

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-737

MEDICAL REVIEW



Original New Drug Application

Submission Date: October 8, 2004
Review Completed: April 8, 2005

Deputy Division Director: Wiley A. Chambers, MD

Trademark: Retisert
Established Name: fluocinolone acetonide intravitreal implant

Applicant: Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
(813) 866-2568

Pharmacologic Category: Corticosteroid

Proposed Indication: Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye

Dosage Form: Intravitreal implant

Route of Administration: Intravitreal

NDA Drug Classification: 3P

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I. Recommendations

A. Recommendation on Approvability

NDA 21-737 is recommended to be approved for the treatment of non-infectious, chronic uveitis affecting the posterior segment of the eye.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

The following postmarketing studies have been recommended by the Division and accepted by the applicant.

1. To ensure that there are no unique complications following cataract extractions, Bausch & Lomb (B&L) will conduct two outcome analyses (one year apart) on patients from Clinical Studies BLP 415-001 and BLP 415-004 who have undergone cataract surgery.

Analysis plan submission:	by July 2005
Initial analysis cataract outcomes report submission	by December 2005
Final analysis cataract outcomes report submission	by December 2006

2. To monitor the potential for delamination of implants manufactures by the modified process, B&L will instruct all participating investigators in Clinical Studies BLP 415-001 and BLP 415-004 to report to B&L, on an ongoing basis, any observations of physical separation of implant components, regardless of cause. B&L will submit all reported instances to the agency on a quarterly basis for the first three years post-approval.

Physician instructions sent to investigators:	by June 2005
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3. To assess the effect of the implant on the corneal endothelium, B&L will complete a case-controlled study using a subset of approximately 100 patients from Clinical Studies BLP 415-001 and BLP 415-004 who have been implanted with Retisert for at least one year.

Case control protocol submission:	by August 2005
Study start:	by January 2006
Final report submission:	by December 2006

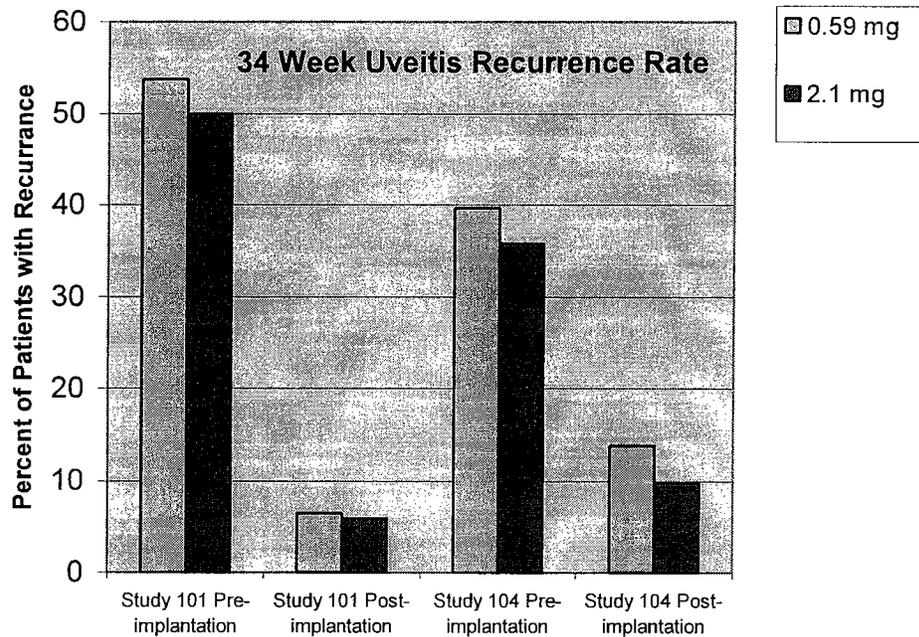
II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Fluocinolone acetonide (FA) intravitreal implant is a corticosteroid implant designed to deliver sustained 0.3 µg/day dose of corticosteroid directly into the vitreous for an extended period of time (target 30 to 36 months). Two phase 3, randomized, multicenter, double-masked, controlled clinical trials were conducted in 517 total enrolled subjects to evaluate the safety and efficacy of 0.59 mg FA intravitreal implant and 2.1 mg FA intravitreal implant for the treatment of patients with chronic non-infectious posterior uveitis. Over 500 total subjects are expected to complete 3 years of follow-up following implantation. Five hundred and three (503) subjects have completed at least one year of follow-up post implantation. Other pertinent clinical data sources utilized in this review include safety data from the ongoing uveitis clinical trials.

B. Efficacy

Clinical studies BLP 415-001 and BLP 415-004 demonstrate a clinically and statistically significant difference for their primary endpoint (i.e., the proportion of patients with recurrence of uveitis in the study eye within 34 weeks following implantation compared to the proportion with recurrence of uveitis in the 34 weeks preceding implantation) for the both the 0.59 mg dose and 2.1 mg dose. The efficacy of the two doses is similar.



C. Safety

The implant requires a surgical operation to be performed in order to place the implant in the vitreous. A temporary decrease in visual acuity was observed initially following the surgical implantation. Additionally, patients are at risk for endophthalmitis as a result of surgery and are at risk for all of the complications known to occur with ophthalmically administered corticosteroids (risk of secondary infection, poor wound healing, local immunosuppression).

Over the course of the weeks following implantation, two significant adverse events have been observed which may lead to the need for another surgical operation. The first is the development of cataracts. The development of posterior subcapsular cataracts is a known complication of corticosteroid use and nearly all patients develop cataracts over the span of approximately 2 years. Patients with chronic uveitis commonly develop cataracts. It is not known whether the cataract development is due to the uveitis or due to the corticosteroids commonly used to treat the uveitis. Based on the data observed to date, patients undergoing cataract operations with the implant in place did better than is generally expected of patients with uveitis undergoing cataract operations. The applicant has committed to a phase 4 study to evaluate the outcome of cataract surgery in patients with an implant in place.

The second significant adverse event is the development of increased intraocular pressure. The development of increased intraocular pressure is a known side effect of corticosteroid treatment, however, it was generally believed to occur only in genetically susceptible individuals. The studies submitted in this NDA, demonstrate that with the local doses provided from the implants, even patients thought not to be genetically susceptible will have elevated intraocular pressure. Approximately two thirds of patients treated with the implant will need additional medications to control their elevated intraocular pressure and approximately one third will need a surgical operation to control their intraocular pressure. While the pressure can be controlled by removing the implant, the vast majority of patients elected to keep their implants in spite of the elevated intraocular pressure.

Additional adverse events are listed in the proposed package insert and include:

Procedural complications (including cataract fragments in the eye post-op, implant expulsion, injury, mechanical complication of implant, migration of implant, post-op complications, post-op wound complications, and wound dehiscence), reduced visual acuity, conjunctival hemorrhage, conjunctival hyperemia, glaucoma, blurred vision, abnormal sensation in the eye, eye irritation, hypotony, pruritus, vitreous floaters, maculopathy, vitreous hemorrhage, ptosis, eye inflammation, eyelid edema, increased tearing, dry eye, macular edema, visual disturbance, eye discharge, conjunctival edema/chemosis, photophobia, blepharitis, corneal edema, photopsia, retinal hemorrhage, choroidal detachment, vitreous opacities, eye swelling, headache, nasopharyngitis, arthralgia, sinusitis,

dizziness, pyrexia, nausea, cough, influenza, upper respiratory tract infection, vomiting, limb pain, back pain, rash, and pain.

D. Dosing, Regimen, and Administration

The RETISERT intravitreal implant is surgically implanted into the posterior segment of the affected eye. Following depletion of fluocinolone acetonide from the RETISERT intravitreal implant, as evidenced by recurrence of uveitis, RETISERT may be replaced.

III. Reviews from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

Reviews have been completed from Chemistry/Manufacturing, Non-clinical Pharmacology/Toxicology, Microbiology (sterility assurance), Clinical Pharmacology, and the Division of Drug Marketing, Advertising and Communications (DDMAC). There are no unresolved issues with respect to sterility assurance, manufacturing, or preclinical studies.

IV. Administrative

The application was submitted as a 505(b)(2), however, it did not reference a listed product, nor did it rely on information from any reference listed products for the non-clinical or clinical studies. There are no fluocinolone acetonide products with unexpired patents in the list of approved new drug products. The dosage form of this product is sufficiently different from the dosage form of all previously approved fluocinolone drug products such that their clinical safety and/or efficacy information does not significantly contribute to the understanding of this new drug product. The applicant has sponsored or conducted all studies necessary to support this application. For these reasons, I do not believe that this application should be considered a 505(b)(2) application, but instead should be considered a 505(b)(1) application.

V. Pediatrics

The proposed indication is an orphan indication and it is unlikely that the implant will be used in a large number of pediatric patients. As an orphan indication, the application qualifies for a waiver of pediatric studies.

VI. Labeling

The applicant has revised the proposed labeling based on comments from the Division. The labeling is considered appropriate and recommended for approval.

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/s/

Wiley Chambers
4/8/05 05:26:37 PM
MEDICAL OFFICER

Wiley Chambers
4/8/05 05:35:13 PM
MEDICAL OFFICER

M.O. Review #2
Labeling Amendment to Original NDA 21-737

Submitted: March 28, 2005; March 31, 2005; April 5, 2005; April 7, 2005

Received: March 30, 2005; April 4, 2005; April 6, 2005; April 7, 2005

Review completed: April 7, 2005

Reviewer: Lucious Lim, M.D., M.P.H.

Proposed Tradename: Retisert 0.59 mg

Established Name: Fluocinolone acetonide intravitreal implant 0.59 mg

Sponsor: Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
(813) 866-2568
Contact: Yelen Concepcion

Pharmacologic Category: Corticosteroid

Proposed Indication: Indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye

Dosage Form and Route of Administration: Intravitreal implant

Submitted:

Submitted are revised labeling (package insert and container and carton labeling) based on previous review and discussion with the applicant. Submitted also is Bausch & Lomb's commitment to perform the following: 1) two post-marketing outcome analyses to evaluate the post-operative course of patients who undergo cataract surgery following implantation of Retisert, 2) monitor on an ongoing basis, any observations of delamination, regardless of cause, and 3) a post-marketing case-controlled study to evaluate the effect of this drug product on the corneal endothelium.

The Division of Medication Errors and Technical Support (DMETS) completed its review of this drug product on April 6, 2005. DMETS's recommendations are taken into consideration in this medical officer's review.

The phase 4 post-marketing proposals are as follow:

- To ensure that there are no unique complications following cataract extractions, Bausch & Lomb (B&L) will conduct two outcome analyses (one year apart) on patients from Clinical Studies BLP 415-001 and BLP 415-004 who have undergone cataract surgery.

Analysis plan submission:	by July 2005
Initial analysis cataract outcomes report submission	by December 2005
Final analysis cataract outcomes report submission	by December 2006

- To monitor the potential for delamination of implants manufactures by the modified process, B&L will instruct all participating investigators in Clinical Studies BLP 415-001 and BLP 415-004 to report to B&L, on an ongoing basis, any observations of physical separation of implant components, regardless of cause. B&L will submit all reported instances to the agency on a quarterly basis for the first three years post-approval.

Physician instructions sent to investigators:	by June 2005
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- To assess the effect of the implant on the corneal endothelium, B&L will complete a case-controlled study using a subset of approximately 100 patients from Clinical Studies BLP 415-001 and BLP 415-004 who have been implanted with Retisert for at least one year.

Case control protocol submission:	by August 2005
Study start:	by January 2006
Final report submission:	by December 2006

Reviewer's Comments:

Acceptable.

M.O. Review #2

NDA 21-737 Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

Reviewer: Lucious Lim, M.D., M.P.H.

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

2 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Medical*_____

Reviewer's Comments:

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

This may be done with the first labeling supplement submission for this drug product.

Recommendations:

NDA 21-737 is recommended for approval for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye with the proposed phase 4 post-marketing proposals and labeling noted in this review.

It is recommended that the applicant revise the established name on the foil pouch and carton labeling to a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name. This may be done with the first labeling supplement submission for this drug product.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc:

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HFD-550/PharmTox/ChenC
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HFD-550/Biopharm TL/Bashaw

M.O. Review #2

NDA 21-737 Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg
Reviewer: Lucious Lim, M.D., M.P.H.

CLINICAL REVIEW

Application Type NDA 21-737
Submission Number 000
Submission Code Original

Letter Date October 7, 2004
Stamp Date October 8, 2004
PDUFA Goal Date April 8, 2005

Reviewer Name Lucious Lim, M.D., M.P.H.
Review Completion Date March 8, 2005

Established Name Fluocinolone acetonide intravitreal
implant 0.59 mg
(Proposed) Trade Name Retisert
Therapeutic Class Corticosteroid
Applicant Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637

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Priority Designation P

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 21-737 is recommended for approval for the treatment of chronic non-infectious posterior uveitis in patients 12 years of age and older with the labeling revisions included in this review.

1.2 Recommendation on Postmarketing Actions

The clinical studies submitted in this NDA to support safety and efficacy, BLP 415-001 and 415-004, are ongoing and will not be completed until the enrolled subjects have completed 3 years of post-implantation follow-up. The applicant is expected to submit all collected data after submission of the original NDA as they become available.

In addition, the applicant should commit to a phase 4 post-marketing plan to adequately address concerns raised by the following: 1) the report of high incidence of cataract extraction and the potential for complications following cataract surgery in this population, 2) the recurrence of delamination after the manufacturing process had been modified, and 3) the lack of an assessment on the effect on the corneal endothelium for this drug product.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	fluocinolone acetonide intravitreal implant 0.59 mg
(Proposed) Trade Name	Retisert
Therapeutic Class	Corticosteroid

Uveitis is defined as inflammation of the uveal tract (iris, ciliary body, choroids) or adjacent structures. The causes of inflammatory reaction of the inner eye can be infectious, traumatic, neoplastic, or autoimmune. Numerous classification schemes have been used to categorize the various types of uveitis. The classification scheme recommended by the International Uveitis Study Group is based on anatomic location i.e., anterior, intermediate, posterior, and panuveitis. Posterior uveitis may be focal, multifocal, or diffused, involving the retina and choroid.

Posterior uveitis is a vision threatening condition and is responsible for approximately 10% of blindness in the United States. This condition occurs in all age groups and affects people of different ethnic origins. This type of inflammation affecting the choroid and retina may be a primary intra-ocular process or an ocular manifestation of systemic disease. Posterior uveitis accounts for most of the loss of vision in uveitis patients due to cystoid macular edema, glaucoma, retinal detachment, subretinal fibrosis, cataract, and optic disk atrophy.

Generally, medical therapy includes topical, periocular, and systemic administration of corticosteroid. Immunosuppressive therapy is used for patients with severe uveitis who are unresponsive to corticosteroid therapy or for patients with severe corticosteroid-induced complications. The goal of therapy is to suppress the inflammation.

Fluocinolone acetonide (FA) intravitreal implant is a corticosteroid implant designed to deliver sustained and controlled levels of corticosteroid directly into the vitreous for an extended period of time (target 30 to _____). This delivery method bypasses the "blood-eye barrier." Thus, the anti-inflammatory effects of corticosteroid can be offered with less systemic side effects and the need for multiple periocular injections.

Two Phase 3, randomized, multicenter, double-masked, controlled clinical trials were conducted in 517 total enrolled subjects to evaluate the safety and efficacy of 0.59 mg FA intravitreal implant and 2.1 mg FA intravitreal implant for the treatment of patients with non-infectious posterior uveitis. A total of 504 subjects are expected to complete 3 years of follow-up following implantation. Five hundred and three (503) subjects have completed at least one year of follow-up post implantation. Other pertinent clinical data sources utilized in this review include safety data from two ongoing uveitis clinical trials and three individual investigator uveitis studies.

1.3.2 Efficacy

Clinical studies BLP 415-001 and BLP 415-004 demonstrate statistical significance ($p < 0.0001$) for their primary endpoint (i.e., the proportion of patients with recurrence of uveitis in the study eye within 34 weeks following implantation compared to the proportion with recurrence of uveitis in the 34 weeks preceding implantation) for the both the 0.59 mg dose and 2.1 mg dose. The efficacy of the two doses is similar.

1.3.3 Safety

There appears to be a clear dose-response relationship between both doses of the FA intravitreal implant and IOP as well as lens opacity. Given this relationship, the incidence of drug-related adverse events is expected to rise as clinical studies BLP 415-001 and BLP 415-004 progress.

With respect to IOP, there are statistically differences in mean IOP at each visit post-implantation as compared to baseline beginning 4 weeks post-implantation for both treatment groups. The number of patients that require IOP lowering medications to control IOP increases over time. By 34 weeks post-implantation, the majority of patients are on IOP lowering medications. The percentage of patients that require a filtering procedure to control IOP ranges from 4% to 9%.

