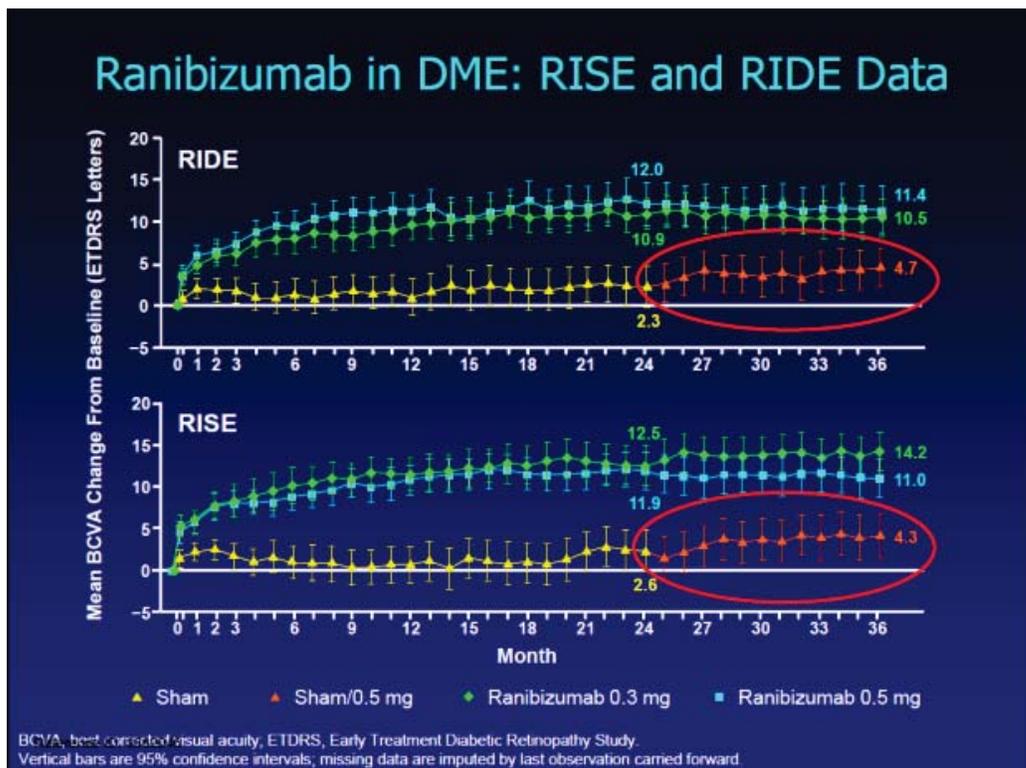
The applicant sent a resubmission May 12, 2011, and the second complete response letter was issued November 10, 2011. This included both clinical and CMC deficiencies. The applicant had not demonstrated that Iluvien was safe and effective in the FAME A and FAME B studies, and had performed a post-hoc analysis of the data (b) (4)

The Division noted that the adverse events rates were still higher in this subset than in the control arm, and comparable to the overall study population. It was also noted that the (b) (4) 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 (b) (4) testing method was not submitted.

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 background for the July 26, 2013 meeting with the Agency.

Two slides from July 26, 2013 meeting are provided below and discussed in Section 13. (Meeting minutes dated August 23, 2013 in DARRTS).





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 that cycle, planning for the Advisory Committee was started.

On October 16, 2013, the Agency met with Alimera to provide an update on the clinical and manufacturing deficiencies before the PDUFA goal date. Alimera was asked to provide a letter of authorization from their contract manufacturer, (b) (4) or to invite (b) (4) to attend the meeting so there could be discussion of the specific manufacturing deficiencies. Alimera did not provide an LOA or invite representatives from (b) (4) 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.

The third Complete Response letter was issued October 17, 2013, and identified the need for studies demonstrating an acceptable risk benefit assessment, and concern about the high rate of adverse reactions, and recommended a new controlled study. The chemistry deficiency was that 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. Finally, the supplementary in-process control during manufacturing of the injector was requested.

In the previous FDA reviews of Iluvien, NDA 201923, the clinical reviewers report the low rate of efficacy and the high rate of adverse reactions, notably increased intraocular pressure (IOP) and cataract formation/cataract surgery. The reviewers concluded that the benefit could not outweigh the risk of using this product. This decision is documented in the Deputy Director's Reviews dated 12/22/2010, 10/19/2011, and 10/17/2013. Specific paragraphs explaining this decision are excerpted below.

“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% of 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.” [Review dated 12/22/2010]

“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.” [Review dated 10/19/2011]

“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.” [Reviews dated 10/19/2011 and 10/17/2013]

“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.” [Review dated 10/17/2013]

Similar language was also used to communicate preliminary responses in preparation for the June 19, 2012 meeting with Alimera [DARRTS 6/14/2012]

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

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

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

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

Because the Division, guided by input from the ophthalmology reviewers over the course of the review of this application, communicated to Alimera that the benefit of the product does not overcome the significant risks, the applicant contacted the Center Director (CDER) and Office of New Drugs (OND) Director and requested assistance. A meeting with upper management from OND and the Office of Antimicrobial Products (OAP) was scheduled and subsequently planning for an advisory committee meeting was initiated. In the October 16, 2013 meeting with the Agency, Alimera expressed their concerns. The minutes summarize this discussion [DARRTS]:

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

During the October 23, 2013 teleconference, Alimera again shared their concerns regarding the objectivity during the clinical review of their application.

During the December 10, 2013 teleconference, one approach for a path forward was discussed, as recorded in the Meeting Minutes in DARRTS, and Memorandum archived August 12, 2014:

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

“A discussion followed (b) (4)

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

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

During the 2013 discussions, a Dermatologic and Ophthalmic Drugs Advisory Committee was being planned for January 2014, to discuss the two applications under review for the indication of diabetic macular edema (DME): Iluvien NDA 201923 and Ozurdex NDA 22315/S-009.

The AC was cancelled after the December 13, 2013 meeting since there appeared to be a path forward to limit the proposed indication.

On March 26, 2014, Alimera submitted the latest resubmission to address the deficiencies in the Complete Response letter.

### **3. CMC/Product Quality Microbiology**

For a complete discussion of the manufacturing of the drug product and drug substance, please refer to the CMC reviews. The following summary is taken from Dr. Qi’s August 6, 2014 review and succinctly summarizes the previous history and current status of the CMC aspects of this application:

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. CMC Labeling comments were conveyed to the review team [and incorporated in labeling. The] Office of Compliance has made an overall recommendation as “Acceptable” for the facilities. Therefore, from the CMC perspective, this NDA is recommended for Approval.

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 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 polymer. The empty tube measures 3.5 mm x

0.37 mm OD and weighs approximately 0.1 mg. This insert is preloaded in a specially 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.

The fluocinolone acetonide drug substance used in clinical trials for this NDA was supplied by (b) (4). The proposed commercial manufacturer is (b) (4). For the chemistry manufacturing and controls information for fluocinolone acetonide drug substance, the reference is made to DMF type II (b) (4) held by (b) (4).

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 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].

*Comment:*

*All CMC deficiencies have been addressed and manufacturing facilities are acceptable. Labeling has been finalized and the Product Quality Reviewers recommend approval.*

## **4. Nonclinical Pharmacology/Toxicology**

There were no additional pharmacology/toxicology studies submitted during this latest review cycle. For a complete summary, see the Pharmacology Reviews. 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.

Labeling has been modified for formatting consistency across Divisions.

### **8.1 Pregnancy**

#### **Pregnancy Category C**

There are no adequate and well-controlled studies of ILUVIEN in pregnant women. Adequate animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. ILUVIEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **8.3 Nursing Mothers**

Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with ILUVIEN is low [see Clinical Pharmacology (12.3)]. It is not known whether intravitreal treatment with ILUVIEN could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when ILUVIEN is administered to a nursing woman.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of ILUVIEN.