With respect to lens opacity, clinically significant increases in lens opacity were observed with increasing frequency over time post-implantation. By 34 weeks post-implantation, the percentage of phakic eyes with clinically significant increases in lens opacity ranges from 20% to

36%. The percentage of patients who had undergone cataract surgery by 34 weeks post-implantation ranges from 9% to 20%. By 1 year the percentage ranges from 25% to 38%.

1.3.4 Dosing Regimen and Administration

The recommended dosing regimen is surgical implantation of Retisert into the posterior segment of the affected eye. The implant contains one tablet of 0.59 mg of fluocinolone acetonide. The Retisert implant is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 $\mu\text{g}/\text{day}$, decreasing over the first month to a steady state between 0.3-0.4 $\mu\text{g}/\text{day}$ over approximately 30 months. Retisert may be replaced following depletion of fluocinolone acetonide from the Retisert implant as evidenced by progression of posterior uveitis.

1.3.5 Drug-Drug Interactions

There was no important drug-drug interactions noted that would affect the product's clinical use.

1.3.6 Special Populations

Subgroup analyses stratified by age (<65, 65-<75, and ≥ 75 years), gender, iris color, and race did not reveal any significant differences in the primary efficacy endpoint and safety profiles.

The clinical trial population in BLP 415-001 was overwhelmingly white whereas the study population for BLP 415-004 was overwhelmingly Asian. This was due to the location of the study sites for each of the clinical trials and does not reflect an issue with recruitment.

There are no adequate and well-controlled studies in the pediatric population. FA intravitreal implant for the posterior uveitis indication is exempted from the pediatric assessment requirement due to its orphan drug designation. The clinical studies allowed enrollment of pediatric subjects, but only 18 subjects below 18 years of age enrolled. No subgroup analysis of pediatric subjects was performed.

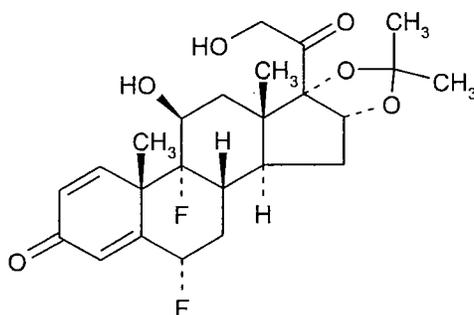
There are no adequate and well-controlled studies in pregnant women. It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name fluocinolone acetonide intravitreal implant, 0.59 mg
(Proposed) Trade Name Retisert
Therapeutic Class Corticosteroid
Structure C₂₄H₃₀F₂O₆



Proposed Indication Treatment of non-infectious uveitis affecting the posterior segment of the eye

Composition of 0.59 mg Fluocinolone Acetonide Implant

Component	Units/implant	Reference	Component Function
Core Tablet			
Fluocinolone acetonide	0.59 mg	USP	Drug substance
Microcrystalline cellulose	/	NF	/
Polyvinyl alcohol		In-house standard	
Magnesium stearate		NF	
Core tablet weight			
Polymer Coatings			
Silicone elastomer cup with orifice	/	In-house standard	/
	/		/

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 NDA 21-737 000
 Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

Polyvinyl alcohol	In-house standard
Silicone adhesive	DMF holder standard
Suture Tab	
Polyvinyl alcohol	In-house standard

Topical dermatologic fluocinolone acetonide is approved and marketed in the United States. Fluocinolone acetonide intravitreal implant is not marketed in the United States nor has it been marketed or withdrawn from the market in any country.

2.2 Currently Available Treatment for Indications

Topical ophthalmic corticosteroids as a class are approved to treat corticosteroid-responsive allergic and inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe. Systemic corticosteroids as a class are approved for ophthalmic use to treat severe acute or chronic allergic and inflammatory ophthalmic conditions including diffuse posterior uveitis.

2.3 Availability of Proposed Active Ingredient in the United States

Topical dermatologic fluocinolone acetonide is approved and marketed in the United States. Systemic fluocinolone acetonide is not currently marketed in the United States.

2.4 Important Issues with Pharmacologically Related Products

There have been no additional safety issues raised with this class of agents outside of those identified in this review.

2.5 Presubmission Regulatory Activity

research IND applications were submitted by individual investigators to study FA intravitreal injection between April 2, 1998, and December 29, 2000. investigations were conducted on subjects with a diagnosis of uveitis. "Pre-IND" meetings were conducted on September 9, 1999, and January 12, 2000. The original IND application (IND 60,000) and a request for Fast-Track designation for the posterior uveitis indication were received on March 6, 2000. Fast-Track designation was granted on April 28, 2000. In addition, the Applicant requested orphan drug designation which was granted on July 31, 2000.

As an orphan drug, FA intravitreal implant is exempted from the pediatric assessment requirement.

An "End-of-Phase 2" (EOP2) meeting was held on February 12, 2003. The Division stated that two adequate and controlled trials would be required to demonstrate efficacy for the drug product.

The Applicant submitted a request for consideration for enrollment in the CMA Pilot 1 program on December 8, 2003, and was accepted into the Pilot 1 program on January 26, 2004. The Division recommended a "Pre-NDA" meeting prior to submitting the first reviewable unit. The "Pre-NDA" meeting was held on May 10, 2004.

2.6 Other Relevant Background Information

To date, there are no marketing applications pending for FA intravitreal implant. It has not been marketed or withdrawn from the market in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

From the chemistry, manufacturing, and controls (CMC) standpoint, the NDA is recommended as approvable pending satisfactory completion of the product microbiology review and inspection of the manufacturing facility at Waterford, Ireland.

3.2 Animal Pharmacology/Toxicology

There were no significant findings from the pre-clinical pharmacology or toxicology reviews that would affect the clinical outcome.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

All submitted clinical study reports, clinical protocols, and literature reports were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth. Proposed draft labeling and Individual Patient Data Listings (i.e., CRF Tabulations) for Studies BLP 415-001 and BLP 415-004 were submitted electronically.

Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 21-737 000
Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

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Clinical Review
 Lucious Lim, M.D., M.P.H.
 NDA 21-737 000
 Retisert (flucinolone acetonide intravitreal implant) 0.59 mg

4.2 Tables of Clinical Studies

Phase 3 Posterior Uveitis Studies in FA Intravitreal Implant Utilized in M.O. Safety and Efficacy Review

Study Number Start Date/ Last 34-Week Visit Date/End Date	Country (No of Study Sites)	Population Studied	Design	Treatment Doses	Study and Treatment Duration	# Pts Treated Age Range Mean Age (yrs)	Sex Race
BLP 415-001 December 28, 2000 May 8, 2003 Ongoing	USA (26) Singapore (1)	Non- infectious posterior uveitis	Randomized, multicenter, double-masked, controlled	0.59 mg implant 2.1 mg implant (2:3)	3 years	278 68 0.59 mg 107 2.1 mg 7-84 yrs 43.5	27.7% Male 72.3% Female 66.2% Caucasian 17.6% Black 7.6% Asian 6.1% Hispanic 1% Other
BLP 415-004 May 28, 2002 January 6, 2004 Ongoing	Canada (5) USA (4) Australia (4) India (3) Philippines (2) Hong Kong (1)	Non- infectious posterior uveitis	Randomized, multicenter, double-masked, controlled	0.59 mg implant 2.1 mg implant (1:1)	3 years	239 88 0.59 mg 74 2.1 mg 12-92 yrs 41.4	43.9% Male 56.1% Female 69.9% Asian 21.8% Caucasian 3.8% Other 2.9% Black 1.7% Hispanic

4.3 Review Strategy

All submitted clinical study reports, and clinical protocols were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth. Proposed draft labeling and Case Report Form (CRF) Tabulations for BLP 415-001 and BLP 415-004 were provided electronically.

4.4 Data Quality and Integrity

Case Report Forms for all discontinued subjects in both BLP 415-001 and BLP 415-004 were reviewed by this medical officer.

4.5 Compliance with Good Clinical Practices

The data was reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the respective trials.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

5 CLINICAL PHARMACOLOGY (FROM THE CLINICAL PHARMACOLOGY REVIEW)

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5.1 Pharmacokinetics

In Vitro Release Rate of 0.59 mg FA Intravitreal Implant in Aqueous Environment: By Lot (µg)

0.59 mg Implant Lot # (Batch Purpose)	0 mo.	0.75 mo.	1.5 mo.	2.25 mo.	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	24 mo.	28 mo.	30 mo.
Lot 00040	0.53				0.34	0.31	0.34	0.31	0.33 ¹			
Lot 00051A/B [Preclinical Tests, BLP 415-001.	0.56					0.44	0.39	0.36	0.33	0.29 ¹		
Lot 01-0065 (Stability)	0.69				0.52	0.46	0.40	0.39	0.34	0.30	0.30	0.26 ¹
Lot 01-0066 (Stability)	0.76				0.54	0.55	0.43	0.46	0.40	0.34	0.31	0.32 ¹
Lot 01-0067 (Stability)	0.71				0.52	0.48	0.41	0.46	0.36	0.32	0.32	0.32 ¹
Lot 02-0065 (BLP 415-004,	0.60				0.37	0.36	0.35	0.31	0.31	0.22 ²		
SR304003A (Stability)	0.61	0.37	0.39	0.35	0.35	0.32 ²						
SR307002A (Stability)	0.61	0.44	0.45	0.40	0.39	0.36 ²						
SR308002A (Stability)	0.53	0.33	0.37	0.33	0.33	0.29 ²						
Average	0.62	0.38	0.40	0.36	0.42	0.40	0.38	0.38	0.35	0.29	0.31	0.30

¹Study terminated or completed at that time point

²Study ongoing

FA Assayed from Explants

Days in Use	Study #	Patient No.	Assay (% Drug Remaining)	Implant Dose (mg)
32	415-004	2139		NA ¹
56	415-004	1011		NA ¹
101	415-004	2122		NA ¹
140	415-004	2124		NA ¹
196	415-001	1318		2.1
203	415-004	1308		NA ¹
224	415-001	2205		0.59
403	415-001	1331		2.1
469	415-001	2037		2.1
522	415-001	2017		0.59

578	415-001	1021	39.0	2.1
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¹NA=Not available (unintentionally not reported)

5.2 Pharmacodynamics

There is no direct metabolism information on ocularly administered FA. The potential metabolism of FA given by the ocular route is extrapolated from information that is available on other corticosteroids. Ocular metabolism of FA is not expected. It is most likely that FA is absorbed systemically but at very low levels (below the LOQ of 200 pg/mL) over a prolonged period of time. Systemically, the most active organ for metabolism of corticosteroids is the liver. Low levels of FA are most likely metabolized by the liver involving esterification reactions. Due to very limited systemic exposure expected from the FA implant, meaningful levels of FA metabolites are not likely to occur.

A one-year GLP rabbit study showed that urinary excretion of FA following FA intravitreal implantation was below the LOQ. Data on excretion of systemically available FA are not available. According to the literature, synthetic steroids are metabolized in the liver to water soluble metabolites/conjugates, and excreted by the kidney. Neither biliary nor fecal excretion is of quantitative importance in humans.

5.3 Exposure-Response Relationships

Blood samples were taken from selected patients at baseline and visits including Day 2, Week 1, Week 4, and Week 34. At none of these visits was the level of FA in the blood above the lower limit of quantitation (200 pg/mL).

See Section 5.2

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is the treatment of patients with non-infectious uveitis affecting the posterior segment of the eye.

6.1.1 Methods

All submitted clinical study reports, clinical protocols, and literature reports were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth. Proposed draft labeling and Individual Patient Data Listings (i.e., CRF Tabulations) for Studies BLP 415-001 and BLP 415-004 were submitted electronically.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in the original protocols was the difference in recurrence rates between the 0.59 mg dose and the 2.1 mg dose. As the study proceeded and prior to the study's completion and unblinding, very few recurrences were observed in the implanted eyes. The Division agreed that it was acceptable to amend the primary efficacy endpoint for protocols BLP 415-001 and BLP 415-004 to the comparison of the proportion of subjects with recurrences of uveitis in the study eye within 34 weeks following implantation to the proportion of subjects with recurrence of uveitis in the 34 weeks preceding implantation. A revised statistical plan for protocol BLP 415-001 and protocol BLP 415-004 were submitted on April 6, 2004 and June 2, 2004, respectively.

6.1.3 Study Design

Clinical Trials BLP 415-001 and BLP 415-004

BLP 415-001 and BLP 415-004 are identical in inclusion/exclusion criteria, study plan, schedule of activities and evaluations, statistical analysis plan, and efficacy and safety endpoints. In protocol BLP 415-001, randomization was 2:3 between the 0.59 mg and the 2.1 mg doses. In protocol BLP 415-004, the subject randomization was changed to a ratio of 1:1.

Enrollment for protocol BLP 415-004 was completed with 236 subjects enrolled (250 subjects were in the original plan). Due to the outbreak of SARS in the countries with clinical sites for this protocol, further recruitment of subjects became very difficult.

Demographic and subject disposition information is provided for each of these trials in this Medical Officer's review.

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Clinical Review
 Lucious Lim, M.D., M.P.H.
 NDA 21-737 000
 Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

Principle Investigators for BLP 415-001

Principal Investigator	Center	City and State	No. Randomized and Enrolled
Rajiv Anand, M.D.	143	Dallas, TX	1
Brian Berger, M.D.	132	Austin, TX	9
David Callanan, M.D.	116	Arlington, TX	34
Kakarla V. Chalam, M.D.	180	Jacksonville, FL	2
Janet L. Davis, M.D.	118	Miami, FL	16
Pravin U. Dugel, M.D.	133	Phoenix, AZ	28
J.P. Dunn, M.D.	119	Baltimore, MD	8
Stephen Foster, M.D.	144	Boston, MA	14
William Freeman, M.D.	120	La Jolla, CA	4
Debra A. Goldstein, M.D.	135	Chicago, IL	9
Allen Ho, M.D.	136	Philadelphia, PA	1
Glenn J. Jaffe, M.D.	122	Durham, NC	21
Baruch Kupperman, M.D., Ph.D.	123	Irvine, CA	1
Paul Latkany, M.D.	148	New York, NY	7
Careen Y. Lowder, M.D., Ph.D.	124	Cleveland, OH	22
Daniel F. Martin, M.D.	125	Atlanta, GA	17
Pauline Merrill, M.D.	142	Chicago, IL	5
Ramana Moorthy, M.D.	147	Indianapolis, IN	8
Lawrence Morse, M.D., Ph.D.	137	Sacramento, CA	1
Stuart Noorily, M.D.	146	Teaneck, NJ	5
Peter "Reed" Pavan, M.D.	126	Tampa, FL	2
Chee Soon Phaik, MBBS	184	Singapore	16
Michael B. Raizman, M.D.	128	Boston, MA	11
James T. Rosenbaum, M.D.	130	Portland, OR	4
John Sheppard, M.D.	145	Norfolk, VA	25
Russell Van Gelder, M.D., Ph.D.	131	St. Louis, MO	4
Albert Vitale, M.D.	140	Salt Lake City, UT	3

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 On Original**

Principle Investigators for BLP 415-004

Principal Investigator	Center	City and State	No. Randomized and Enrolled
Thomas M. Aaberg, M.D.	240859	Grand Rapids, MI	7
Jean Deschenes, M.D.	142956	Montreal, QC, Canada	10
Robert Devenyi, M.D.	146952	Toronto, ON, Canada	1
William Hodges, M.D., M.P.H., Ph.D.	143955	Ottawa, ON, Canada	7
Phil Hooper, M.D.	144954	London, ON, Canada	7
Rajiv Maturi, M.D.	244855	Indianapolis, IN	10
Don Perez-Ortiz, M.D.	246853	Tampa, FL	7
Theodore Rabinovitch, M.D.	189910	Toronto, ON, Canada	8
William Rodden, M.D.	247852	Ashland, OR	1
Peter McCluskey, M.D.	157946	Darlinghurst, Australia	6
Richard Stawell, M.D.	159945	East Melbourne, Australia	7
Mei-Ling Tay-Kearney, M.D.	160944	Nedlands, Australia	5
Diana Conrad, M.D.	161943	Brisbane, Australia	1
J. Biswas, M.D.	156947	Chennai, India	3
S.P. Garg, M.D.	155948	New Delhi, India	41
V.S. Sangwan, M.D.	154949	Hyderabad, India	50
Dennis Lam Shun-Chiu, M.D.	147951	Kowloon, HK	12
Harvey Siy Uy, M.D.	227872	Makati City, Philippines	18
Juan S. Lopez, M.D.	228871	Quezon City, Philippines	11

Reviewer's Comments:

It is preferred to have at least 10 subjects per center to allow for an interaction analysis.

Inclusion Criteria:

Patients must have fulfilled all the following criteria to be eligible for study admission:

- 1) Males and non-pregnant females at least 6 years of age
- 2) One or both eyes having:
 - a history of recurrent non-infectious uveitis affecting the posterior segment of ≥ 1 year duration requiring either:
 - systemic corticosteroid or other equivalent systemic therapy for at least three months prior to enrollment

OR

- at least 2 sub-Tenon's injections of corticosteroid for the management of uveitis during the six months prior to enrollment

OR

- at least 2 separate recurrences within the six months prior to enrollment requiring either systemic corticosteroid therapy or sub-Tenon's injection of corticosteroid

AND, AT THE TIME OF ENROLLMENT THE IMPLANTED EYE MUST HAVE HAD

- ≤ 10 anterior chambers cells/HPF and a vitreous haze \leq grade 2 (patients may be treated prior to entry in order to qualify). *NOTE: These criteria were chosen to ensure that patients being enrolled in the study had clinically quiet eyes at the time of implantation. Patients were allowed to receive appropriate treatment for an episode of uveitis in order to quiet the eye(s) to meet the enrollment criteria. The patient was not permitted to enter the study until the above criteria were met.*
- visual acuity of at least 1.4 logMAR in the study eye
- for the Singapore site only, due to IRB requirements, a minimum visual acuity of 20/200 for the non-study eye (equivalent to 1.0 logMAR).

3) Ability to understand and sign informed consent form.

Exclusion Criteria:

Patients with any of the following were excluded from study entry:

- 1) Allergy to fluocinolone acetonide or any component of the delivery system
- 2) History of only posterior uveitis not accompanied by vitritis or macular edema
- 3) History of iritis only and no vitreous cells or vitreous haze
- 4) Uveitis with infectious etiology
- 5) Patients with vitreous hemorrhage
- 6) Presence of a toxoplasmosis scar in the study eye
- 7) Peripheral retinal detachment in area of implantation
- 8) Media opacity precluding evaluation of the retina and vitreous
- 9) Presence or history of uncontrolled intraocular (IOP) while on steroid therapy resulting in loss of vision, or IOP >25 mm Hg requiring ≥ 2 types of anti-glaucoma medication to lower the IOP to <25 mmHg
- 10) Ocular surgery on the study eye within 3 months prior to enrollment
- 11) Patients requiring chronic systemic corticosteroid therapy (>15 mg prednisone daily) or systemic immunosuppressive therapy to manage non-ocular disease
- 12) Patients who had tested positive for human immunodeficiency virus
- 13) Pregnant or lactating females
- 14) Fertile females considering becoming pregnant during the course of the study and those not taking precautions to avoid pregnancy
- 15) Patients for whom, in the physician's opinion, any of the protocol procedures may pose a special risk not outweighed by the potential benefits of participating in the study
- 16) Patients who were unlikely to comply with the study protocol or who are likely to be moving and lost to follow up in 3 years

- 17) Patients who were currently enrolled in any other IND study or who have participated in an IND study within 1 month of enrollment.

Study Plan

These were 3-year multicenter, randomized, double-masked, controlled, safety and efficacy studies of FA intravitreal implants in patients with unilateral or bilateral posterior uveitis. In patients with unilateral disease, the affected eye was the study eye. In patients with bilateral disease the study eye was the more severely affected eye, (i.e., the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA or if equal, the eye clinically judged to be the more severely affected eye).

The implant is a polymer-coated, intravitreal, sustained-release delivery system for FA. The implants contain one of 2 dose levels of FA and are designed to deliver the drug for approximately . The implants are composed of a central core consisting of FA  tablet. The dimensions of the implants are approximately 2 mm x 2 mm x 6 mm. The implants are to be implanted into the posterior segment of the eye through a pars plana incision.

The two doses of FA were selected based on previous clinical studies conducted under individual investigator INDs utilizing implant dosage form ranging from 15 mg to 0.59 mg. Results from these studies suggested that release rates in excess of 3.0 $\mu\text{g}/\text{day}$ may result in excessive increases in intraocular pressure. Thus, the two lower doses, 0.59 mg and 2.1 mg, were selected for the clinical trials.

Patients were randomly assigned to receive one of two doses of FA intravitreal implant in a ratio of 3:2 between 2.1 mg and 0.59 mg in BLP 415-001 and in a ratio of 1:1 between 2.1 mg and 0.59 mg in BLP 415-004. Enrollment was stratified according to whether or not patients were receiving systemic or local therapy consisting of corticosteroids or other immunosuppressive drugs at the time of their enrollment.

The following tests and assessments were performed at the Screening visit (within 14 days prior to implantation): Eligibility determination, informed consent, medical history, a detailed history of the management of their uveitis over the previous 12 months, physical examination, clinical laboratory tests (serum chemistry, EST, hematology, urinalysis), complete ophthalmic examination (including visual acuity, IOP recorded as the mean of three measurements), slit lamp biomicroscopy, bilateral ophthalmoscopy), fluorescein angiography, visual field, bilateral fundus photography, FA serum concentration (at selected sites), ERG (in selected sites), serum pregnancy test, validated SF36 and VFQ Quality-of-Life surveys, VDRL, FTA-ABS, PPD tests obtained within 6 months unless previous positive result was recorded.

On Day 1 (implantation), patients must meet the enrollment criteria for AC cells and vitreous haze on the day of surgery. Immediately after surgery, the patient will be given, in addition to any chronic medication required prior to surgery, a standardized post-op course of topical

antifective and corticosteroid eye drops for one week. Pre-existing therapy will then be tapered off over at least 6 weeks.

Over the 34 weeks follow-up period, the following follow-up visits and assessments were to be performed:

- Day 2 and Weeks 1 (± 2 days), 4, 8, 12, 24, 30, and 34 (± 1 week) and for additional long-term follow-up visits approximately every 3 months (± 1 month) for a total duration of 3 years post-implantation: Procedures performed at these visits (except Day 2) include a complete bilateral ophthalmic examination (including visual acuity, IOP using Goldman Applanation Tonometer (recorded as a mean of three measurements), slit lamp biomicroscopy and bilateral ophthalmoscopy), and adverse event reports.
- Day 2: Procedures performed include ophthalmic examination (bilateral visual acuity, IOP (implanted eye only-recorded as a mean of three measurements), ophthalmoscopy (implanted eye only), and slit lamp biomicroscopy (implanted eye only)], and adverse event reports. Anterior chamber cell/flare counts were to be conducted at selected sites.
- Week 1: medication for ocular inflammation was to be tapered in accordance with a schedule described in the protocol over a period of at least 6 weeks.
- Fluorescein angiography and bilateral fundus photographs were to be performed at screening (baseline), at Week 8, and at any time that a study endpoint was reached, and at Week 34; as well as Months 12, 24, and 36.
- Clinical laboratory tests were to be performed at Weeks 1, 4, and 34, and as necessary.
- Blood sampling (in selected patients) for determination of FA serum concentration was to be performed on Day 2 and Weeks 1, 4, and 34. Approximately ten patients at 2 centers (total 20 patients) were to be selected for blood sampling for FA concentration.
- Visual field and Quality-of-Life (QOL) surveys (SF36, VFQ-25 if validated in patients' native language) were to be done at Week 34; as well as Months 12, 24, and 36.
- Week 34: Patients were additionally to have a brief medical history, physical examination.

At selected sites, retinal function were to be assessed at baseline and Weeks 12 and 34 and approximately every 6 months thereafter, by ERG-measured dark-adapted white flash (a and b-wave amplitude, and implicit time) and light-adapted flicker response.

At selected sites a cell/flare meter was to be used to obtain a masked AC cell/flare count at each visit.

Long-term follow-up: Patients were to return for visits at least every 3 months for 2.5 years following the 34 week follow-up visit (i.e., 3 years after implantation). Procedures to be performed at these visits include adverse event reports and complete ophthalmic examination. Fluorescein angiography, fundus photography, visual field and QOL surveys were to be repeated at Months 12, 24, and 36.

Treatment of recurrences: In the event of a clinical recurrence in either eye patients will be treated as clinically appropriate. Periocular corticosteroid injections will be the first line of

therapy; systemic immunosuppressants or systemic steroids (or an increase in systemic steroid dosing) will be used only as second line therapy. Once the recurrence is under control (i.e. meeting the initial enrollment criteria) therapy will again be tailed off as indicated in the protocol. Each recurrence was to be treated in the same fashion. Patients who have a recurrence will receive treatment and continue in the study.

Efficacy Endpoint

The primary efficacy endpoint in the original protocols was the difference in recurrence rates between the 0.59 mg dose and the 2.1 mg dose. As the study proceeded, very few recurrences were observed in the implanted eyes. The Division agreed that it was acceptable to amend the primary efficacy endpoint for protocols BLP 415-001 and BLP 415-004 to the comparison of the proportion of subjects with recurrence of uveitis in the study eye within 34 weeks following implantation to the proportion of subjects with recurrence of uveitis in the 34 weeks preceding implantation. A revised statistical plan for protocol BLP 415-001 and protocol BLP 415-004 were submitted on April 6, 2004, and June 2, 2004, respectively.

A recurrence of uveitis with onset within 34 weeks prior to implantation is defined by the investigator's assessment that the patient satisfied the definition of a "protocol defined" recurrence as recorded on the Uveitis History CRF. This can be contradicted by the following:

- A maximum anterior chamber cell score <2 as recorded on the Uveitis History CRF
AND
- A maximum vitreous haze score <2 as recorded on the Uveitis History CRF
AND
- A maximum change in visual acuity <0.3 logMAR or Snellen equivalent as recorded on the Uveitis History CRF.

The CRF included a checkbox for the investigator to indicate whether the recurrence satisfied the definition of a "protocol defined" recurrence. If this box is checked, the recurrence will be counted unless there are scores for cells, haze, and visual acuity that do not satisfy the criteria for a recurrence.

The Uveitis History CRF called for the recording of maximum anterior chamber cells and vitreous haze during each recurrence. This is in contrast with the post-implantation criteria that are scored on a protocol specified scale and defined as a change from baseline. It is reasonable to assume that a customary rating scale was employed by ophthalmologists treating posterior uveitis and that a grade of <2 implies that the change in inflammation during the pre-study recurrence was less than 2 steps and therefore did not satisfy the inflammatory criteria of a protocol defined recurrence.

A recurrence of uveitis in the 34 week period following implantation was based on the occurrence of one or more of the following events:

- A ≥ 2 step increase compared to baseline in the number of cells in the anterior chamber per high power field (1.6 X using 1 1-mm beam) not attributable to conditions other than non-infectious posterior uveitis

OR

- An increase in the vitreous haze of ≥ 2 steps compared to baseline not attributable to conditions other than non-infectious uveitis

OR

- A deterioration in visual acuity of at least 0.30 logMAR units from screening (baseline), not attributable to conditions other than non-infectious uveitis

OR

- Failure to be observed after the 24-week visit.

For any eye not observed after the 24-week visit it was assumed, due to lack of evidence to the contrary, that the eye experienced a recurrence.

The determination of post-implantation recurrences was based on the visual acuity and slit lamp examination findings. In general the information requested on the Uveitis Recurrence CRF was completed if a criterion change was observed. However, it is possible that the investigator initiated therapy for uveitis before one or more criteria defining a recurrence had been met. In these cases, the investigators were instructed to record the episode on the uveitis recurrence form and to respond NA (not applicable) to the CRF question about which of the 3 recurrence criteria were met. These cases will be considered as recurrences in the analysis.

To prevent post-operative inflammatory reactions following the original implantation procedure from being reported as uveitis recurrences, assessments for recurrence of uveitis began one week after complete tapering of pre-study anti-inflammatory and/or immunosuppressive medications. When other intercurrent ocular surgical procedures were required, assessments for recurrence will resume one week after discontinuation of post-operative topical anti-inflammatory medications. Post-operative inflammation requiring immunosuppressant or anti-inflammatory therapy for 12 weeks or more were considered a recurrence despite the fact that the original inflammation may have been brought about by the surgical procedure.

Prior to unmasking treatment assignment, the Sponsor reviewed all cases meeting any of the above criteria to determine whether a recurrence of posterior non-infectious uveitis has been observed. All cases in which the Sponsor review and the investigator's recording differ was individually described.

All patients who received an implant and had at least one post-implantation observation were included in "Intent-to-Treat (ITT)" population. The primary efficacy analysis was conducted on the ITT population. Patients were analyzed "as treated" and "as randomized".

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Schedule of Visits and Assessments

Procedure/Assessment	Screening Visit	Day 1	Day 2	Week 1	Week 4	Week 8	Week 12	Week 18	Week 24	Week 30	Week 34	1-year	Follow Up ^a
Screening ^b (w/in 14 days)	X												
Physical exam, medical history	X										X		
Randomization		X											
Clinical lab tests ^c	X			X	X						X		
Quality-of-life survey ^d	X										X	X	X ^e
Ophthalmic exam ^e	X	X	X	X	X	X	X	X	X	X	X	X	X ^a
Implantation, peri-operative medication		X											
Fluorescein angiography	X					X					X	X	X ^g
Bilateral fundus photo.	X					X					X	X	X ^g
Visual field	X										X	X	X ^g
A/C cell/flare count ^f	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event report		X	X	X	X	X	X	X	X	X	X	X	X ^a
Electroretinogram ^f	X						X				X	X	X ^h
Blood sampling for drug concentration ^f	X		X	X	X						X		

- a. Every 3 months (final visit is 3 years from implantation)
- b. Eligibility determination, informed consent, serum pregnancy test, events history
- c. Serum chemistry, hematology, urinalysis (VDRL, PPD, FT4-ABS, serum ACE, HLA - B-27 or HLA-A29 or Lymc-Disease Ah Tier (if applicable))
- d. Validated SF-36 and VFO-25 surveys (validated in the patient's native language) will be administered at applicable sites
- e. Visual acuity, intraocular pressure (using Goldmann Applanation Tonometry and recorded as the mean of three measurements), slit lamp biomicroscopy, ophthalmoscopy (both eyes)
- f. At selected study sites
- g. Yearly (24 months and 36 months)
- h. Every 6 months

BLP 415-001: Patient Populations

Number of Patients	0.59 mg	2.1 mg	Both Doses
Randomized	108	170	278
Completed	104 (96.3%)	167 (98.2%)	271 (97.5%)
Safety Population	110	168	278
ITT			
As randomized ¹	108	170	278
As treated	110	168	278
Evaluable Population (EP) ²	68	107	175

¹ Two patients were treated with the incorrect dose (received 0.59 mg implant, rather than 2.1 mg implant).

² Patients who were managed in a manner that was substantially compliant with the protocol.

BLP 415-004: Patient Populations

Number of Patients	0.59 mg	2.1 mg	Both Doses
Randomized ¹	116	123	239
Completed	113 (97.4%)	120 (97.6%)	233 (97.5%)
Safety Population	117	122	239
ITT			
As randomized ²	116	123	239
As treated	117	122	239
Evaluable Population (EP) ³	88	74	162

¹ The planned enrollment was approximately 250 patients. Enrollment was suspended at 239 patients due to the SARS epidemic in Asia.

² One patient was treated with the incorrect dose (received 0.59 mg implant, rather than 2.1 mg implant).

³ Patients who were managed in a manner that was substantially compliant with the protocol

Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 21-737 000
Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

Reviewer's Comments:

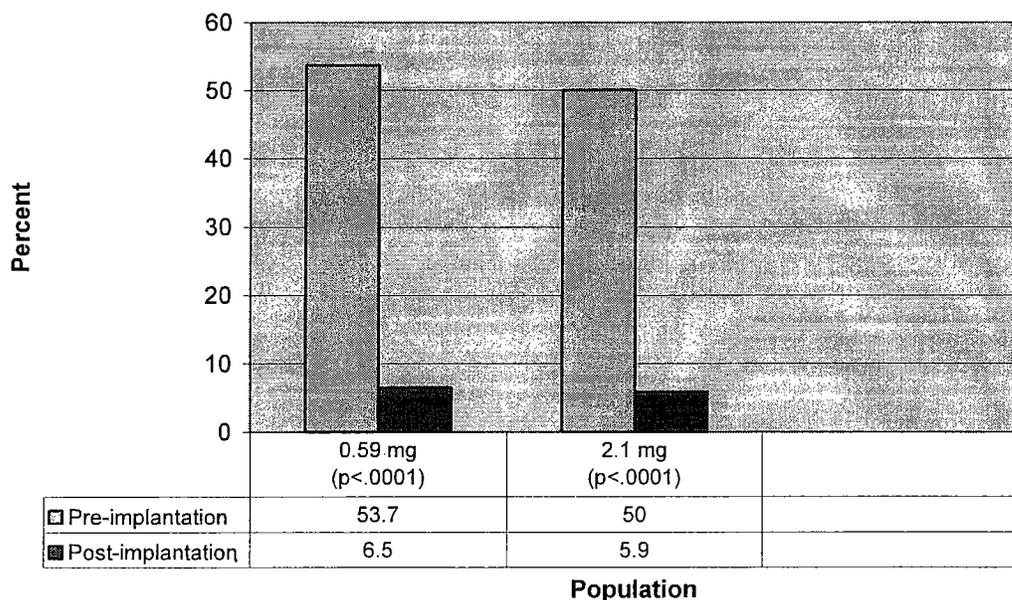
The "as randomized" ITT population was utilized to evaluate the primary efficacy variable in the review of this NDA.