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.

*Comment: The Pharmacology/Toxicology Reviewers recommend approval from the pharmacology/toxicology standpoint.*

## **5. Clinical Pharmacology/Biopharmaceutics**

There were no new clinical pharmacology studies submitted in this resubmission. The systemic and ocular pharmacokinetic results were reviewed during the original review cycle 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.

The reviewer 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 (b) (4) contains 0.19 mg FA versus the clinical development product (manufactured at pSivida, Inc.) that averaged (b) (4) mg.

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

(Refer to the ONDQA Biopharmaceutics Reviewer's review). The Applicant claimed that the dose response relationship established for both safety and efficacy (0.2 µg/day and 0.5 µg/day) supports the selection of a low dose insert.

However, it should be noted that the FA release rate for the proposed product is estimated to be 0.25 µg/day (b) (4)

*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

### Brief Summary of Clinical Trials

The applicant did not submit results of any new clinical studies in the current resubmission.

As noted in the previous Division Director reviews, 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 clinical and statistical reviews.

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  $\geq 15$  letters from baseline of BCVA at 24 months. Secondary endpoints included mean BCVA.

In the March 26, 2014 resubmission, the applicant proposed the indication:

(b) (4)

However, based on the review of the submission, the Division recommended the indication to be:

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated 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.

The reason for this decision was made

(b) (4)

Therefore, the analysis of the primary endpoint was based on the ITT population, not a subset of the population, and the Statistical Reviewer reports the following results, tables and figures in the statistical review.

Efficacy of ILUVIEN (0.2 $\mu$ g/day) for the treatment of diabetic macular edema was demonstrated in two phase 3, three-arm, Sham-controlled studies (Study FAME A and Study FAME B) based on statistically significant results for the primary efficacy endpoint of the proportion of subjects with a 15 letter or more gain from baseline evaluated at Month 24. Compared to Sham, approximately 12% [95% CI: (2.6%, 21.6%)] more subjects in Study A and 13% [95% CI: (2.6%, 23.2%)] more subjects in Study B in the ILUVIEN (0.2  $\mu$ g/day) arm gained 15 letters or more in best-corrected visual acuity (BCVA) at Month 24.

The treatment effect was not statistically significant at Month 36 in either of the two studies; however, the observed differences were numerically in favor of the ILUVIEN (0.2  $\mu$ g/day) arm:

(b) (4)

The analysis of the mean change from baseline in BCVA at months 24 and 36, the secondary efficacy endpoint, was supportive of the results of the primary endpoint in Study B but not in Study A. In Study B, subjects in the ILUVIEN (0.2  $\mu$ g/day) arm on average gained 5 [95% CI: (1, 9)] more letters in BCVA from baseline at Month 36 compared to Sham, whereas in Study A the result was 2 [95% CI: (-2, 6)].

**Visual Acuity outcomes at Month 24 (All randomized subjects with LOCF)**

<b>Study</b>	<b>Outcomes</b>	<b>ILUVIEN N=190</b>	<b>Sham N=95</b>	<b>Estimated Difference (95% CI)</b>
<b>A*</b>	Baseline BCVA, Mean (SD), Letters	53 (13)	55 (11)	
	Baseline BCVA, Median (Range), Letters	57 (19-75)	58 (25-69)	
	Gain of $\geq 15$ letters in BCVA (n (%))	51 (27%)	14 (15%)	12.1% (2.6%, 21.6%)
	Loss of $\geq 15$ letters in BCVA (n (%))	26 (14%)	5 (5%)	8.4% (1.8%, 15.1%)
	Mean change from baseline in BCVA (SD)	3.7 (18.7)	3.2 (13.1)	1.8 (-2.8, 6.3)
		<b>ILUVIEN N=186</b>	<b>Sham N=90</b>	
<b>B*</b>	Baseline BCVA, Mean (SD), Letters	53 (12)	55 (11)	
	Baseline BCVA, Median (Range), Letters	56 (20-70)	58 (21-68)	
	Gain of $\geq 15$ letters in BCVA (n (%))	57 (31%)	16 (18%)	13.0% (2.7%, 23.4%)
	Loss of $\geq 15$ letters in BCVA (n (%))	22 (12%)	9 (10%)	1.8% (-5.9%, 9.6%)
	Mean change from baseline in BCVA (SD)	5.2 (18.0)	0.0 (15.6)	6.1 (1.4, 10.8)

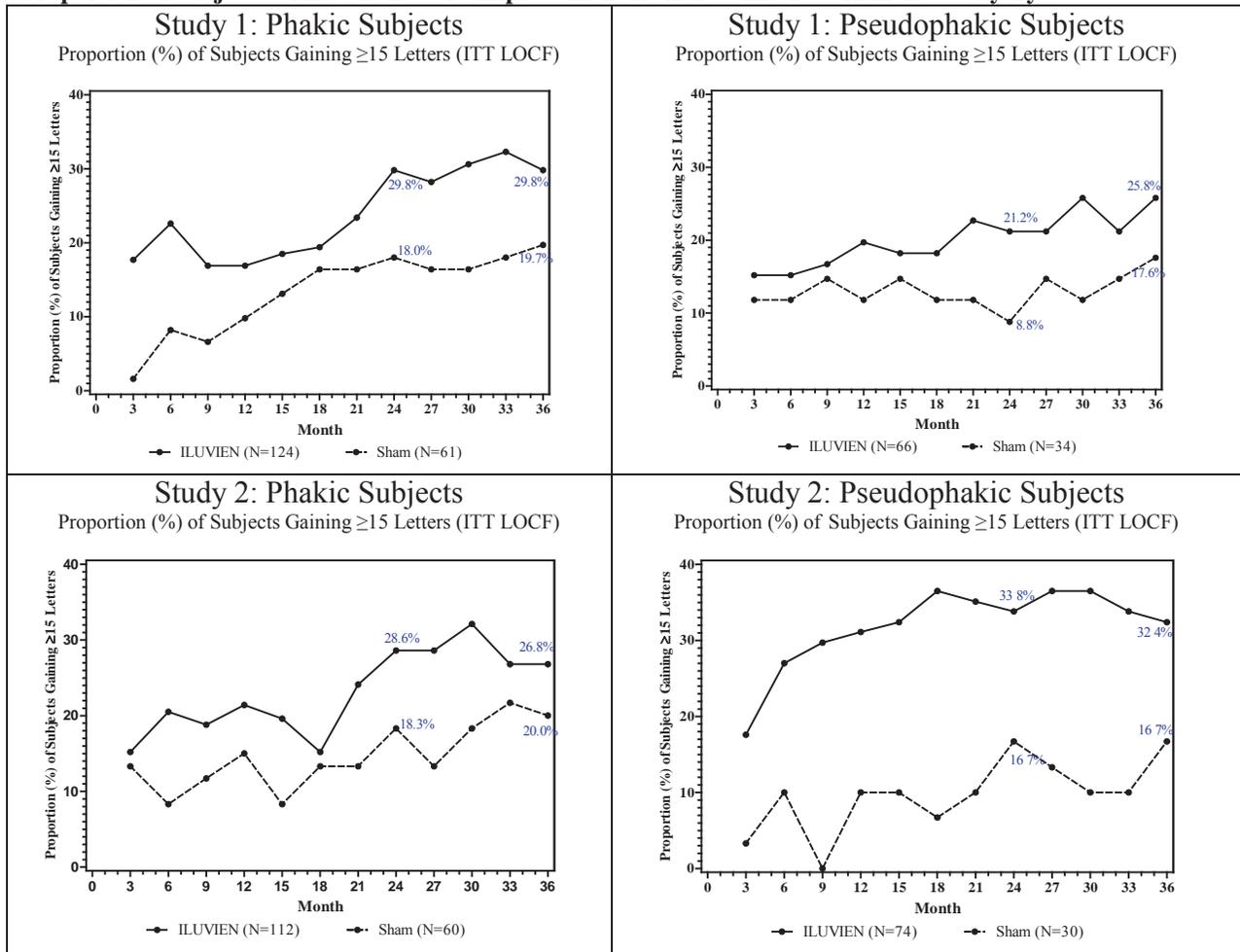
\*Fame A, Fame B

One possible explanation for the relatively poor mean BCVA outcome in Study A is also discussed in the Statistical Review; the confounding effect of treatment induced cataract formation that led to cataract surgery. In both studies, a substantially large proportion of subjects in the ILUVIEN (0.2  $\mu\text{g}/\text{day}$ ) arm reported cataract formation and a significantly high proportion of them had cataract surgery.

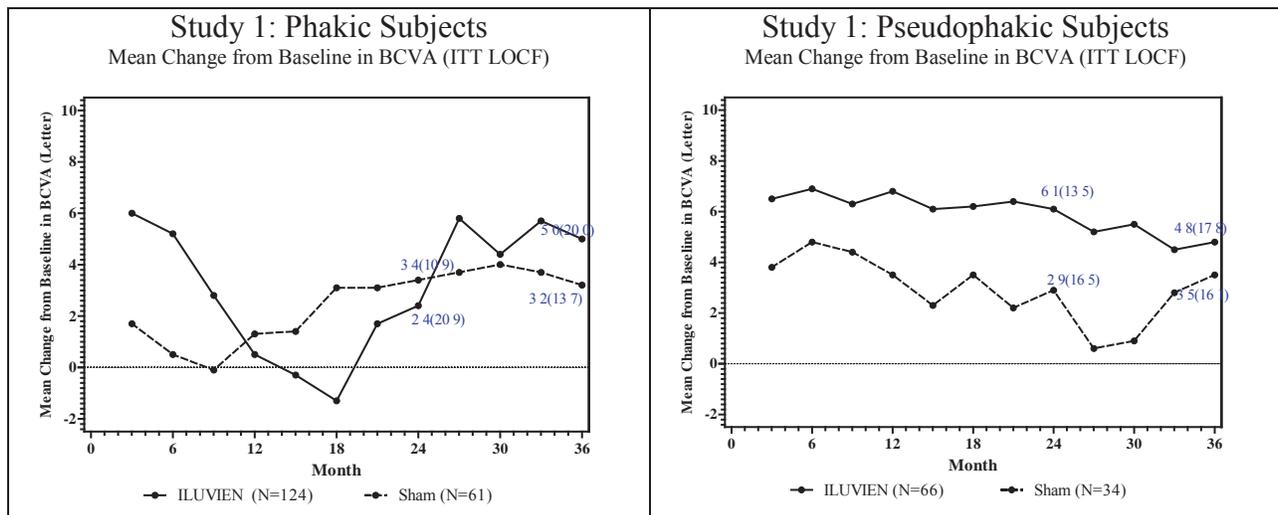
To evaluate the possible confounding effect of cataract, the Statistical Reviewer performed subgroup analyses based on baseline lens status. In both studies, phakic subjects in the ILUVIEN (0.2  $\mu\text{g}/\text{day}$ ) arm exhibited a steep decline in BCVA starting from Month 6 up to around Month 18. This timeframe coincides with the time during which the majority of subjects had cataract surgery. On the other hand, the Statistical Review noted that pseudophakic subjects, who are not susceptible to cataract formation, showed an improved efficacy for ILUVIEN (0.2  $\mu\text{g}/\text{day}$ ) throughout the study course. Among subjects who reported cataract formation, those who had cataract surgery during the study appeared to have better BCVA outcome compared to those who did not. Because subjects in both studies were mainly phakic and reported cataract formation and subsequently underwent cataract surgery, it is reasonable to assume that the decline in vision over time could be partly attributed to cataract formation and that cataract surgery might have reversed the decline to some degree.

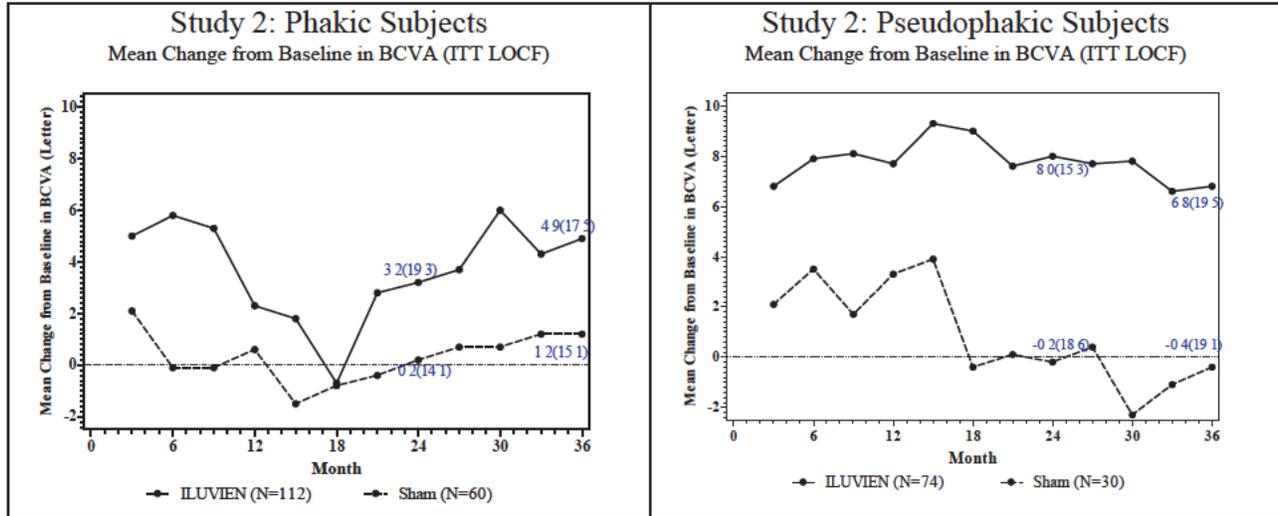
The figures below illustrate the proportion of subjects with  $\geq 15$  letter improvement from baseline BCVA in the study eye by lens status, and also illustrate the mean BCVA change from baseline by lens status, over the 3-year course of the studies.

**Proportion of subjects with  $\geq 15$  Letters Improvement from Baseline BCVA in the Study Eye**



**Mean BCVA Change from Baseline**





The following table shows the visual acuity outcomes at 24 months based on lens status.

Visual Acuity outcomes at Month 24 (Subgroup for pooled data with LOCF)

Lens Status	Outcomes	ILUVIEN	Sham	Estimated Difference (95% CI)
<sup>a</sup> Pseudophakic	Gain of ≥15 letters in BCVA (n (%))	39 (28%)	8 (13%)	15.4% (4.4%, 26.3%)
	Loss of ≥15 letters in BCVA (n (%))	7 (5%)	7 (11%)	-5.9% (-14.4%, 2.5%)
	Mean change from baseline in BCVA (SD)	7.1 (14.5)	1.5 (17.4)	5.6 (0.7, 10.6)
<sup>b</sup> Phakic	Gain of ≥15 letters in BCVA (n (%))	69 (29%)	22 (18%)	11.1% (2.1%, 20.1%)
	Loss of ≥15 letters in BCVA (n (%))	41 (17%)	7 (6%)	11.6% (5.2%, 18%)
	Mean change from baseline in BCVA (SD)	2.8 (20.1)	1.8 (12.6)	1 (-2.5, 4.4)

<sup>a</sup>Pseudophakic : ILUVIEN, N=140; Sham, N=64

<sup>b</sup>Phakic: ILUVIEN, N=236; Sham, N=121

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)

(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 for retinal vein occlusion 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 April 26, 2013 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). This study 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. 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.”