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6.1.4 Efficacy Findings

BLP 415-001:

Uveitis Recurrence: 34-week periods pre- and post-implantation (ITT - study eyes - as randomized)

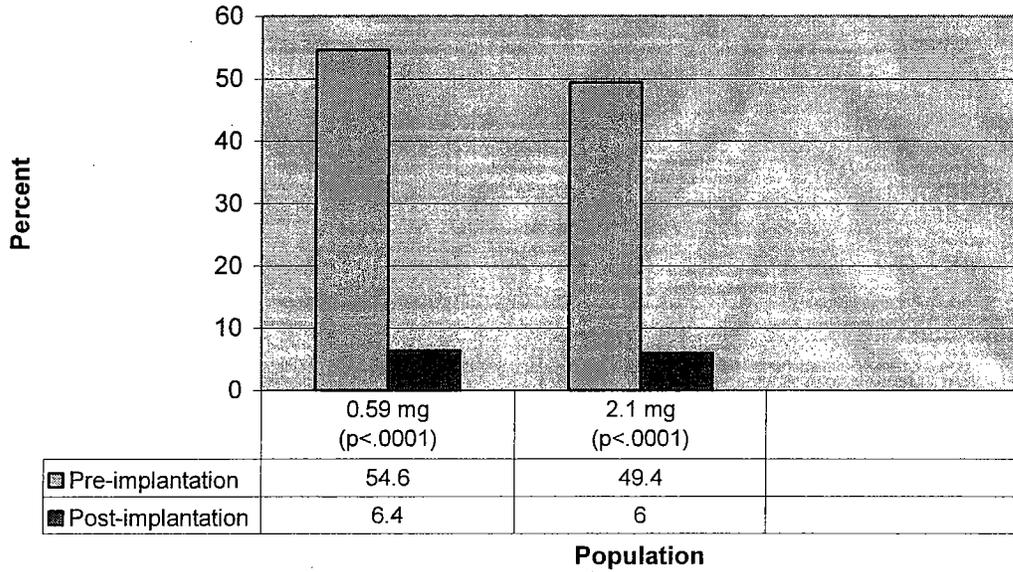


Reviewer's Comments:

The primary efficacy endpoint is statistically significant for both the 0.59 mg (p < 0.0001, McNemar's test) and 2.1 mg (p < 0.0001, McNemar's test) doses.

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Uveitis Recurrence: 34-week periods pre- and post-implantation (ITT - study eyes - as treated)

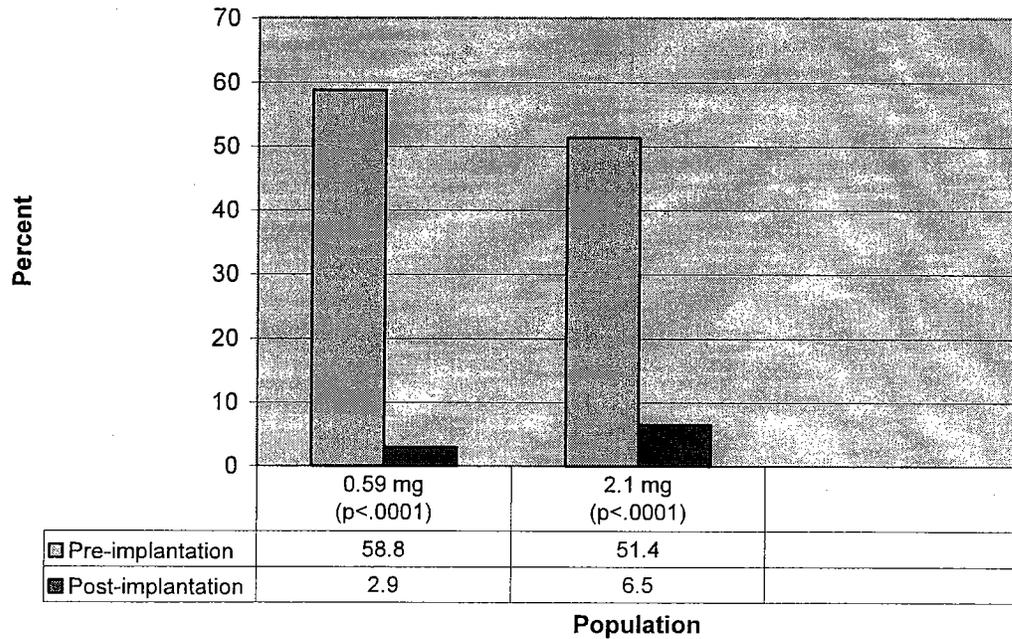


Reviewer's Comments:

The "ITT as treated" analysis is similar to the "ITT as randomized" analysis.

**Appears This Way
 On Original**

**Uveitis Recurrence: 34 week periods pre- and post-implantation
 (Evaluable population - study eyes)**



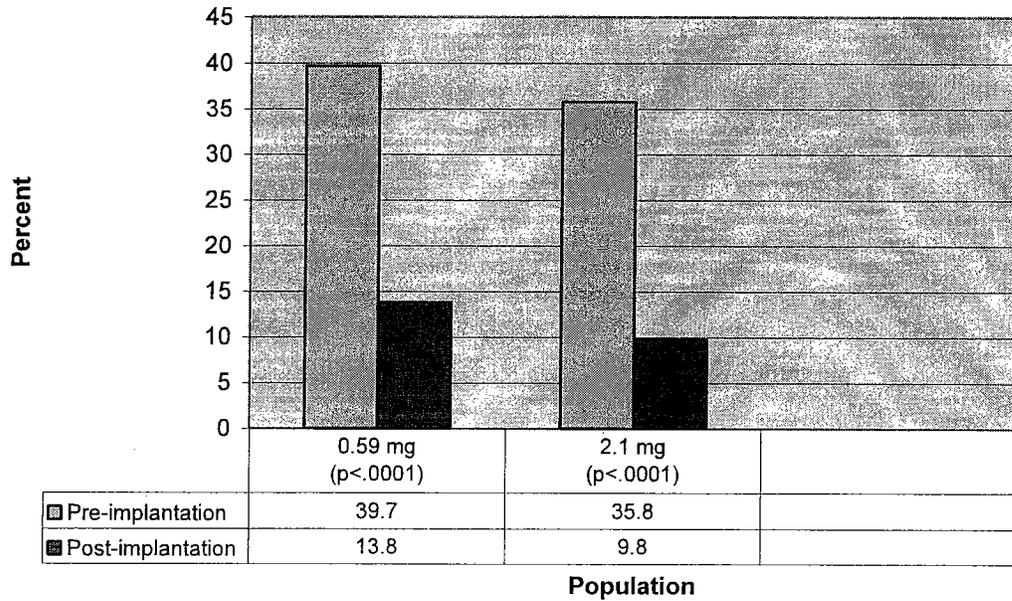
Reviewer's Comments:

The "Evaluable population" analysis is similar to the "ITT as randomized" analysis.

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BLP 415-004:

**Uveitis Recurrence: 34-week periods pre- and post-implantation
 (ITT - study eyes - as randomized)**

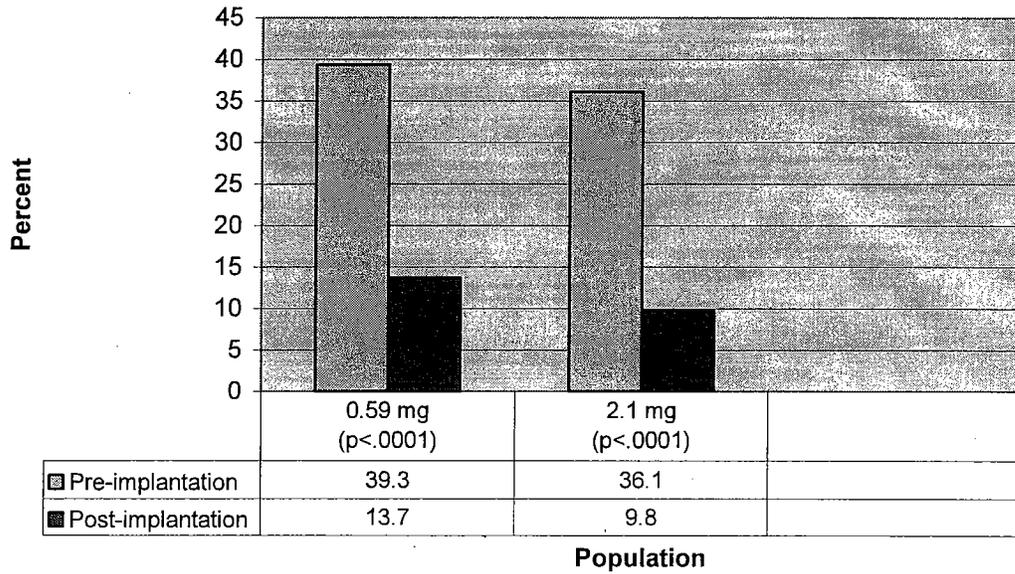


Reviewer's Comments:

The primary efficacy endpoint is statistically significant for both the 0.59 mg ($p < 0.0001$, McNemar's test) and 2.1 mg ($p < 0.0001$, McNemar's test) doses.

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Uveitis Recurrence: 34-week periods pre- and post-implantation (ITT - study eyes - as treated)

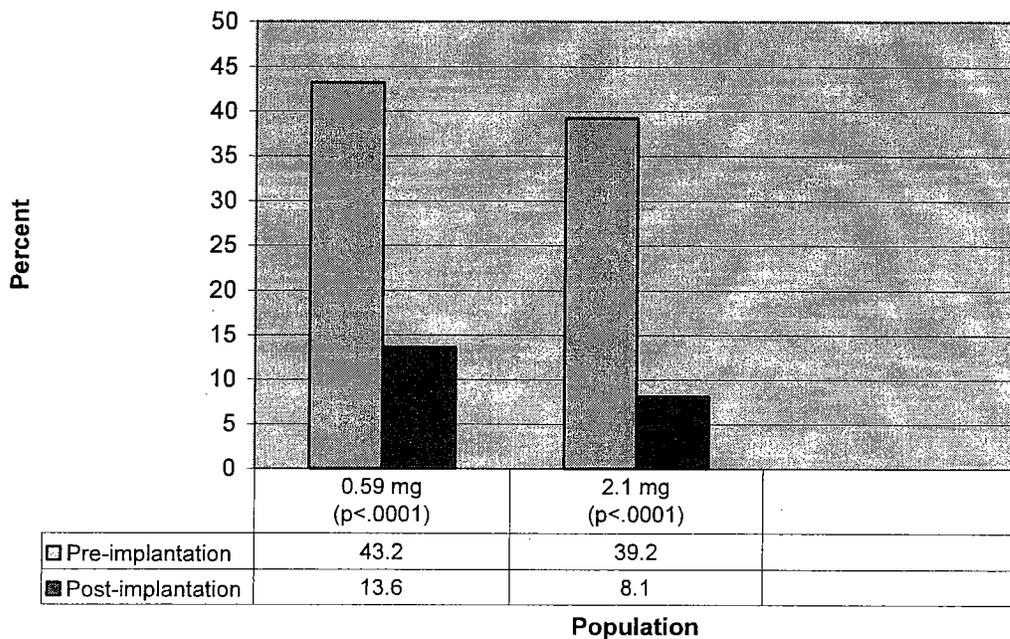


Reviewer's Comments:

The "ITT as treated" analysis is similar to the "ITT as randomized" analysis.

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 On Original

**Uveitis Recurrence: 34 week periods pre- and post-implantation
 (Evaluable population - study eyes)**



Reviewer's Comments:

The "Evaluable population" analysis is similar to the "ITT as randomized" analysis.

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**Proportion of Patients with Uveitis Recurrence:
 34 Week Periods Pre- and Post-implantation
 Study BLP 415-001 and Study BLP 415-004**

Population Analysis	0.59 mg n/N (%)	2.1 mg n/N (%)	p-value
			Pre-implant vs. Post-implant
BLP 415-001			
Pre-implant, ITT, as randomized	58/108 (53.7%)	85/170 (50.0%)	<0.0001
Post-implant, ITT, as randomized	7/108 (6.5%)	10/170 (5.9%)	
Pre-implant, ITT, as treated	60/110 (54.6%)	83/168 (49.4%)	<0.0001
Post-implant, ITT, as treated	7/110 (6.4%)	10/168 (6.0%)	
Pre-implant, EP	40/68 (58.8%)	55/107 (51.4%)	<0.0001
Post-implant, EP	2/68 (2.9%)	7/107 (6.5%)	
BLP 415-004			
Pre-implant, ITT, as randomized	46/116 (39.7%)	44/123 (35.8%)	<0.0001
Post-implant, ITT, as randomized	16/116 (13.8%)	12/123 (9.8%)	
Pre-implant, ITT, as treated	46/117 (39.3%)	44/122 (36.1%)	<0.0001
Post-implant, ITT, as treated	16/117 (13.7%)	12/122 (9.8%)	
Pre-implant, EP	38/88 (43.2%)	29/74 (39.2%)	<0.0001
Post-implant, EP	12/88 (13.6%)	6/74 (8.1%)	

Reviewer's Comments:

The primary efficacy endpoint is statistically significant for the 0.59 mg dose ($p < 0.0001$), 2.1 mg ($p < 0.0001$), and when both doses are combined ($p < 0.0001$) in the ITT "as randomized", ITT "as treated", and Evaluable populations.

6.1.5 Clinical Microbiology

This drug is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The individual clinical trials BLP 415-001 and BLP 415-004 demonstrate statistical significance for their primary efficacy endpoint (i.e., the proportion of patients with recurrence of uveitis in the 34 weeks following implantation compared to the proportion of patients with recurrence of uveitis in the 34 weeks prior to implantation) in both the 0.59 mg dose and the 2.1 mg dose.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

All submitted clinical study reports, clinical protocols, and literature reports were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth. Proposed draft labeling and Individual Patient Data Listings (i.e., CRF Tabulations) for Studies BLP 415-001 and BLP 415-004 were submitted electronically.

7.1.1 Deaths

Deaths in the Safety Population BLP 415-001 (n=278) Both Doses (0.59 mg, n= and 2.1 mg)

Investigator No.- Patient No.	Days since implantation	Event
0.59 mg		
132-1086	324	Lung cancer

Deaths in the Safety Population BLP 415-004 (n=239) Both Doses (0.59 mg and 2.1 mg)

Investigator No.- Patient No.	Days since implantation	Event
0.59 mg		
244855-1254	49	Abdominal aortic aneurysm rupture
2.1 mg		
154949-2028	324	Myocardial infarction

Reviewer's Comments:

The death rate in the BLP 415-001 and BLP 415-004 clinical trials is less than 1%.

7.1.2 Other Serious Adverse Events

Serious Adverse Events Reported for at least 2% of Patients in Any Treatment Group BLP 415-001 – Safety Population

Coded Adverse Event	0.59 mg (N=110) n (%)	2.1 mg (N=168) n (%)
OCULAR		
Cataract ¹	16 (14.6%)	21 (12.5%)

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Glaucoma ²	8 (7.3%)	15 (8.9%)
Intraocular pressure increased	8 (7.3%)	10 (6.0%)
Hypotony	4 (3.6%)	4 (2.4%)
Maculopathy	1 (0.9%)	6 (3.6%)
Vitreous hemorrhage	3 (2.7%)	3 (1.8%)

¹Cataract=cataract NOS aggravated, cataract NOS, cataract subcapsular, and posterior capsule opacification

²Glaucoma=glaucoma NOS, open angle glaucoma, and ocular hypertension

**Serious Adverse Events Reported for at least 2% of Patients in Any Treatment Group
 BLP 415-004 – Safety Population**

Coded Adverse Event	0.59 mg (N=117) n (%)	2.1 mg (N=122) n (%)
OCULAR		
Cataract ¹	20 (17.1%)	18 (14.8%)
Intraocular pressure increased	8 (6.8%)	13 (10.7%)
Glaucoma ²	6 (5.1%)	6 (4.9%)
Hypotony	4 (3.4%)	7 (5.7%)
Retinal detachment	5 (4.3%)	3 (2.5%)
Endophthalmitis	2 (1.7%)	5 (4.1%)
Maculopathy	2 (1.7%)	3 (2.5%)
Vitreous hemorrhage	3 (2.6%)	2 (1.6%)
Device expulsion	3 (2.6%)	2 (1.6%)

¹Cataract=cataract NOS aggravated, cataract NOS, cataract subcapsular, and posterior capsule opacification

²Glaucoma=glaucoma NOS and open angle glaucoma

Reviewer's Comments:

The most frequent serious adverse events for both treatment groups and in both clinical trials were cataracts (12.5%-17.1%), increased intraocular pressure (6.0%-10.7%), and glaucoma (4.9%-8.9%).

7.1.3 Dropouts and Other Significant Adverse Events

**Discontinued Patients in BLP 415-001 (n=278)
 Both Doses (0.59 mg and 2.1 mg)**

Dose	Patient No.	Days in Study	Reason for Discontinuation	Comment
0.59 mg	2050	140	Adverse event(s)	Uncontrolled IOP
0.59 mg	2057	25	Adverse event(s)	Lost of vision in OD. Implant removed. Vitrectomy. Endophthalmitis
0.59 mg	1086	324	Death	Lung cancer
0.59 mg	2198	309	Adverse event(s)	Ureteric calculus
0.59 mg	2230	361	Lost to follow-up	Last visit-18 weeks
2.1 mg	1227	76	Adverse event(s)	Hypotony
2.1 mg	1009	266	Adverse event(s)	Cholelithiasis, cholecystectomy
2.1 mg	2041	190	Adverse event(s)	Cataract , increased IOP on meds

Reviewer's Comments:

The "reason for discontinuation" for patients 2198, 2041, and 1009 were re-classified by this reviewer. It is the judgment of this reviewer that the revised classification seen in the preceding table more accurately reflects the circumstances surrounding the patients' discontinuation from the study.

Overall, 271 (97.5%) subjects completed Week 34 post-implantation and 270 (97.1%) subjects completed beyond the 34 week post-implantation period.

Section 7.1.3.1 gives a patient disposition breakdown by treatment group and reason for discontinuation.

**Discontinued Patients in BLP 415-004 (n=239)
 Both Doses (0.59 mg and 2.1 mg)**

Dose	Patient No.	Days in Study	Reason for Discontinuation	Comment
0.59 mg	2124	219	Adverse event(s)	Uncontrolled IOP
0.59 mg	2025	551	Adverse event(s)	Cataract progression
0.59 mg	1327	448	Adverse event(s)	Implant extrusion
0.59 mg	2137	419	Adverse event(s)	Cataract, cataract extraction
0.59 mg	1254	49	Death	Abdominal aortic aneurysm rupture
0.59 mg	1205	245	Adverse event(s)	Increased IOP on meds
2.1 mg	2122	374	Adverse event(s)	Implant extrusion
2.1 mg	1296	445	Adverse event(s)	Post-op wound complication
2.1 mg	1011	185	Adverse event(s)	Implant extrusion
2.1 mg	2139	91	Adverse event(s)	Hypotony
2.1 mg	2028	324	Death	Myocardial infarction

Reviewer's Comments:

The "reason for discontinuation" for patients 2137 and 1205 were re-classified by this reviewer. It is the judgment of this reviewer that the revised classification more accurately reflects the circumstances surrounding the patients' discontinuation from the study.

Overall, 233 (97.5%) subjects completed Week 34 post-implantation and 228 (95.4%) completed beyond the 34 week post-implantation period. A comparable number of subjects in each treatment group discontinued before Week 34 and after Week 34, 0.59 mg (2.6%) and 2.1 mg (2.4%) and 0.59 mg (5.2%) and 2.1 mg (4.1%), respectively.

Section 7.1.3.1 gives a patient disposition breakdown by treatment group and reason for discontinuation

7.1.3.1 Overall profile of dropouts

Patient Disposition at 34 Week and Post 34 Week in BLP 415-001

Number (%) of Patients	0.59 mg (N=108) n (%)	2.1 mg (N=170) n (%)	Both Doses (N=278) n (%)
Completed Week 34 Post Week 34	104 (96.3%) 103 (95.4%)	167 (98.2%) 167 (98.2%)	271 (97.5%) 270 (97.1%)
Discontinued before Week 34/ before and after Week 34	4 (3.7%)/5 (4.6%)	3 (1.8%)/3 (1.8%)	7 (2.5%)/8 (2.9%)
Adverse event	3 (75.0%)/3 (60.0%)	3 (100%)/3 (100%)	6 (85.7%)/6 (75.0%)
Lost to follow-up	1 (25.0%)/1 (20.0%)	-----/-----	1 (14.3%)/1 (12.5%)
Death	-----/1 (20.0%)	-----/-----	-----/1 (12.5%)

Patient Disposition at 34 Week and Post 34 Week in BLP 415-004

Number (%) of Patients	0.59 mg (N=116) n (%)	2.1 mg (N=123) n (%)	Both Doses (N=239) n (%)
Completed Week 34 Post Week 34	113 (97.4%) 110 (94.8%)	120 (97.6%) 118 (95.9%)	233 (97.5%) 228 (95.4%)
Discontinued before Week 34/ before and after Week 34	3 (2.6%)/6 (5.2%)	3 (2.4%)/5 (4.1%)	6 (2.5%)/11(4.6%)
Adverse event	2 (66.7%)/5 (83.3%)	3 (100%)/4 (80.0%)	4 (66.7%)/8 (72.7%)
Death	1 (33.3%)/1 (16.7%)	-----/1 (20.0%)	1 (16.7%)/2 (18.2%)

7.1.3.2 Adverse events associated with dropouts

The majority of the subjects listed in Section 7.1.3.1 appear to discontinue due to adverse event(s) associated with the study drug.

The most frequently cited adverse events in both trials which led to discontinuation of subjects were cataract/cataract progression, uncontrolled/increased IOP, and implant extrusion.

7.1.3.3 Other significant adverse events

See section 7.1.2.

7.1.4 Other Search Strategies

Case Report Forms for all discontinued subjects in both BLP 415-001 and BLP 415-004 were reviewed by this medical officer.

7.1.5 Common Adverse Events

Adverse Events Reported for at least 5% of Patients in any Treatment Group BLP 415-001 – Safety Population

Coded Adverse Event	0.59 mg (N=110) n (%)	2.1 mg (N=168) n (%)
OCULAR		
Intraocular pressure increased	54 (49.1%)	90 (51.2%)
Cataract ¹	28 (25.5%)	52 (31.0%)
Eye pain	23 (20.9%)	52 (31.0%)
Conjunctival hemorrhage	29 (26.4%)	45 (26.8%)
Ocular/conjunctival hyperemia	25 (22.7%)	47 (28.0%)
Procedural complication ²	27 (24.6%)	41 (24.4%)
Implant site pain ³	17 (15.5%)	32 (19.1%)
Glaucoma ⁴	17 (15.5%)	30 (17.9%)
Visual acuity reduced	20 (18.2%)	27 (16.1%)
Eye irritation	14 (12.7%)	28 (16.7%)
Eye pruritus	17 (15.5%)	21 (12.5%)
Vitreous floaters	16 (14.6%)	21 (12.5%)
Eye Abnormal sensation	13 (11.8%)	23 (13.7%)
Maculopathy	13 (11.8%)	18 (10.7%)
Vision blurred	14 (15.5%)	16 (9.5%)
Vitreous hemorrhage	17 (12.7%)	13 (7.7%)
Hypotony	9 (8.2%)	17 (10.1%)
Eyelid ptosis	6 (5.5%)	20 (11.9%)
Macular edema	10 (9.1%)	11 (6.6%)
Photophobia	9 (8.2%)	11 (6.6%)
Eyelid edema	7 (6.4%)	8 (4.8%)
Photopsia	2 (1.8%)	11 (6.6%)
Vision abnormal	3 (2.7%)	9 (5.4%)
NON-OCULAR		
Body as a Whole – General Disorders		
Fatigue	6 (5.5%)	6 (3.6%)
Gastrointestinal Disorders		
Nausea	12 (10.9%)	12 (7.1%)
Vomiting	10 (9.1%)	4 (2.4%)
Infections and Infestations		
Nasopharyngitis	11 (10.0%)	13 (7.7%)
Sinusitis	9 (8.2%)	11 (6.6%)
Urinary tract infection NOS	8 (7.3%)	11 (6.6%)
Upper respiratory tract infection	5 (4.6%)	11 (6.6%)
Influenza	6 (5.5%)	5 (3.0%)
Nervous System Disorders		

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 Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

Headache NEC ⁵	20 (18.2%)	44 (26.2%)
Dizziness	6 (5.5%)	7 (4.2%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	5 (4.6%)	13 (7.7%)
Back pain	7 (6.4%)	2 (1.2%)
Psychiatric Disorders		
Depression	2 (1.8%)	9 (5.4%)

¹Cataract=cataract NOS aggravated, cataract NOS, cataract subcapsular, posterior capsule opacification, cataract cortical, cataract nuclear, and lenticular opacities

²Procedural complications=post-op complications NOS, post-op wound complications NOS, post procedural pain, and wound dehiscence

³Implant site pain=pain NOS, tenderness NOS, and discomfort NOS

⁴Glaucoma=optic nerve cupping, ocular hypertension, glaucoma NOS, and borderline glaucoma

⁵Headache NEC=headache NOS, sinus headache, tension headache, and post-traumatic headache

Reviewer's Comments:

The most frequently reported ocular adverse events for both treatment groups were increased IOP (49% - 51%), cataract (26% - 31%), eye pain (21% -31%), conjunctival hemorrhage (26% - 27%), ocular/conjunctival hyperemia (23% -28%), and procedural complication (25%).

The most frequently reported non-ocular adverse events were headache (18% -26%), nausea (7% -11%), and nasopharyngitis (8% -10%).

For pooled data, see Section 7.1.5.4.

**Adverse Events Reported for at least 5% of Patients in any Treatment Group
 BLP 415-004 – Safety Population**

Coded Adverse Event	0.59 mg (N=117) n (%)	2.1 mg (N=122) n (%)
OCULAR		
Intraocular pressure increased	63 (54.7%)	67 (54.9%)
Procedural complication ¹	48 (41.0%)	53 (43.4%)
Eye pain	50 (42.7%)	50 (41.0%)
Cataract ²	44 (37.6%)	49 (40.2%)
Visual acuity reduced	39 (33.3%)	46 (37.7%)
Conjunctival hemorrhage	39 (33.3%)	41 (33.6%)
Ocular/conjunctival hyperemia ³	44 (37.6%)	33 (27.0%)
Hypotony	20 (17.1%)	28 (23.0%)
Eye abnormal sensation	20 (17.1%)	26 (21.3%)
Eye irritation	21 (18.0%)	25 (20.5%)
Eye inflammation	18 (15.4%)	15 (12.3%)
Vision blurred	15 (12.8%)	17 (13.9%)
Eye pruritus	13 (11.1%)	18 (14.8%)
Eyelid edema	19 (16.2%)	12 (9.8%)
Vitreous hemorrhage	15 (12.8%)	16 (13.1%)
Maculopathy	12 (10.3%)	13 (10.7%)

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 NDA 21-737 000
 Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg

Glaucoma ⁴	9 (4.3%)	15 (12.3%)
Lacrimation increased	12 (10.3%)	12 (9.8%)
Eye discharge	8 (6.8%)	11 (9.0%)
Vitreous floaters	10 (8.6%)	9 (7.4%)
Conjunctival edema	6 (5.1%)	9 (7.4%)
Eyelid ptosis	6 (5.1%)	7 (5.7%)
Visual disturbance NOS	7 (6.0%)	6 (4.9%)
Choroidal detachment	4 (3.4%)	7 (5.7%)
Retinal detachment	6 (5.1%)	3 (2.5%)
Corneal edema	6 (5.1%)	2 (1.6%)
NON-OCULAR		
Body as a Whole – General Disorders		
Pyrexia	12 (10.3%)	14 (11.5%)
Gastrointestinal Disorders		
Vomiting	7 (6.0%)	8 (6.6%)
Infections and Infestations		
Nasopharyngitis	13 (11.1%)	9 (7.4%)
Influenza	6 (5.1%)	7 (5.7%)
Investigations		
C-reactive protein increased	6 (5.1%)	5 (4.1%)
WBC count increased	6 (5.1%)	2 (1.6%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	9 (7.7%)	11 (9.0%)
Pain in limb	6 (5.1%)	4 (3.3%)
Nervous System Disorder		
Headache NEC ⁵	21 (18.0%)	26 (21.3%)
Dizziness	6 (5.1%)	11 (9.0%)
Respiratory, thoracic and Mediastinal Disorders		
Cough	12 (10.3%)	4 (3.3%)
Sinusitis	1 (0.9%)	7 (5.7%)

¹Procedural complication=post-op wound complication NOS, post-op complications NOS, post-op wound site erythema, wound dehiscence, post procedural pain, therapeutic procedural complication, and procedural site reaction

²Cataract=cataract NOS aggravated, cataract NOS, posterior capsule opacification, cataract subcapsular, and lenticular opacities

³Ocular hyperemia and conjunctival hyperemia AEs are combined.

⁴Glaucoma=optic nerve cupping, glaucoma NOS, and open angle glaucoma NOS

⁵Headache NEC=headache NOS and sinus headache

Reviewer's Comments:

The most frequently reported ocular adverse events were increased IOP (55%), procedural complication (41% - 43%), eye pain (41% - 43%), cataract (38% -40%), reduced visual acuity 33% -38%), conjunctival hemorrhage 33% -34%), and ocular/conjunctival hyperemia (27% - 38%).

The most frequently reported non-ocular adverse events were headache (18% -21%), pyrexia (10% -12%), and nasopharyngitis (7% -11%).

For pooled data, see Section 7.1.5.4.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events in both BLP 415-001 and BLP 415-004 were assessed at each scheduled visit (Day 1 through Year 3) and unscheduled visit. Duration, investigator's perceived relationship between event and study drug, action(s) taken, and outcome were recorded on the Adverse Event form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant's categorization of events is comparable to the investigators' categorization of events when case report forms are reviewed. The applicant utilized the MedDRA dictionary to classify adverse events.

7.1.5.3 Incidence of common adverse events

See Sections 7.1.5 and Section 7.1.5.4.

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7.1.5.4 Common adverse event tables

**Adverse Events Reported for at least 5% of Patients in any Treatment Group
BLP 415-001 and BLP 415-004 – Safety Populations Pooled**

Coded Adverse Event	0.59 mg (N=227) n (%)	2.1 mg (N=290) n (%)	Both Doses (N=517) n (%)
OCULAR			
Intraocular pressure increased	117 (51.5%)	157 (54.1%)	274 (53.0%)
Eye pain	73 (32.2%)	102 (35.2%)	175 (33.8%)
Cataract ¹	72 (31.7%)	101 (34.8%)	173 (33.5%)
Procedural complication ²	75 (33.0%)	94 (32.4%)	169 (32.7%)
Conjunctival hemorrhage	68 (30.0%)	86 (30.0%)	154 (29.8%)
Ocular/conjunctival hyperemia ³	69 (30.4%)	80 (27.6%)	149 (28.8%)
Visual acuity reduced	59 (26.0%)	73 (25.2%)	132 (25.5%)
Eye irritation	35 (15.4%)	53 (18.3%)	88 (17.0%)
Eye abnormal sensation	33 (14.5%)	49 (16.9%)	82 (15.9%)
Hypotony	29 (12.8%)	45 (15.5%)	74 (14.3%)
Glaucoma ⁴	26 (11.5%)	45 (15.5%)	71 (13.7%)
Eye pruritus	30 (13.2%)	39 (13.4%)	69 (13.3%)
Vision blurred	29 (12.8%)	33 (11.4%)	62 (12.0%)
Vitreous hemorrhage	32 (14.1%)	29 (10.0%)	61 (11.8%)
Maculopathy	25 (11.0%)	31 (10.7%)	56 (10.8%)
Vitreous floaters	26 (11.5%)	30 (10.3%)	56 (10.8%)
Implant site pain ⁵	17 (7.8%)	32 (11.0%)	49 (9.5%)
Eyelid edema	26 (11.5%)	20 (6.9%)	46 (8.9%)
Eye inflammation	23 (10.1%)	17 (5.9%)	40 (7.7%)
Eyelid ptosis	12 (5.3%)	27 (9.3%)	39 (7.5%)
Lacrimation increased	15 (6.6%)	19 (6.6%)	34 (6.6%)
Macular edema	14 (6.1%)	16 (5.5%)	30 (5.8%)
Eye discharge	9 (4.0%)	18 (6.2%)	27 (5.2%)
Photophobia	11 (4.8%)	15 (5.2%)	26 (5.0%)
Visual disturbance	12 (5.3%)	12 (4.1%)	24 (4.6%)
NON-OCULAR			
Body as a Whole – General Disorders			
Pyrexia	12 (5.3%)	14 (4.8%)	26 (5.0%)
Gastrointestinal Disorders			
Nausea	16 (7.0%)	15 (5.2%)	31 (6.0%)
Vomiting	17 (7.5%)	12 (4.1%)	29 (5.6%)
Infections and Infestations			
Nasopharyngitis	25 (11.0%)	22 (7.6%)	47 (9.1%)
Sinusitis	10 (4.4%)	18 (6.2%)	28 (5.4%)
Influenza	12 (5.3%)	12 (4.1%)	24 (4.6%)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	14 (6.2%)	24 (8.3%)	38 (7.4%)
Nervous System Disorders			
Headache NEC ⁶	41 (18.1%)	44 (24.1%)	85 (16.4%)
Dizziness	12 (5.3%)	18 (6.2%)	30 (5.8%)
Respiratory, thoracic and Mediastinal			

Disorders			
Cough	14 (6.2%)	9 (3.1 %)	23 (4.4%)

¹Cataract=cataract NOS aggravated, cataract NOS, posterior capsule opacification, cataract subcapsular, and lenticular opacities

²Procedural complication=post-op wound complication NOS, post-op complications NOS, post-op wound site erythema, wound dehiscence, post procedural pain, therapeutic procedural complication, and procedural site reaction

³Ocular hyperemia and conjunctival hyperemia AEs are combined.