The Deputy Director 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 was 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 recommendations 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)

Based on the review of the March 26, 2014 resubmission, the Deputy Director notes that to address the observed difficulties with the inserter and 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 (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.

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.

### 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)

(MOR, p.13)

The clinical reviewers disagreed with the way in which DME (b) (4) 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 (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.*

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 provided 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  $\geq$  and  $<$  the Median. (page 168)

Assuming that patients were examined based on “above and below median duration of DME,” the expectation would be that the number of patients in the below median group would equal the number of patients in the above median 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  $\geq$  15 Letter Increase from baseline best corrected visual acuity (BCVA) in the Study Eye**

(b) (4)



[Redacted]

[Redacted]

(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
(b) (4)	410 (43.1%)	6 (0.6%)
	65 (6.8%)	471 (49.5%)
<b>kappa</b>		0.8508
<b>p-value</b>		<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:

<i>FAME A + B</i>	Sham			0.2 mcg/day			0.5 mcg/day		
	<u>N</u>	<u>n</u>	<u>%</u>	<u>N</u>	<u>n</u>	<u>%</u>	<u>N</u>	<u>n</u>	<u>%</u>
<i>&lt;1.73 years</i>									
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
<i>≥1.73 years</i>									
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
<i>FAME A</i>									
<i>&lt;1.73 years</i>									
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
<i>≥1.73 years</i>									
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
<i>FAME B</i>									
<i>&lt;1.73 years</i>									
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
<i>≥1.73 years</i>									
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

Following review of the March 26, 2014 resubmission, the Statistical Reviewer reported that additional subgroup efficacy analyses conducted based on demographic and other baseline characteristics showed results that were consistent with the overall population. Of note in these analyses were the subgroup of subjects with longer DME duration (more than the median duration of 1.73 years), which the applicant referred to as “Chronic DME”, and those with longer diabetes mellitus (DM) duration (>15 years). Subgroup of subjects in ILUVIEN (0.2 µg/day) arm with longer DME duration appeared to show a significantly improved efficacy both at Month 24 and Month 36 and a slightly better safety profile compared to other subgroups. A similarly improved efficacy was observed for subjects who had diabetes mellitus for more than 15 years, pooled studies.

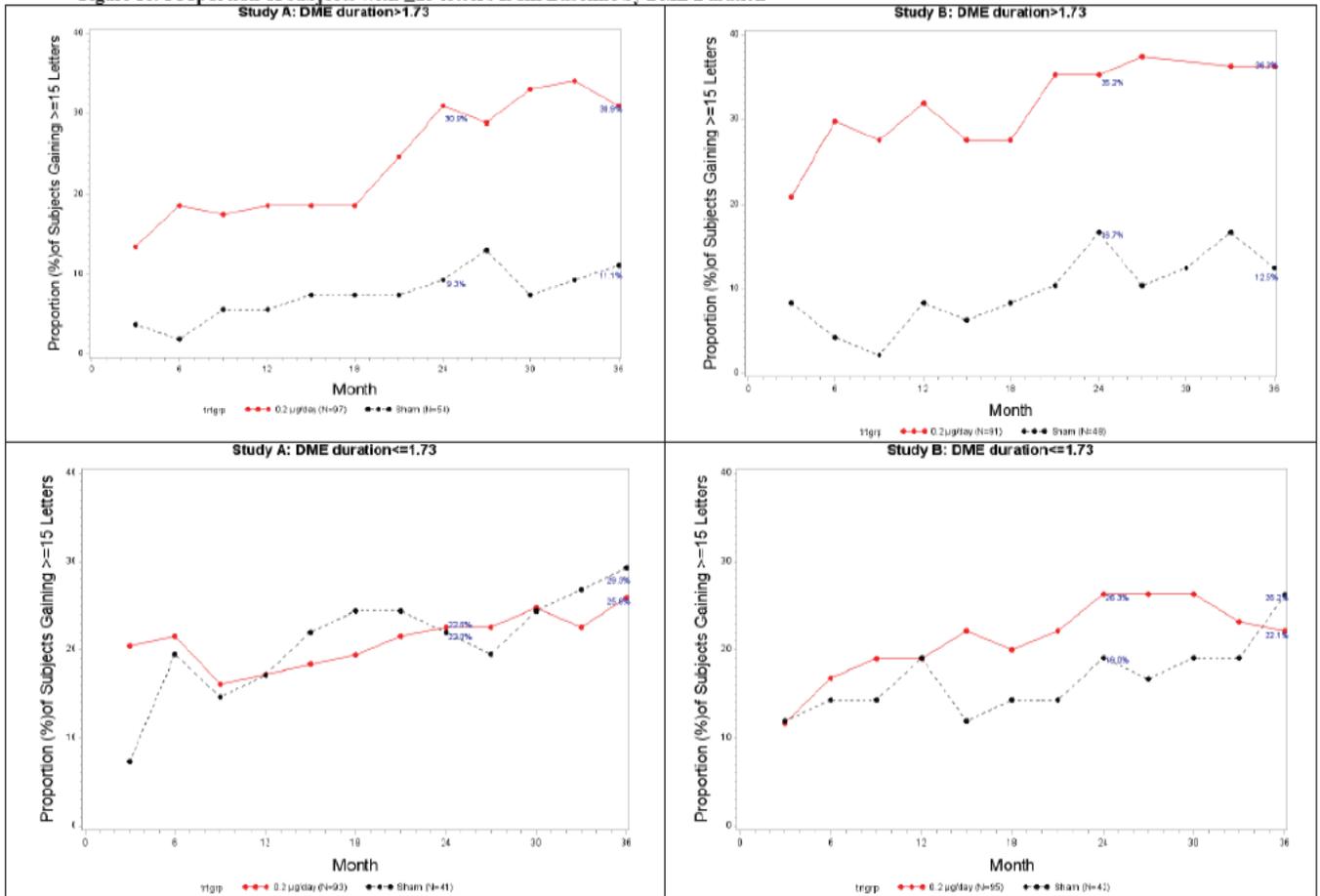
<b>15 or more letter gain BCVA, Iluvien vs. Sham</b>	<b>24 months</b>	<b>36 months</b>
DM > 15 years	18% (9%, 28%)	18% (8%, 28%)
DME > 1.73 years	20% (11%, 30%)	22% (13%, 31%)
<b>Change in BCVA from Baseline, Letters, Iluvien vs. Sham</b>	<b>24 months</b>	<b>36 months</b>
DM > 15 years	4 (0, 8)	4 (0, 99)
DME > 1.73 years	5 (1, 9)	7 (3, 11)