⁴Glaucoma=optic nerve cupping, glaucoma NOS, open angle glaucoma NOS, ocular hypertension, and borderline glaucoma

⁵Implant site pain=pain NOS, tenderness NOS, and discomfort NOS

⁶Headache=headache NOS, sinus headache, tension headache, and post-traumatic headache

Reviewer's Comments:

The most frequently reported ocular adverse events were increased IOP (52%-55%), eye pain (32% -35%), cataract (32% - 35%), procedural complication (32%-33%), conjunctival hemorrhage (30%), ocular/conjunctival hyperemia (28% -30%), and reduced visual acuity (25% -26%).

The most frequently reported non-ocular adverse events were headache (18% -24%) and nasopharyngitis (8% -11%).

7.1.5.5 Identifying common and drug-related adverse events

Intraocular pressure adverse events

**Mean IOP Change from Baseline (mm Hg) by Visit
 BLP 415-001 – Safety Population – Study Eye**

Visit	Measure	0.59 mg (N=110)	2.1 mg (N=168)
Baseline IOP	n	110	168
	Mean	14.7	14.6
	SD	4.3	4.4
Surgery	n	22	34
	Mean	1.4	0.2
	SD	4.0	3.8
	p-value ¹	0.1160	0.7558
Day 2	n	107	164
	Mean	-0.2	-0.018
	SD	7.8	7.0
	p-value	0.7578	0.9735
1 Week	n	108	167
	Mean	1.2	1.0
	SD	7.3	7.6
	p-value	0.0868	0.0851
4 Week	n	109	166
	Mean	2.8	3.2
	SD	7.3	6.7
	p-value	0.0002	<0.0001
8 Week	n	108	164
	Mean	3.3	2.8
	SD	7.8	6.3

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	p-value	<0.0001	<0.0001
12 Week	n	107	165
	Mean	2.7	3.6
	SD	7.6	6.8
	p-value	0.0004	<0.0001
18 Week	n	105	160
	Mean	4.4	4.9
	SD	9.0	7.1
	p-value	<0.0001	<0.0001
24 Week	n	106	159
	Mean	4.0	5.2
	SD	8.7	7.5
	p-value	<0.0001	<0.0001
30 Week	n	100	154
	Mean	5.3	6.0
	SD	8.4	8.5
	p-value	<0.0001	<0.0001
34 Week	n	103	165
	Mean	3.8	4.9
	SD	7.6	8.2
	p-value	<0.0001	<0.0001
LOCF ²	n	110	168
	Mean	3.4	4.4
	SD	7.4	8.2
	p-value	<0.0001	<0.0001

¹p-value=paired t-test comparing baseline vs. post-implantation means

²LOCF=last observation carried forward summary is based on the final visit over the time interval beginning one day after implantation and ending at 34 Week visit.

**Mean IOP Change from Baseline (mm Hg) by Visit
 BLP 415-004 – Safety Population – Study Eye**

		0.59 mg (N=117)	2.1 mg (N=122)
Baseline IOP	n	115	122
	Mean	14.3	14.3
	SD	4.1	4.7
Surgery	n	18	28
	Mean	0.1	1.2
	SD	3.3	4.1
	p-value ¹	0.8930	0.1219
Day 2	n	115	121
	Mean	0.2	-1.0
	SD	6.7	7.4
	p-value	0.7277	0.1483
1 Week	n	115	122
	Mean	1.9	1.8
	SD	7.3	8.2
	p-value	0.0063	0.0161
4 Week	n	115	121
	Mean	4.1	3.0
	SD	6.8	7.2
	p-value	<0.0001	<0.0001

8 Week	n	113	121
	Mean	2.7	3.2
	SD	6.5	7.1
	p-value	<0.0001	<0.0001
12 Week	n	113	120
	Mean	3.3	4.3
	SD	7.0	8.2
	p-value	<0.0001	<0.0001
18 Week	n	112	121
	Mean	4.9	5.4
	SD	9.0	8.1
	p-value	<0.0001	<0.0001
24 Week	n	113	119
	Mean	4.4	6.1
	SD	8.1	9.4
	p-value	<0.0001	<0.0001
30 Week	n	113	119
	Mean	3.7	4.6
	SD	7.3	7.9
	p-value	<0.0001	<0.0001
34 Week	n	111	120
	Mean	2.4	4.1
	SD	7.6	8.0
	p-value	0.0003	<0.0001
LOCF ²	n	115	122
	Mean	1.9	3.9
	SD	6.8	8.1
	p-value	0.0027	<0.0001

¹p-value=paired t-test comparing baseline vs. post-implantation means

²LOCF=last observation carried forward summary is based on the final visit over the time interval beginning one day after implantation and ending at 34 Week visit.

Reviewer's Comments:

The mean IOP at each visit post-implantation as compared to baseline mean IOP was statistically significant ($p=0.0003$, $p<0.0001$) beginning at the 4 Week visit and continuing through the 34 Week visit for each treatment group in both Studies BLP 415-001 and BLP 415-004.

Incidence of Patients Requiring IOP Lowering Medications to Control IOP BLP 415-001 – Safety Population – Study Eye

Visit	0.59 mg N=110 n/N (%)	2.1 mg N=168 n/N (%)
Baseline	15/110 (13.6%)	24/168 (14.3%)
Surgery	18/110 (16.4%)	26/168 (15.5%)
Day 2	17/110 (15.5%)	30/168 (17.9%)
1 Week	25/110 (22.7%)	44/168 (26.2%)
4 Week	34/110 (30.9%)	59/168 (35.1%)
8 Week	39/109 (35.8%)	65/168 (38.7%)

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12 Week	41/109 (37.6%)	69/167 (41.3%)
18 Week	44/109 (40.4%)	76/167 (45.5%)
24 Week	46/107 (43.0%)	77/166 (46.4%)
30 Week	51/106 (48.1%)	86/165 (52.1%)
34 Week	52/106 (49.1%)	87/166 (52.4%)
Overall	65/110 (59.1%)	103/168 (61.3%)

Reviewer's Comments:

The number of subjects requiring IOP lowering medications to control IOP increased over time in both treatment groups. This began immediately post-implantation. By 34 weeks post-implantation, 52 (49.1%) subjects in the 0.59 mg treatment group and 87 (52.4%) subjects in the 2.1 mg treatment group were on IOP lowering medications. Overall, the number of subjects that required IOP lowering medications in the 0.59 mg treatment group and 2.1 mg treatment group was 65 (59.1%) and 103 (61.3%), respectively.

**Incidence of Patients Requiring IOP Lowering Medications to Control IOP
 BLP 415-004 – Safety Population – Study Eye**

Visit	0.59 mg N=117 n /N (%)	2.1 mg N=122 n /N (%)
Baseline	0/117 (0.0%)	4/122 (3.3%)
Surgery - 4 Week	71/117 (60.7%)	75/122 (61.5%)
8 Week	71/116 (61.2%)	75/121 (62.0%)
12 Week	71/116 (61.2%)	74/120 (61.7%)
18 Week	71/116 (61.2%)	74/119 (62.2%)
24 Week	70/115 (60.9%)	74/119 (62.2%)
30 Week	70/115 (60.9%)	74/119 (62.2%)
34 Week	70/115 (60.9%)	75/120 (62.5%)
Overall	71/117 (60.7%)	75/122 (61.5%)

Reviewer's Comments:

The number of subjects requiring IOP lowering medications to control IOP began immediately post-implantation in both treatment groups, 71(60.7%) subjects in the 0.59 mg treatment group and 75 (61.5%) subjects in the 2.1 mg treatment group. At 34 weeks post-implantation, the number of subjects on IOP lowering medications was approximately the same as immediately post-implantation, 70 (60.9%) in the 0.59 mg treatment group and 75 (62.5%) in the 2.1 mg treatment group.

There is a marked difference in the time of initiation of IOP lowering pharmacotherapy between the two studies, Study BLP 415-001 and Study BLP 415-004. This observed difference may be a function of different glaucoma management practice in the United States versus Asia or it may reflect a difference in the study populations.

**Incidence of Patients Requiring Filtering Procedures to Control IOP
 BLP 415-001 – Safety Population – Study Eye**

Visit	0.59 mg N=110 n /N (%)	2.1 mg N=168 n /N (%)
Baseline	0/110 (0.0%)	0/168 (0.0%)
Surgery – 8 Week	0/110 (0.0%)	0/168 (0.0%)
12 Week	0/109 (0.0%)	1/167 (0.6%)
18 Week	1/109 (0.9%)	3/167 (1.8%)
24 Week	1/107 (0.9%)	0/166 (0.0%)
30 Week	2/106 (1.9%)	8/165 (4.9%)
34 Week	0/106 (0.0%)	0/166 (0.0%)
Overall	4/110 (3.6%)	12/168 (7.1%)

Reviewer’s Comments:

One (0.6%) subject in the 2.1 mg treatment group had undergone a filtering procedure to control IOP by 12 weeks post-implantation. By 34 weeks post-implantation, 4 (3.6%) subjects in the 0.59 mg treatment group and 12 (7.1%) subjects in the 2.1 mg treatment group had undergone a filtering procedure.

**Incidence of Patients Requiring Filtering Procedures to Control IOP
 BLP 415-004 – Safety Population – Study Eye**

Visit	0.59 mg N=117 n /N (%)	2.1 mg N=122 n /N (%)
Baseline	0/117 (0.0%)	0/122 (0.0%)
Surgery – 12 Week	0/117 (0.0%)	0/122 (0.0%)
18 Week	0/116 (0.0%)	1/120 (0.8%)
24 Week	4/115 (3.5%)	2/120 (1.7%)
30 Week	1/115 (0.9%)	2/120 (1.7%)
34 Week	2/115 (1.7%)	6/120 (5.0%)
Overall	7/117 (6.0%)	11/122 (9.0%)

Reviewer’s Comments:

One (0.8%) subject in the 2.1 mg treatment group had undergone a filtering procedure to control IOP by 18 weeks post-implantation. By 34 weeks post-implantation, 7 (6.0%) subjects in the 0.59 mg treatment group and 11 (9.0%) subjects in the 2.1 mg treatment group had undergone a filtering procedure.

Cataract adverse events

Lens opacity was graded using the Lens Opacity Classification System (LOCS II) where a change in two grades or more is considered clinically relevant.

**Incidence of Increases in Lens Opacity of Any Type¹
 BLP 415-001 – Safety Population – Study Eye**

Visit	0.59 mg N=110 n /N (%)	2.1 mg N=168 n /N (%)
Surgery	0/7 (0.0%)	0/9 (0.0%)
Day 2	1/48 (2.1%)	0/81 (0.0%)
1 Week	1/48 (2.1%)	1/78 (1.3%)
4 Week	2/48 (4.2%)	0/78 (0.0%)
8 Week	4/49 (8.2%)	1/80 (1.3%)
12 Week	3/49 (6.1%)	1/80 (1.3%)
18 Week	4/49 (8.2%)	4/77 (5.2%)
24 Week	8/48 (16.7%)	6/74 (8.1%)
30 Week	6/41 (14.6%)	7/70 (10.0%)
34 Week	12/42 (28.6%)	14/73 (19.2%)
Overall	18/50 (36.0%)	18/81 (22.2%)

¹Lens opacity=nuclear, cortical, and subcapsular

Reviewer's Comments:

A criterion increase in lens opacity was observed with increasing frequency over time post-implantation. By 34 weeks post-implantation, a criterion increase in lens opacity was observed in 12 (28.6%) phakic eyes in the 0.59 mg treatment group and in 14 (28.6%) phakic eyes in the 2.1 mg treatment group. Overall, the number of phakic eyes with a criterion increase in lens opacity in the 0.59 mg treatment group and 2.1 mg treatment group was 18 (36.0%) and 18 (22.2%), respectively.

**Incidence of Increases in Len Opacity of Any Type¹
 BLP 415-004 – Safety Population – Study Eye**

Visit	0.59 mg N=117 n /N (%)	2.1 mg N=122 n /N (%)
Surgery	0/13 (0.0%)	0/15 (0.0%)
Day 2	0/69 (0.0%)	0/64 (0.0%)
1 Week	0/69 (0.0%)	0/63 (0.0%)
4 Week	0/69 (0.0%)	2/63 (3.2%)
8 Week	2/69 (2.9%)	5/64 (7.8%)
12 Week	5/65 (7.7%)	6/60 (10.0%)
18 Week	6/63 (9.5%)	7/61 (11.5%)
24 Week	7/59 (11.9%)	7/57 (12.3%)
30 Week	11/56 (19.6%)	14/57 (24.6%)
34 Week	11/53 (20.8%)	14/54 (25.9%)
Overall	22/69 (31.9%)	20/64 (31.3%)

¹Lens opacity=nuclear, cortical, and subcapsular

Reviewer's Comments:

A criterion increase in lens opacity was observed with increasing frequency over time post-implantation. By 34 weeks post-implantation, a criterion increase in lens opacity was observed in 11 (19.6%) phakic eyes in the 0.59 mg treatment group and in 14 (24.6%) phakic eyes in the 2.1 mg treatment group. Overall, the number of phakic eyes with a criterion increase in lens opacity in the 0.59 mg treatment group and 2.1 mg treatment group was 22 (31.9%) and 20 (31.3%), respectively.

**Incidence of Cataract Surgery¹
 BLP 415-001 – Safety Population – Study Eye**

Visit	0.59 mg N=110 n /N (%)	2.1 mg N=168 n /N (%)
Baseline	0/55 (0.0%)	0/87 (0.0%)
Surgery – 8 Week	0/55 (0.0%)	0/87 (0.0%)
12 Week	0/55 (0.0%)	1/86 (1.2%)
18 Week	0/55 (0.0%)	0/86 (0.0%)
24 Week	3/55 (5.5%)	2/86 (2.3%)
30 Week	3/54 (5.6%)	3/85 (3.5%)
34 Week	0/54 (0.0%)	2/86 (2.3%)
Overall	6/55 (10.9%)	8/87 (9.2%)

¹Performed on phakic eyes

Reviewer's Comments:

One (1.2%) subject in the 2.1 mg treatment group had undergone cataract surgery 12 weeks post-implantation. By 34 weeks post-implantation, 6 (10.9%) subjects in the 0.59 mg treatment group and 8 (9.2%) subjects in the 2.1 mg treatment group had undergone cataract surgery.

**Incidence of Cataract Surgery¹
 BLP 415-004 – Safety Population – Study Eye**

Visit	0.59 mg N=117 n /N (%)	2.1 mg N=122 n /N (%)
Baseline	0/70 (0.0%)	0/66 (0.0%)
Surgery – 4 Week	0/70 (0.0%)	0/66 (0.0%)
8 Week	1/70 (1.4%)	0/66 (0.0%)
12 Week	3/70 (4.3%)	2/66 (3.0%)
18 Week	2/70 (2.9%)	2/66 (3.0%)
24 Week	4/69 (5.8%)	3/66 (4.6%)
30 Week	2/69 (2.9%)	1/66 (1.5%)
34 Week	2/69 (2.9%)	2/66 (3.0%)
Overall	14/70 (20.0%)	10/66 (15.2%)

¹Performed on phakic eyes

Reviewer's Comments:

One (1.4%) subject in the 0.59 mg treatment group had undergone cataract surgery 8 weeks post-implantation. By 34 weeks post-implantation, 14 (20.0%) subjects in the 0.59 mg treatment group and 10 (15.2%) subjects in the 2.1 mg treatment group had undergone cataract surgery.