Adapted from Statistical Review

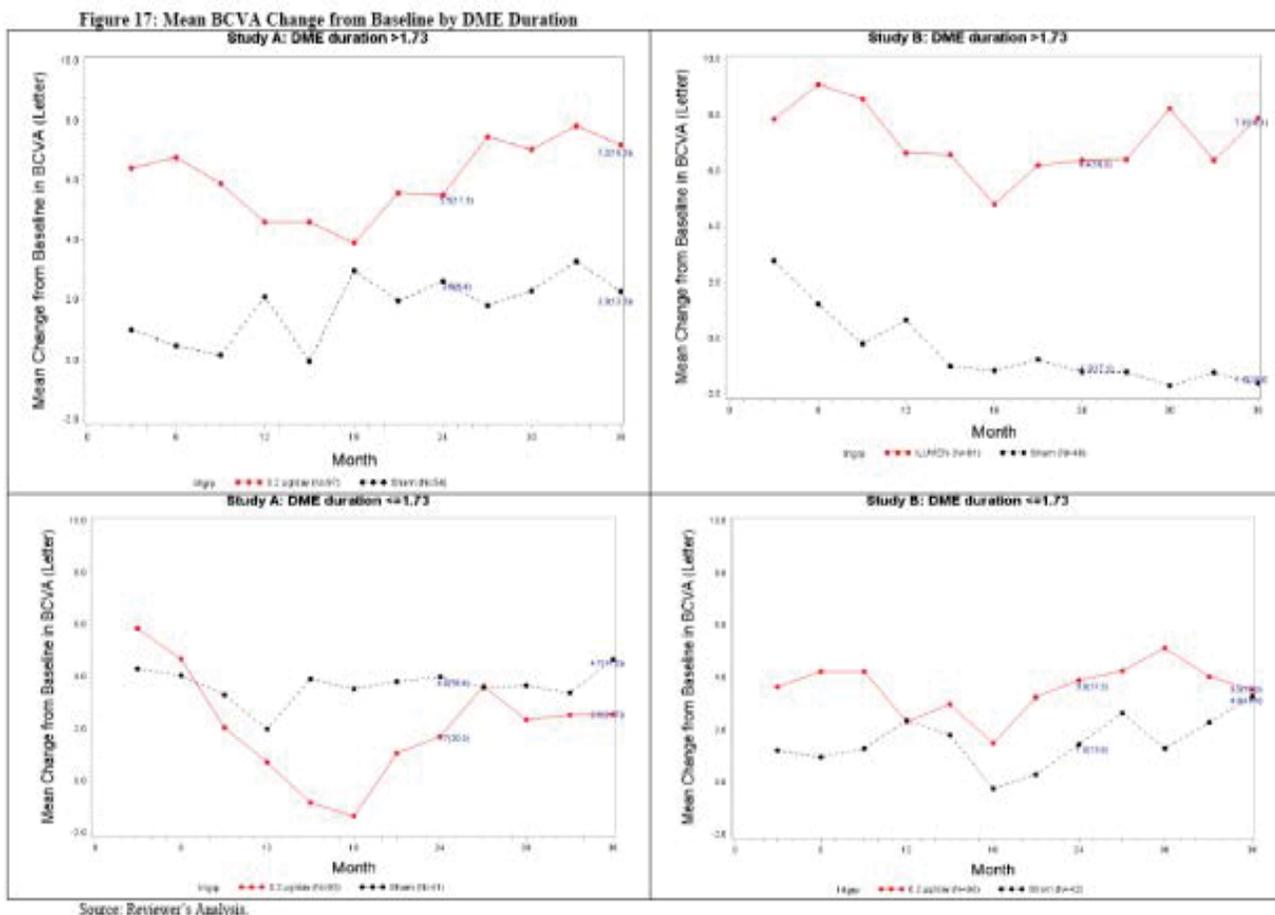
For subgroup of subjects with a DME duration of more than 1.73 years, the ILUVIEN (0.2 µg/day) arm had consistently higher proportion of subjects with a BCVA gain of at least 15 letters compared to Sham. This result is supported by the result in the mean change from baseline BCVA over time. The ILUVIEN (0.2 µg/day) arm had consistently higher mean change from baseline BCVA compared to subjects in the Sham arm for the subgroup of subjects with longer DME duration. A similar efficacy pattern was observed for subjects with longer duration of diabetes mellitus.

APPENDIX E: ADDITIONAL SUBGROUP ANALYSIS

Figure 16: Proportion of subjects with ≥15 letters from Baseline by DME Duration



Source: Reviewer's Analysis.



## 8. Safety

See comprehensive clinical and statistical reviews.

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%).

Based on the three-year data from the two studies combined, the Statistical Reviewer noted that ILUVIEN (0.2 µg/day) treated subjects exhibited a significantly increased risk of cataract formation (subsequently leading to cataract surgery) and elevated intraocular pressure (IOP) in both studies. For phakic subjects, the net-risk of cataract formation was 31% [95% CI: (21%, 41%)] higher in the ILUVIEN (0.2 µg/day) arm compared to Sham; and the net-risk of cataract surgery was 53% [95% CI: (43%, 62%)] higher. For all subjects, the net-risk of elevated IOP adverse event was 25% [95% CI: (18%, 32%)] higher in the ILUVIEN (0.2 µg/day) arm compared to Sham.

The most common ocular (study eye) and non-ocular adverse reactions are shown below.

**Ocular Adverse Reactions Reported by  $\geq 1\%$  of Patients and Non-ocular Adverse Reactions Reported by  $\geq 5\%$  of Patients**

<b>Adverse Reactions</b>	<b>ILUVIEN (N=375) n (%)</b>	<b>Sham (N=185) n (%)</b>
<b>Ocular</b>		
Cataract <sup>1</sup>	192/235 <sup>2</sup> (82%)	61/121 <sup>2</sup> (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)
<b>Non-ocular</b>		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal Failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

<sup>1</sup> Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

<sup>2</sup> 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

## 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.

**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 <sup>1</sup>	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%. As summarized in the CDTL review 9/19/2014, the labeling will include information on IOP elevations ≥ 10 mmHg and ≥ 30 mmHg from baseline, IOP lowering medication and surgical intervention for elevation IOP.

**Summary of Elevated IOP Related Adverse Reactions**

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
IOP elevation ≥ 10 mmHg from Baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mmHg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

**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.

**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)

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 (%)
<b>All Phakic Subjects</b>		
Any Cataract	61/121 (50.4)	192/235 (81.7)
Cataract Operation	33/121 (27.3)	188/235 (80.0)
<b>Phakic Subjects with Chronic DME</b>		
Any Cataract	34/66 (51.5)	98/114 (86.0)
Cataract Operation	24/66 (36.4)	97/114 (85.1)
<b>Phakic Subjects with Acute DME</b>		
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.

At baseline, 235 of the 375 ILUVIEN subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the ILUVIEN group (82%) compared with Sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the ILUVIEN group and 9 months in the Sham group. Among these patients, 80% of ILUVIEN subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both ILUVIEN group and for Sham) of the studies.

As summarized in Section 7, the Statistical Reviewer evaluated the impact of treatment induced cataract formation on the BCVA over time. In both studies, phakic subjects in the ILUVIEN (0.2 µg/day) arm exhibited a steep decline in BCVA starting from Month 6 up to around Month 18.

This timeframe coincides with the time during which the majority of subjects had undergone cataract surgery. Compared with Study B, cataracts appeared to cause vision loss at a much faster rate in Study A. It also appears that in Study A, phakic subjects in the Sham arm had a better BCVA outcome compared to phakic Sham subjects in Study B. At Month 24, the net-gain in mean BCVA among phakic subjects was -1 [95% CI: (-6, 4)] letter in Study A and 3 [95% CI: (-2, 8)] letters in Study B. Similarly, at Month 36, a net-gain of 2 [95% CI: (-3, 7)] letters was seen in phakic subject in Study A, and 4 [95% CI: (-3, 7)] letters in Study B.

In both studies, the Statistical Reviewer notes that pseudophakic subjects in the ILUVIEN (0.2 µg/day) arm had consistently higher mean change from baseline compared to subjects in the Sham arm throughout the study course. The treatment difference in mean BCVA change from baseline at Month 24 was 3 [95% CI: (-3, 10)] letters in Study A, and 8 [95% CI: (1, 16)] letters in Study B.

The Statistical Reviewer summarizes that subjects who underwent cataract surgery seem to have re-gained their vision after the cataract surgery. There was a steady decline in vision for phakic subjects who reported cataract related adverse event but did not have cataract surgery during the study. It is therefore possible to assume that cataract formation and subsequent surgery indeed played a confounding role in the evaluation of the treatment effect.

*Comment:*

*I agree with the current recommendation to approve the application*

## **9. Advisory Committee Meeting**

The application was not presented before an advisory committee (See Section 2.)

## **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 Acceptable.

### **11.2 Office of Scientific Investigation (OSI) Audits**

The OSI Reviewer 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

None

## 12. Labeling

The package insert and carton and container labeling have been reviewed with input from reviewers and consultants.

- **Package insert (PI):** The PI submitted September 18, 2014 is written in PLR format and input from all disciplines and consultants have been addressed.
- **Carton and Container Labels:** The labels submitted on September 18, 2014 are acceptable and address the reviewers and consultants recommendations.
- **Proprietary Name:** The proposed proprietary name Iluvien was reviewed and found acceptable by DMEPA; a letter stating that the name is acceptable was issued on October 13, 2010. The name was again reviewed and found acceptable, a letter to the applicant accepting the name was issued on August 6, 2014.

## 13. Decision/Action/Risk Benefit Assessment

### 13.1 Regulatory Action

The clinical, statistical, pharmacology/toxicology, clinical pharmacology, product quality, office of scientific investigations and compliance reviewers recommend the application should be approved. Labeling has been finalized. The application will be approved.

### 13.2 Risk Benefit Assessment

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

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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)

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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 that runs a variable course and can improve and worsen over years. Management of underlying diabetes may also contribute to improvement in ocular changes.

The moderate versus tight control of blood glucose levels was studied in the Diabetes Control and Complications Trial (DCCT) and the Division<sup>3</sup> interpreted this study as showing an initial worsening in diabetic retinopathy with tight insulin control and concluding that sustained benefit was seen after approximately 3 years of treatment, as seen in the figure below. Therefore, all sponsors who planned DME trials were advised that these trials should be 3 years in duration. This advice was given to all sponsors (b) (4) including Alimera (Iluvien), Genentech (Lucentis), Allergan (Ozurdex) and Regeneron (Eylea).

Some details about the DCCT trial were summarized by the Deputy Director: The DCCT randomized over 1400 patients to either intensive insulin therapy or conventional insulin therapy over 10 years. During the first three years of the clinical trial, the group receiving intensive insulin therapy had a more rapid decrease in hemoglobin A<sub>1c</sub>, (HbA<sub>1c</sub>), a higher incidence of diabetic retinopathy progression, and an increase in the episodes of diabetic macular edema. This difference peaked at approximately 16 months after the initiation of the trial and reversed thereafter. At the three year time point, the intensive therapy group and conventional therapy were approximately equal. After three years and for the next seven years, the intensive insulin therapy group had less diabetic retinopathy, diabetic macular edema, and better visual acuity. The reduction in HbA<sub>1c</sub> became a validated surrogate endpoint for reducing the consequences of diabetic retinopathy with the caveat that a rapid decrease in HbA<sub>1c</sub> resulted in an initial increase in diabetic retinopathy.

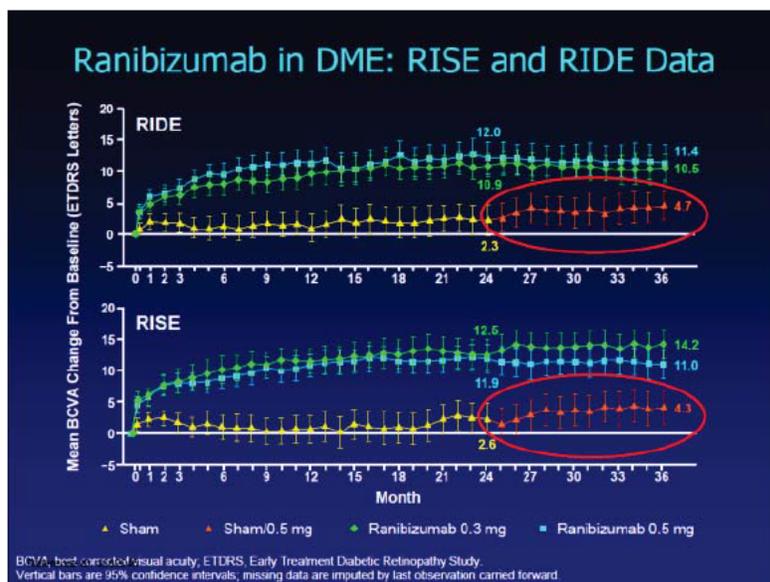
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Iluvien was submitted in 2010 with 2 year data and 2011 with 3 year data as summarized in the clinical and statistical reviews. It is currently in the fourth review cycle and the main subject of this review.

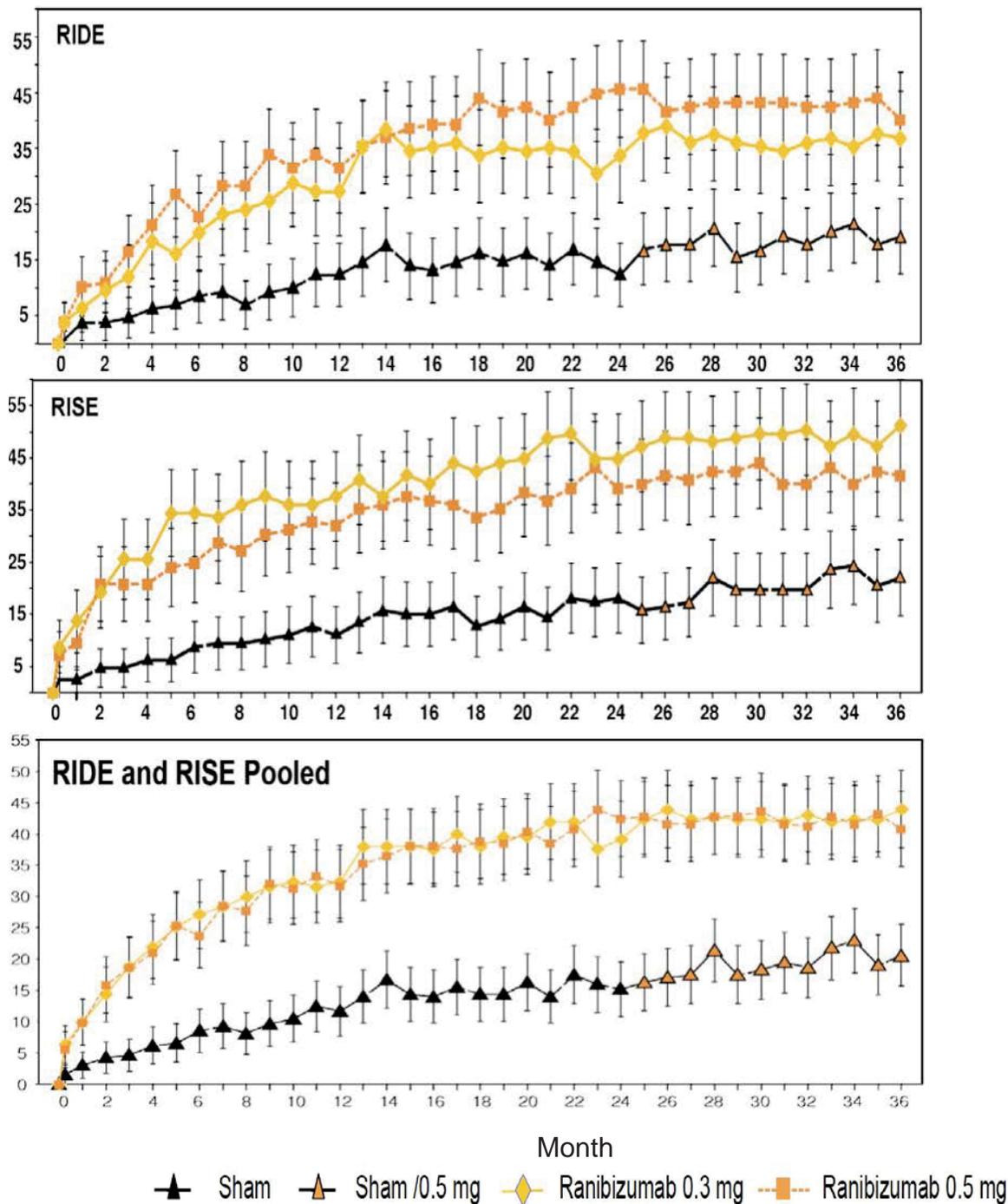
<sup>3</sup> The Division of AntiInfective and Ophthalmology Products (DAIOP), subsequently the Division of Transplant and Ophthalmology Products (DTOP) following the reorganization in May 2011.