Visual acuity adverse events

**Change in Visual Acuity from Baseline to 34 Week
 BLP 415-001 – Safety Population¹ – Study Eye**

Line Changes	0.59 mg N=110 n (%)	2.1 mg N=165 n (%)
≥ 3 lines loss	12 (10.9%)	15 (9.1%)
2+ line loss	7 (6.4%)	3 (1.8%)
1 line loss	5 (4.5%)	9 (5.5%)
No Change	36 (32.7%)	58 (35.2%)
1 line gain	18 (16.4%)	23 (13.9%)
2+ lines gain	11 (10.0%)	18 (10.9%)
≥ 3 lines gain	21 (19.1%)	39 (23.6%)

¹Last observation carried forward

**Change in Visual Acuity from Baseline to 34 Week
 BLP 415-004 – Safety Population¹ – Study Eye**

Line Changes	0.59 mg N=116 n /N (%)	2.1 mg N=121 n /N (%)
≥ 3 lines loss	12 (10.3%)	20 (16.5%)
2+ line loss	4 (3.4%)	1 (0.8%)
1 line loss	8 (6.9%)	6 (5.0%)
No Change	28 (24.1%)	38 (31.4%)
1 line gain	25 (21.6%)	20 (16.5%)
2+ lines gain	13 (11.2%)	13 (10.7%)
≥ 3 lines gain	26 (22.4%)	23 (19.0%)

¹Last observation carried forward

Reviewer's Comments:

The visual acuity changes in the study eye over 34 weeks are similar between Studies BLP 415-001 and BLP 415-004 and between treatment groups in both studies.

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Explant adverse events

**Patients Requiring Explantation of Implant through 15 February (Cut-Off-Date)
 BLP 415-001**

Dose	Patient No.	Days in Study	Explanted Eye	Reason for Explantation
0.59 mg	124-2057	25	OD	Endophthalmitis OD
0.59 mg	118-2050	140	OD	IOP increased, glaucoma NOS, visual field defect NOS, vitreous hemorrhage, visual acuity reduced.
0.59 mg	124-2205	224	OS	Intraocular lymphoma
0.59 mg	125-2017	346	NA ¹	Cataract
0.59 mg	133-2005	717	NA ¹	Post-operative complications
0.59 mg	125-1023	756	NA ¹	Migration of implant
2.1 mg	144-1227	76	OS	Severe late post-operative hypotony causing implant to move anteriorly, in opposition to the crystalline lens. This in turn, caused secondary peripheral crystalline lens opacity.
2.1 mg	119-1318	192	NA ¹	Ocular hypertension
2.1 mg	119-1318	196	OS	Elevated IOP
2.1 mg	133-2037	275	NA ¹	Iris disorder
2.1 mg	125-1021	560	NA ¹	Elevated IOP
2.1 mg	125-1022	610	NA ¹	Elevated IOP
2.1 mg	124-1102	643	NA ¹	Implant expulsion

¹NA=Not Available (not reported unintentionally)

Reviewer's Comments:

As of the February 12, 2004 cut-off-date, the implant has been explanted in approximately 5% (13/278) of subjects in Study BLP 415-001. The number of subjects is similar for each treatment group. The reason for explantation in a majority of the explanted patients was drug related or related to the implantation procedure.

**Patients Requiring Explantation of Implant through February 15, 2004 (Cut-Off-Date)
 BLP 415-004**

Dose	Patient No.	Days in Study	Explanted Eye	Reason for Explantation
0.59 mg	1296	129	NA ¹	Post-operative complications
0.59 mg	2124	140	OS	Uncontrolled in spite of maximal topical therapy and Diamox.
0.59 mg	2142	303	NA ¹	Elevated IOP
0.59 mg	1327	313	NA ¹	Device expulsion
2.1 mg	2139	32	OD	Unresolved hypotony, maculopathy.
2.1 mg	1001	56	OD	Complaints of sudden diminution of vision. Choroidal and retinal detachment. Scleral wound leak.
2.1 mg	2122	101	OD	Explanted due to partially extruded implant. Unable to reinsert due to infection and unstable wound structure.

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2.1 mg	1308	203	OD	Evisceration OD due to complications from endophthalmitis.
2.1 mg	2138	349	NA ¹	Glaucoma
2.1 mg	2002	513	NA ¹	Device expulsion

¹NA=Not Available (not reported unintentionally)

Reviewer's Comments:

As of the February 12, 2004 cut-off-date, the implant has been explanted in approximately 4% (10/239) of subjects in Study BLP 415-004. The number of subjects is similar for each treatment group. The reason for explantation in all of the explanted patients was drug related or related to the implantation procedure.

Delamination of FA intravitreal implant

Delamination involves the separation of the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the PVA suture tab that anchors the implant to the back of the eye.

Three cases of clinical delamination were reported to the agency on June 24, 2003 while clinical studies BLP 415-001 and BLP 415-004 were ongoing. At the time, enrollment in all ongoing studies was suspended pending an investigation. The investigation determined that when delamination occurs, the silicone adhesive that attaches the cup to the suture tab separates at the interface between the silicone adhesive and the suture tab. As a result, the manufacturing process was modified with the objective of increasing the strength of the silicone adhesive bond between the silicone cup and the suture tab. On January 18, 2005, the applicant reported the first case of delamination since the modified manufacturing process was implemented.

Summary of Delamination Cases

Dose	Patient No.	Study	Weeks in Study	Manufacturing Process	Comment
0.59 mg	510052	CDS FL-005 (DME)	NA ¹	Modified	Delamination occurred during explantation surgery
0.59 mg	2005	BLP 415-001 (uveitis)	102	Original	Delamination occurred during explantation surgery
0.59 mg	1023	BLP 415-001 (uveitis)	108	Original	Delamination occurred spontaneously
0.59 mg	20017	BLP 415-001 (uveitis)	49	Original	Delamination occurred during explantation surgery

¹NA=Not Available (not reported unintentionally)

7.1.5.6 Additional analyses and explorations

Not applicable. There were no additional analyses and explorations performed regarding adverse events.

7.1.6 Less Common Adverse Events

See Section 7.1.5.4.

7.1.7 Laboratory Findings

Hematology tests, blood chemistry tests including liver function tests, and urinalysis were performed at screening, Week 1, Week 4, Week 34, and as necessary.

Changes in clinical laboratory values were similar across treatment groups; there were no clinically significant differences between treatment groups with respect to changes in any laboratory parameter.

7.1.7.1 Special assessments

Electroretinogram (ERG) was measured at Screening, Week 12, and Week 34 at selected sites. Based on very small numbers (22 subjects in the 0.59 mg treatment group and 37 subjects in the 2.1 mg treatment group), there does not appear to be a difference in changes from baseline in amplitude and latency between treatment groups.

Visual Field was measured at Screening, Week 34, Year 1, and then annually (24 months and 36 months) for all enrolled subjects. There was no difference in changes from baseline in visual field parameters between treatment groups.

Biomicroscopy to evaluate the lid, conjunctiva, cornea, iris, and anterior chamber was performed at each follow-up visit. No clinically significant changes were observed between treatment groups and at 34 Week as compared to baseline.

Ophthalmoscopy to evaluate vitreal haze, retina, macula, fovea, and optic nerve was performed at each follow-up visit. No clinically significant changes were observed between treatment groups and at 34 Week as compared to baseline.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (body temperature, heart rate, respiration rate, BP, weight, and height) were assessed at Screening and Week 34. There were no clinically significant differences noted between of the treatment groups with respect to changes in vital signs. There were no clinically significant within-group changes noted for vital signs.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not applicable. Based on knowledge regarding therapeutic drug class, there were no scheduled ECGs performed in either BLP 415-001 or BLP 415-004.

7.1.10 Immunogenicity

Not applicable. Drug product would be expected to mask immunogenicity, not cause it.

7.1.11 Human Carcinogenicity

The Agency has granted a waiver for performing carcinogenicity studies. FA did not have positive genotoxicity or animal carcinogenicity findings to warrant carcinogenicity studies.

7.1.12 Special Safety Studies

No special safety studies were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no abuse potential associated with the FA intravitreal implant due to its route of administration (i.e., surgical implantation by physician). There is a potential for withdrawal which may be addressed by replacing the implant when FA is depleted as evidenced by recurrence of uveitis.

7.1.14 Human Reproduction and Pregnancy Data

The Agency has granted a waiver for performing reproductive toxicity studies. There are no adequate and well-controlled studies in pregnant women. There is negligible, if any systemic uptake of FA from the implant. FA could potentially be teratogenic. This is considered a class effect of glucocorticosteroids, and the prescribing information will include a warning not to use the implant during pregnancy unless clearly necessary (Pregnancy category C).

7.1.15 Assessment of Effect on Growth

There are no adequate and well-controlled studies in the pediatric population. FA intravitreal implant for the posterior uveitis indication is exempted from the pediatric assessment requirement pursuant to 21 CFR §314.55(d) due to its orphan drug designation.

7.1.16 Overdose Experience

There is no overdose experience in humans with this product for the submitted indication. Overdose is unlikely to occur due to its route of administration (i.e., surgical implantation by physician). The signs and symptoms of an over dosage are treatable.

7.1.17 Postmarketing Experience

FA intravitreal implant is not currently marketed in the United States. To date, there are no marketing applications pending for FA intravitreal implant. It has not been marketed or withdrawn from the market in any country. No post-marketing data is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

All submitted clinical study reports, clinical protocols, and literature reports were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

See Section 4.2 for the table of clinical studies.

7.2.1.1 Study type and design/patient enumeration

See Section 4.2 for the table of clinical studies.

7.2.1.2 Demographics

Demographic and Baseline Characteristics for ITT “as treated” Population BLP 415-001

	0.59 mg (N=110)	2.1 mg (N=168)	p-value ¹
Age (years)			
Mean	44.72	42.77	0.3063
Median	44.50	42.00	
SD	17.02	14.37	
Range	7-84	9-76	
Sex			
Male	29 (26.4%)	48 (28.6%)	0.6875
Female	81 (73.6%)	120 (71.4%)	
Race			
Caucasian	75 (68.2 %)	109 (64.9%)	0.7214
Black	19 (17.3%)	30 (17.9%)	
Asian	9 (8.2%)	12 (7.1%)	

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Hispanic	4 (3.6%)	13 (7.7%)	
Other	3 (2.7%)	4 (2.4%)	
Iris Color ²			0.9932
Brown	62 (56.4%)	96 (57.1%)	
Hazel	16 (14.6%)	27 (16.1%)	
Green	7 (6.4%)	10 (6.0%)	
Blue	23 (20.9%)	32 (19.1%)	
Other	2 (1.8%)	3 (1.8%)	
Laterality of uveitis			0.8438
Unilateral	26 (23.6%)	38 (22.6%)	
Bilateral	84 (76.4%)	130 (77.4%)	
Previous uveitis treatment			0.3004
Systemic	68 (61.8%)	114 (67.9%)	
Local	42 (38.2%)	54 (32.1%)	

¹P-value for continuous measures by ANOVA and for categorical measures by Chi-Square test

²One patient had an OD iris color of brown and an OS iris color of other, grey. For this patient, the iris color of the surgical eye was summarized.

**Demographic and Baseline Characteristics for ITT “as treated” Population
 BLP 415-004**

	0.59 mg (N=117)	2.1 mg (N=122)	p-value ¹
Age (years)			0.2213
Mean	42.48	40.37	
Median	42.00	40.00	
SD	14.07	12.51	
Range	12-74	15-92	
Sex			0.2511
Male	47 (40.2%)	58 (47.5%)	
Female	70 (59.8%)	64 (52.5%)	
Race ²			0.9770
Caucasian	24 (20.5%)	28 (23.0%)	
Black	3 (2.6%)	4 (3.3%)	
Asian	93 (70.9%)	84 (68.9%)	
Hispanic	2 (1.7%)	2 (1.6%)	
Other	5 (4.3%)	4 (3.3%)	
Iris Color			0.6574
Brown	89 (76.1%)	91 (74.6%)	
Hazel	3 (2.6%)	7 (5.7%)	
Green	2 (1.7%)	4 (3.3%)	
Blue	11 (9.4%)	9 (7.4%)	
Other	12 (10.3%)	11 (9.0%)	
Laterality of uveitis			0.9978
Unilateral	23 (19.7%)	24 (19.7%)	
Bilateral	94 (80.3%)	98 (80.3%)	
Previous uveitis treatment			0.4041
Systemic	89 (76.1%)	87 (71.3%)	
Local	28 (23.9%)	35 (28.7%)	

¹P-value for continuous measures by ANOVA and for categorical measures by Chi-Square test

²Patients from the Indian sub-continent were classified as "Asian".

Reviewer's Comments:

There are no remarkable differences between treatment groups in baseline demographic characteristics.

Subgroup analyses stratified by age, gender, iris color, and race did not reveal any significant differences in the primary efficacy endpoint and safety profiles.

The clinical trial population in BLP 415-001 was overwhelmingly white whereas the study population for BLP 415-004 was overwhelmingly Asian. This was due to the location of the study sites for each of the clinical trials and does not reflect an issue with recruitment.

7.2.1.3 Extent of exposure (dose/duration)

**Extent of Exposure (Implant Duration in Days)
 Safety Population in BLP 415-001**

	0.59 mg (N=110) Days	2.1 mg (N=168) Days
Mean	239.1	241.7
Median	239.0	240.5
SD	24.9	18.4
Range	25-287	77-301

**Extent of Exposure (Implant Duration in Days)
 Safety Population in BLP 415-004**

	0.59 mg (N=117) Days	2.1 mg (N=122) Days
Mean	239.0	234.2
Median	239.0	239.0
SD	10.8	28.4
Range	140-259	32-261

Reviewer's Comments:

The FA intravitreal implant is designed to release FA over approximately 30 months.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

7.2.2.1 Other studies

The study reports submitted from the individual investigator research IND applications in this NDA were not of sufficient duration or quality (i.e., enrollment size, lack of control or mask, etc.) to provide safety data comparable in quality to the two Phase 3 clinical trials. The safety data from the research IND applications did not raise additional safety issues. The reported adverse events were similar to those identified in the two Phase 3 clinical trials.

7.2.2.2 Postmarketing experience

FA intravitreal implant is not currently marketed in the United States. To date, there are no marketing applications pending for FA intravitreal implant. It has not been marketed or withdrawn from the market in any country. No post-marketing data is available.

The active ingredient, FA, has been marketed in many formulations and strengths worldwide since the 1960's, mainly for dermatological use. The adverse events are similar to those of dermatological corticosteroid (e.g., irritation, thinning, etc.) and are not relevant to an intravitreal application.

7.2.2.3 Literature

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug product, including adequate demographic subsets. The doses and duration of exposure were adequate to assess safety for the intended use. The study subjects will be followed for 3 years post-implantation.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There has been special animal and in vitro testing to assess the safety of the FA intravitreal implant. Route-specific (intravitreal) studies were performed in dogs and rabbits to assess FA's ocular and systemic uptake, as well as the safety of FA as released from the implant. The biocompatibility of the implant itself (minus an FA tablet) or its extracts were assessed with respect to acute (systemic) toxicity, *in vitro* and *in vivo* genotoxicity, and local *in vitro* and *in vivo* tolerance (cytotoxicity, hemolysis, dermal sensitization and local tissue reaction). See the Pharmacology/Toxicology review for more detail.

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7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing in BLP 415-001 and BLP 415-004 utilized adequate hematological, blood chemistry, and urinalysis evaluations for this drug class.

The methods and tests used and their frequency was adequate to effectively monitor the patient population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There is no direct metabolism information on ocularly administered FA. The potential metabolism of FA given by the ocular route is extrapolated from information that is available on other corticosteroids. Ocular metabolism of FA is not expected. It is most likely that FA is absorbed systemically, but at very low levels (below the LOQ) over a prolonged period of time. Systemically, the most active organ for metabolism of corticosteroids is the liver. Low levels of FA are most likely metabolized by the liver involving esterification reactions. Due to very limited systemic exposure expected from the FA implant, meaningful levels of FA metabolites are not likely to occur.

A one-year GLP rabbit study showed that urinary excretion of FA following FA intravitreal implantation was below the LOQ. Data on excretion of systemically available FA are not available. According to the literature, synthetic steroids are metabolized in the liver to water soluble metabolites/conjugates, and excreted by the kidney. Neither biliary nor fecal excretion is of quantitative importance in humans.