Three products have been approved for treatment of DME: Lucentis was approved in 2012, and Ozurdex and Eylea were approved in 2014. Initially Ozurdex (a corticosteroid-containing intravitreal insert) had a limited indication for the treatment of patients with DME who were pseudophakic or scheduled for cataract surgery, a limitation based on the concerns expressed unanimously by the ophthalmology reviewers regarding the rates of cataracts, cataract surgery and increased IOP with Iluvien (a corticosteroid-containing intravitreal insert). Because the rates of these adverse reactions with Ozurdex at 3 years were comparable to rates reported with Iluvien at 3 years (see Appendix A) the recommendation made by the ophthalmology reviewers for Ozurdex (to approved DME with no limitation) appeared inconsistent with the recommendation made by the ophthalmology reviewers for Iluvien (benefit does not outweigh the significant risk of adverse reactions). Now, (b) (4) the cataract-related limitation in the indication is removed from (b) (4) the Ozurdex labeling. The Ozurdex indication is revised to DME in NDA 22315/S-010.

For the approval of Lucentis, Genentech conducted two Phase 3 trials; patients received Lucentis or sham treatment for 2 years, at which time the sham arm could convert to Lucentis treatment. This being the first ophthalmic product for the indication of DME, the application was discussed at the Dermatologic and Ophthalmic Advisory Committee (DODAC) meeting on July 26, 2012. The following graphs provided in the briefing package for the DODAC meeting show the results. Of note, the response to treatment is seen within a few months after start of treatment and is maintained. It was also noted that when the sham group was switched to Lucentis at 2 years into the trial, the gain of 15 letters or more in BCVA is lower and the mean BCVA change from baseline is also lower than was seen in the patients who were randomized to ranibizumab at the beginning of the trials. This is shown in the figures below as well as the Figure in Section 2 (and copied below) of this document, respectively.



**Figure 11 Percentage of Patients (y axis) Gaining  $\geq 15$  Letters from Baseline in BCVA Score in the Study Eye over Time (x axis)**



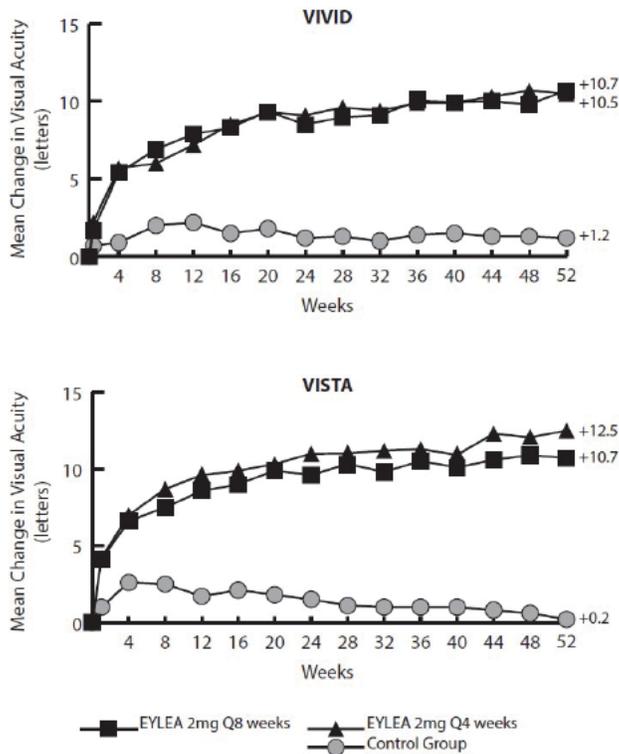
Missing data were imputed by last observed value. Vertical bars are 95% CI of the mean.

.Source: Genentech briefing material for July 26, 2012 DODAC meeting <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM313089.pdf>

For the approval of Ozurdex, Allegan conducted two, 3-arm Phase 3 trials, comparing 2 doses of Ozurdex to sham treatment, in clinical trials lasting 3 years. The efficacy supplement for NDA 22315/S-09 was submitted on June 13, 2013, amended April 7, 2014 and approved June 28, 2014 for the indication of diabetic macular edema in patients who are pseudophakic or scheduled for cataract surgery. The results of the trials and the reason for this limitation are explained in detail in Appendix A. Subsequently, the limitation was removed in NDA 22315/S-010.

For the approval of Eylea, Regeneron conducted two Phase 3 trials, planning 3-year trials. In these trials two doses of Eylea were compared to baseline laser control. Regeneron did not wait to complete the 3 year trials, but asked to submit their results when 1 year data were available, given the European authorities requested 1 year data. The efficacy supplement, BLA 125387/S-37 was submitted October 18, 2013 and Eylea was approved for DME on July 29, 2014. The results are presented below.

**Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIVID and VISTA Studies**



The submission of Eylea with one year data represented the first modification in the handling of the DME indication, and understanding the role of vascular endothelial growth factor (VEGF) inhibitors in the treatment of DME. These studies demonstrated that there was no paradoxical decline in BCVA early as seen in the DCCT trial. Informed by the DRCRN study comparing

Lucentis with triamcinolone and sham in DME,<sup>4</sup> the benefit seen early in the trial was maintained, and the agency approved this anti-VEGF product on 12 month data.

The submission of Iluvien and Ozurdex represents a second modification in the handling of the DME indication, and understanding the role of corticosteroid use in the treatment of DME. Until these two corticosteroids were each studied for the 3-year duration, the specific and similar incidence of cataract formation and increased IOP with each product had not been appreciated. The shorter duration studies with Ozurdex in uveitis and retinal vein occlusion reported lower rates of adverse reactions for Ozurdex, but the 3 year rates were comparable for Ozurdex and Iluvien. The benefit risk consideration did not look at the outcome in patients by lens status; analysis of the phakic versus pseudophakic population helps present the efficacy unconfounded” (pseudophakic) and confounded (phakic) by cataract formation, giving a more informative presentation of treatment effect and toxicity. During the initial reviews of Iluvien, it would appear that cataract surgery and use of IOP lowering medication were considered part of the problem associated with the adverse reactions or cataract formation and increased IOP, respectively, without fully appreciating that one could look at these procedures as a means to manage the toxicities instead, often successfully. This view was expressed by Alimera during the meetings with the Division, but did not lead to an evolution in the understanding of the role of corticosteroids in DME until the review of the Ozurdex application, where the uncanny similarities in the results of the trials were seen. The following table provides a side-by-side presentation of the trial design and the trial results (also shown in Appendix A):

	<b>Fluocinolone Acetonide Intravitreal Insert #</b>	<b>Ozurdex</b>
<b>STUDY OVERVIEW</b>	Two randomized (2:2:1) double- masked Phase 3 trials	Two randomized (1:1:1) double-masked Phase 3 trials
Duration of trials	3 years	3 years
Number of planned study visits	>=16	>= 16
Number of patients receiving test drug – 2 doses tested	768	642
Number of patients receiving control	185	328
Location where studies conducted	US and outside US	US and outside US
<b>OUTCOME</b>		
Duration of Diabetes Mellitus	16.1-17.1 years	15.9-16.2 years
Duration of DME	3.5-3.9 years ##	15-17 months

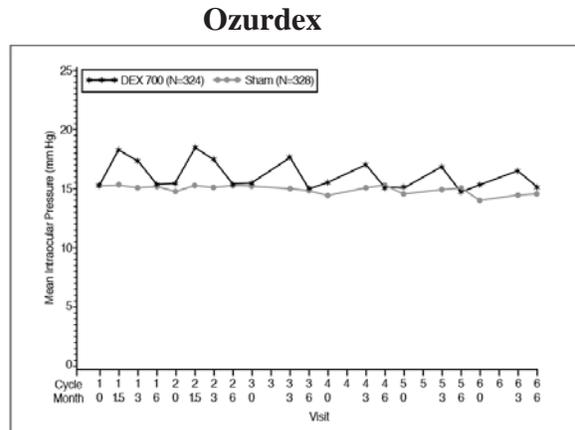
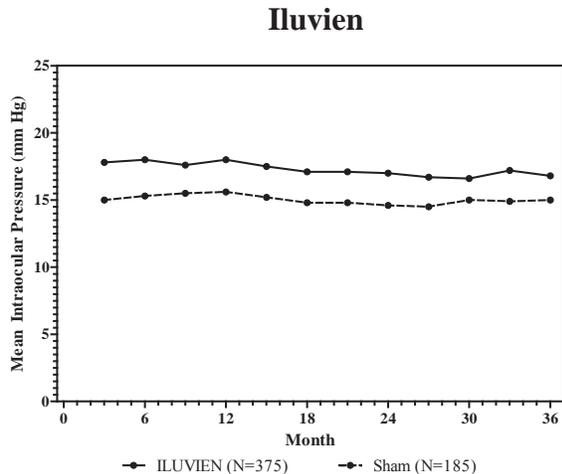
<sup>4</sup> The Diabetic Retinopathy Clinical Research Network (DRCRN) provided a letter of authorization dated February 12, 2013 for FDA personnel to cross-reference all data contained in the DRCRN IND (b) (4) in support of an Information Amendment to IND (b) (4) DRCRN consider the information contained in this submission to be confidential and ask that the FDA not disclose its contents to any parties (b) (4) without prior written consent from Diabetic Retinopathy Clinical Research Network. (b) (4)

Number of treatments, mean (range)	1 (range 1-3)	4 (range 1-7)
Rescue therapy given/discontinued due to lack of efficacy	~ 20%-25%	~20%-25%
Difference between test and control arms		
Primary endpoint: >=15 letter improvement in BCVA, difference between test drug arm and sham control arm	~ 10%	~ 10%
Cataract formation	~ 30%	~ 30%
Difference between test and control arms		
Cataract surgery	~ 50%	~ 50%
Difference between test and control arms		
Increased IOP	~ 30%	~ 30%
Difference between test and control arms		
IOP lowering medications	~ 30%	~ 30%
Difference between test and control arms		
Glaucoma surgery	~ 5%	~ 1%
Difference between test and control arms		
Mean change in BCVA from baseline (letters)	4 to 5 letters	0 to 3 letters
Difference between test and control arms		

# Information for the FA intravitreal insert in this table is based on the Campochiaro 2012 publication; the Acknowledgment section of the publication states that the study was supported by Alimera Sciences, Atlanta, Georgia. This fact probably led to Allergan referring to this product as Iluvien in the Ozurdex application.  
## Based on FDA review, the median duration is ~ 1.7 years

Regarding the issue of increased IOP, there is no difference in the incidence of IOP elevations, but there is an apparent difference in the profile over time, as shown in the figures below. The figures use the same scale for the mean IOP mm Hg and show that IOP elevation persists during the entire 3 year duration of the trial with Iluvien (left graph) while it rises and decreases within six month (to baseline) in the Ozurdex trials.

**Mean IOP during the study**



Regarding IOP elevation: the labeling for both Ozurdex and Iluvien presents the IOP elevations by proportion of patients with 10 mmHg and 30 mmHg elevation of IOP, as well as use of IOP lowering medications and IOP lowering surgical procedures. As noted, approximately 30-35% of patients had an increased IOP. The patient and clinician could discuss whether IOP elevation during a previous cycle of corticosteroid treatment was effectively managed with IOP lowering agents, and the intervention maintained the IOP at a level both considered clinically acceptable. Other labeling recommendations are summarized in the CDTL review.

Brought up during the discussion of Iluvien, another potential change in the understanding of the effect of DME duration and DM duration and treatment response may be emerging. This issue will need additional discussion and probably additional analyses of available DME trials. The currently identified observations include the following:

Lucentis:

In the Lucentis trials, sham patients who were switched to Lucentis treatment after two years in the studies had a smaller percentage of patients gaining  $\geq 15$  letters from baseline in BCVA as well as a smaller response in mean BCVA change from baseline than the patients who were originally randomized and treated initially with anti-VEGF therapy. Figures showing these results were presented during the DODAC meeting (Section 13, above) and during the July 26, 2012 meeting with Alimera (Section 2), respectively. As noted earlier in the review, patients who were randomized to Lucentis at the beginning of the trial had a better response in terms of change in BCVA than patients who were switched from the sham control arm to Lucentis at the 2-year point of the ongoing trials.<sup>5</sup>

Iluvien:

Various parameters were analyzed in the Iluvien trials, including outcome by median duration of DME and DM. Alimera first presented a DME analysis during the meeting of July 26, 2012 (Section 2)

(b) (4)

Based on Alimera's submission of May 21, 2013, the calculated median duration of DME was 1.73 years. The analysis in the current review (Section 7) examined both duration of DME and DM and other parameters. The results show that in the group with shorter duration of DM and also DME, the treatment effect was not statistically significant. In the group with longer duration of DM and DME, the treatment effect was statistically significant. (See Section 7)

There were additional patterns observed

(b) (4)

The

<sup>5</sup> Brown DM et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials RISE and RIDE. *Ophthalmology* 2013;10; 2013-22.

interpretation Alimera proposed during the meeting is that the effect of Iluvien, a corticosteroid, may offer greater apparent benefit to patients who have had longer duration of DME.

(b) (4)

In summary, in the Lucentis trials, patients had a higher rate of BCVA response when randomized to Lucentis at the start of the study than the sham patients who were switched to Lucentis at 2-years into the study. In the Iluvien trials, patients had a higher response if they had duration of DME >1.73 years and duration of DM > 15 years, than patients who had shorter durations. These observations need further study.

The Iluvien analyses and interpretations were planned prospectively, but these analyses were not adjusted for multiplicity. These were two of many subpopulation analyses (others include age, race, gender, HbA1c, country, etc.), as presented in the Statistical Review, but it is noteworthy that the effect seen in DME as well as DM and is reproduced in each of two studies for each of the underlying conditions. Although the specific cut-off of 1.73 years (versus 2 years, 3 years, etc.) was not pre-specified in the protocol, and was not adjusted for multiplicity, this finding was weighed by the European regulators in deciding on the indication accepted in Europe.

For completeness, the summary of the deficiencies and their resolution in the four review cycles from the Deputy Director's review is presented below:

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)

In summary, Alimera had addressed all the deficiencies in the October 17, 2013 letter. All disciplines recommend approval, and labeling has been finalized. NDA 201923 will be approved.

### 13.3 Recommendation for other Postmarketing Requirements and Commitments

None

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert)

Indication: treatment of diabetic macular edema (DME)

(b) (4)

## **APPENDIX A:**

### **Division Director Review of NDA 22315/S-009**

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