There are not thought to be any drug interactions of note with this product. See the Clinical Pharmacologist's review for more detail.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's evaluation of potential adverse events for this pharmacological class of drug is adequate.

7.2.8 Assessment of Quality and Completeness of Data

For clinical studies BLP 415-001 and BLP 415-004, the safety and efficacy data submitted to NDA 21-737 include data through 34 weeks post-implantation (the protocol defined primary efficacy analysis timepoint). The cut off date for reporting serious adverse events was through February 15, 2004 (regardless of time lapsed since implantation).

Reviewer's Comments:

The applicant was instructed at the Pre-NDA meeting of May 10, 2004, to include all safety and efficacy available at the time of NDA submission.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update includes: 1) exposure information from all clinical studies through June 30, 2004, 2) a listing of all adverse events through January, 2005, 3) 1-year efficacy data from clinical studies BLP 415-001 and BLP 415-004, and 4) a revised package insert updated with new information on safety and efficacy.

There were no additional deaths reported since the original NDA submission for clinical studies BLP 415-001 and BLP 415-004.

**Incidence of Cataract Surgery¹
 Study Eye**

Study	0.59 mg n /N (%)	2.1 mg n /N (%)
BLP 415-001		
34 weeks post-implantation	6/55 (10.9%)	8/87 (9.2%)
1 year post-implantation	15/55 (27.3%)	21/87 (24.1%)
~ 2 years post-implantation	52/55 (94.6%)	77/87 (88.5%)
~ 2.25 years post-implantation	52/55 (94.6%)	77/87 (88.5%)
BLP 415-004		
34 weeks post-implantation	14/70 (20.0%)	10/66 (15.2%)
1 year post-implantation	25/70 (35.7%)	27/66 (40.9%)
~ 2 years post-implantation	61/70 (87.1%)	61/66 (92.4%)
~ 2.25 years post-implantation	63/70 (90.0%)	64/66 (97.2%)
Both Studies		
34 weeks post-implantation	20/125 (16.0%)	18/153 (11.8%)
1 year post-implantation	40/125 (32.0%)	48/153 (31.4%)
~ 2 years post-implantation	113/125 (90.4%)	138/153 (90.2%)
~ 2.25 years post-implantation	115/125 (92.0%)	141/153 (92.2%)

¹Performed on phakic eyes

Reviewer's Comments:

By approximately 2 years post-implantation, nearly all (> 90%) phakic eyes had undergone cataract extraction.

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**Incidence of Patients Requiring Filtering Procedures to Control IOP
 Study Eye**

Study	0.59 mg n /N (%)	2.1 mg n /N (%)
BLP 415-001		
34 weeks post-implantation	4/110 (3.6%)	12/168 (7.1%)
1 year post-implantation	12/110 (10.9%)	20/168 (11.9%)
~ 2 years post-implantation	41/110 (37.3%)	60/168 (35.7%)
~ 2.25 years post-implantation	41/110 (37.3%)	64/168 (38.1%)
BLP 415-004		
34 weeks post-implantation	7/117 (6.0%)	11/122 (9.0%)
1 year post-implantation	12/117 (10.3%)	20/122 (16.4%)
~ 2 years post-implantation	25/117 (21.4%)	37/122 (30.3%)
~ 2.25 years post-implantation	26/117 (22.2%)	39/122 (32.0%)
Both Studies		
34 weeks post-implantation	11/227 (4.8%)	23/290 (7.9%)
1 year post-implantation	24/227 (10.6%)	40/290 (13.8%)
~ 2 years post-implantation	66/227 (29.1%)	97/290 (33.5%)
~ 2.25 years post-implantation	67/227 (29.5%)	103/290 (35.5%)

Reviewer's Comments:

The number of patients that required filtering procedures to control IOP consistently increased over time. By 2 years post-implantation, more than 30% of patients had undergone a filtering procedure.

Summary of Explantation of Implant by Study through September 30, 2004 (Cut-Off-Date)

Study	0.59 mg n /N (%)	2.1 mg n /N (%)	Both Doses n/N (%)
BLP 415-001	10/110 (9.1%)	14/168 (8.3%)	24/278 (8.6%)
BLP 415-004	5/117 (4.3%)	10/122 (8.2%)	15/239 (6.3%)
IND	(0.0%)	(0.0%)	0/35 ² (0.0%)
IND	---	2/4 (%)	2/4 ³ (50.0%)
IND	---	0/1 (50.0%)	0/1 ⁴ (0.0%)
Total	15/227 (6.6%)	16/295 (5.4%)	41/557 (7.4%)

¹Study is ongoing

²Treatment is masked

³Open label study. A total of 4 eyes of 2 patients were implanted with 2.1 mg FA intravitreal implant.

⁴A total of 1 eye of 1 patient was implanted with a 2.1 mg FA intravitreal implant. The patient died 123 weeks after implantation due to sequelae from an osteosarcoma in the sella turcica.

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**Serious Adverse Events Reported for at least 2% of Patients in Any Treatment Group
 (~ 2 years post-implantation)
 BLP 415-001 and BLP 415-0004 - Safety Populations Pooled**

Coded Adverse Event	0.59 mg (N=227) n (%)	2.1 mg (N=290) n (%)
OCULAR		
Cataract ¹	116 (51.1%)	140 (48.3%)
Glaucoma ²	38 (16.7%)	58 (20.0%)
Intraocular pressure increased	47 (20.7%)	62 (21.4%)
Hypotony	15 (6.6%)	23 (7.9%)
Procedural complication ³	16 (7.0%)	20 (6.9%)
Retinal detachment	7 (3.1%)	11 (3.8%)
Maculopathy	7 (3.1%)	8 (2.8%)
Vitreous hemorrhage	6 (2.6%)	5 (1.7%)
Endophthalmitis	3 (1.3%)	8 (2.8%)
Visual acuity reduced	2 (0.9%)	6 (2.1%)

¹Cataract=cataract NOS aggravated, cataract NOS, cataract subcapsular, and posterior capsule opacification

²Glaucoma=glaucoma NOS, open angle glaucoma, and ocular hypertension

³Procedural complication=wound dehiscence, post-op wound complications NOS, post-op complications NOS, device expulsion, migration of implant, mechanical complication of implant, injury NOS, wound complication, cataract fragments in eye post-op, and implant expulsion

Reviewer's Comments:

The serious adverse events reported in the 4 month safety update are essentially the same as the ones that were reported in the original NDA. The number of reports of cataract, glaucoma, and increased IOP more than doubled compared to the number reported in the original NDA.

**Adverse Events Reported for at least 5% of Patients in any Treatment Group
 (~ 2 years post-implantation)
 BLP 415-001 and BLP 415-004 – Safety Populations Pooled**

Coded Adverse Event	0.59 mg (N=227) n (%)	2.1 mg (N=290) n (%)
OCULAR		
Cataract ¹	178 (78.4%)	222 (76.6%)
Intraocular pressure increased	140 (61.7%)	193 (66.6%)
Procedural complication ²	131 (57.7%)	170 (58.6%)
Eye pain	105 (46.3%)	151 (52.1%)
Visual acuity reduced	78 (34.4%)	102 (35.2%)
Conjunctival hemorrhage	72 (31.7%)	104 (35.9%)
Conjunctival hyperemia	74 (32.6%)	92 (31.7%)
Glaucoma ³	64 (28.2%)	102 (35.2%)
Vision blurred	52 (22.9%)	71 (24.5%)
Abnormal sensation in eye	50 (22.0%)	72 (24.8%)
Eye irritation	52 (22.9%)	67 (23.1%)
Hypotony	42 (18.5%)	63 (21.7%)
Eye pruritus	38 (16.7%)	55 (19.0%)

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Vitreous floaters	41 (18.1%)	51 (17.6%)
Maculopathy	43 (18.9%)	40 (13.8%)
Vitreous hemorrhage	33 (14.5%)	35 (12.1%)
Eyelid ptosis	21 (9.3%)	42 (14.5%)
Eye inflammation	29 (12.8%)	31 (10.7%)
Eyelid edema	32 (14.1%)	26 (9.0%)
Lacrimation increased	23 (10.1%)	34 (11.7%)
Dry eye	19 (8.4%)	33 (11.4%)
Macular edema	21 (9.3%)	27 (9.3%)
Visual disturbance	19 (8.4%)	29 (10.0%)
Eye discharge	14 (6.2%)	29 (10.0%)
Conjunctival edema/chemosis	14 (6.2%)	25 (8.6%)
Photophobia	14 (6.2%)	24 (8.3%)
Blepharitis	15 (6.6%)	19 (6.6%)
Corneal edema	17 (7.5%)	14 (4.8%)
Photopsia	8 (3.5%)	23 (7.9%)
Retinal hemorrhage	12 (5.3%)	13 (4.5%)
Choroidal detachment	8 (3.5%)	16 (5.5%)
Vitreous opacities	8 (3.5%)	15 (5.2%)
Eye swelling	12 (5.3%)	11 (3.8%)
NON-OCULAR		
Body as a Whole – General Disorders		
Pyrexia	21 (9.3%)	24 (8.3%)
Pain NOS	9 (4.0%)	17 (5.9%)
Gastrointestinal Disorders		
Nausea	20 (8.8%)	24 (8.3%)
Vomiting NOS	19 (8.4%)	18 (6.2%)
Infections and Infestations		
Nasopharyngitis	38 (16.7%)	44 (13.1%)
Sinusitis NOS	26 (11.5%)	32 (11.0%)
Influenza	18 (7.9%)	22 (7.6%)
Upper respiratory tract infection NOS	16 (7.0%)	24 (8.3%)
Urinary tract infection NOS	8 (3.5%)	15 (5.2%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	21 (9.3%)	44 (15.2%)
Pain in limb	14 (6.2%)	17 (5.9%)
Back pain	13 (5.7%)	18 (6.2%)
Nervous System Disorders		
Headache NEC ⁴	57 (25.1%)	104 (35.9%)
Dizziness	18 (7.9%)	28 (9.7%)
Psychiatric Disorders		
Depression	2 (1.0%)	18 (6.2%)
Respiratory, thoracic and Mediastinal Disorders		
Cough	21 (9.3%)	20 (6.9%)
Skin and Subcutaneous Tissue Disorders		
Rash NOS	7 (3.1%)	20 (6.9%)

¹Cataract=cataract NOS aggravated, cataract NOS, posterior capsule opacification, cataract subcapsular, lenticular opacities, cataract cortical, and cataract nuclear

²Procedural complication=post-op wound complication NOS, post-op complications NOS, post-op wound site erythema, wound dehiscence, post procedural pain, therapeutic procedural complication, and procedural site reaction

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³Glaucoma=optic nerve cupping, glaucoma NOS, open angle glaucoma NOS, angle closure glaucoma, ocular hypertension, borderline glaucoma, and glaucoma aggravated

⁴Headache NEC=headache NOS, sinus headache, tension headaches, frequent headaches, and post-traumatic headache

Reviewer's Comments:

The most frequently reported ocular adverse events were cataract (77%-78%), increased IOP (62%-67%), procedural complication (58%-59%), eye pain (46%-52%), reduced visual acuity (34%-35%), conjunctival hemorrhage (32%-36%), conjunctival hyperemia (32%-33%), and glaucoma (28%-35%).

The most frequently reported non-ocular adverse events were headache (25%-36%), nasopharyngitis (13%-17%), arthralgia (9%-15%), and sinusitis (11-12%).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There appears to be a clear dose-response relationship between both doses of the FA intravitreal implant and IOP as well as lens opacity. Given this relationship, the incidence of drug-related adverse events is expected to rise as clinical studies BLP 415-001 and BLP 415-004 progress.

With respect to IOP, there are statistically differences in mean IOP at each visit post-implantation as compared to baseline beginning 4 weeks post-implantation for both treatment groups. The number of patients that require IOP lowering medications to control IOP increases over time. By 34 weeks post-implantation, the majority of patients are on IOP lowering medications. The percentage of patients that require a filtering procedure to control IOP ranges from 4% to 9%.

With respect to lens opacity, clinically significant increases lens opacity was observed with increasing frequency over time post-implantation. By 34 weeks post-implantation, the percentage of phakic eyes with clinically significant increases in lens opacity ranges from 20% to 36%. The percentage of patients who had undergone cataract surgery by 34 weeks post-implantation ranges from 9% to 20%.

See Section 7.1.5.4.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Individual safety and efficacy data is presented for each of the Phase 3 trials. Polled efficacy results are located in Section 6.1.4 of this review. Pooled Adverse event data is located in Section 7.1.5.4 of this review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosing regimen is surgical implantation of Retisert into the posterior segment of the affected eye. The implant contains one tablet of 0.59 mg of fluocinolone acetonide. The Retisert implant is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 $\mu\text{g}/\text{day}$, decreasing over the first month to a steady state between 0.3-0.4 $\mu\text{g}/\text{day}$ over approximately 30 months. Following depletion of fluocinolone acetonide from the Retisert implant as evidenced by progression of posterior uveitis, Retisert may be replaced.

8.2 Drug-Drug Interactions

There was no important drug-drug interactions noted that would affect the product's clinical use.

8.3 Special Populations

Subgroup analyses stratified by age (<65, 65-<75, and ≥ 75 years), gender, iris color, and race did not reveal any significant differences in the primary efficacy endpoint and safety profiles.

The clinical trial population in BLP 415-001 was overwhelmingly white whereas the study population for BLP 415-004 was overwhelmingly Asian. This was due to the location of the study sites for each of the clinical trials and does not reflect an issue with recruitment.

There are no adequate and well-controlled studies in pregnant women. It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

8.4 Pediatrics

Fluocinolone acetonide intravitreal implant for the posterior uveitis indication is exempted from the pediatric assessment requirement pursuant to 21 CFR §314.55(d) due to its orphan drug designation.

Summary of Patients Between Age 0-18 Years BLP 415-001 and BLP 415-004

Study	Patient No.	Dose	Age (years)
BLP 415-001	135-1239	0.59 mg	7
	116-1282	0.59 mg	8
	146-1251	2.1 mg	9
	118-2071	2.1 mg	11
	116-1096	0.59 mg	12

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	116-1285	2.1 mg	14
	116-2281	2.1 mg	14
	119-1318	2.1 mg	14
	148-1210	2.1 mg	14
	116-1035	2.1 mg	15
	119-1319	0.59 mg	16
	144-2121	0.59 mg	16
	140-2242	2.1 mg	16
	116-1058	2.1 mg	17
	124-2203	2.1 mg	17
	125-1061	0.59 mg	18
	146-2252	0.59 mg	18
	184-1351	2.1 mg	18
BLP 415-004			
	155948-1010	0.59 mg	12
	155948-2005	0.59 mg	15
	246853-1263	2.1 mg	15
	227872-1222	2.1 mg	16
	155948-1003	0.59 mg	18
	155948-1015	2.1 mg	18

8.5 Advisory Committee Meeting

Not applicable. No advisory meeting was held for this drug product.

8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There is no significant new information found in the published literature.

8.7 Postmarketing Risk Management Plan

The clinical studies submitted in this NDA to support safety and efficacy, BLP 415-001 and 415-004, are ongoing and will not be completed until the enrolled subjects have completed 3 years of post-implantation follow-up. The applicant is expected to submit all data that are collected after submission of the original NDA as they become available.

In addition, the applicant should commit to a phase 4 post-marketing plan to adequately address concerns raised by the following: 1) the report of high incidence of cataract extraction and the potential for complications following cataract surgery in this population, 2) the recurrence of delamination after the manufacturing process had been modified, and 3) the lack of an assessment on the effect on the corneal endothelium for this drug product.

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8.8 Other Relevant Materials

A consultation has been forwarded to the Division of Drug Marketing, Advertising, and Communications (DDMAC).

A review was completed by the Office of Post-Marketing Drug Risk Assessment (OPDRA), now known as the Division of Medication Errors and Technical Support (DMETS) on September 21, 2001 regarding two tradenames provided by the sponsor, Retisert and . OPDRA's conclusion is that it had no objection to the tradename, Retisert and recommends that the name be re-evaluated approximately 90 days prior to the expected approval of the NDA. A consultation is currently pending with DMETS.

9 OVERALL ASSESSMENT

9.1 Conclusions

The clinical trials BLP 415-001 and BLP 415-004 demonstrate statistical significance for their primary efficacy endpoint.

9.2 Recommendation on Regulatory Action

NDA 21-737 is recommended for approval for the treatment of chronic non-infectious posterior uveitis in patients 12 years of age and older with the labeling revisions included in this review.

Clinical studies BLP 415-001 and BLP 415-004 demonstrate statistical significance for their primary endpoint (i.e., the proportion of patients with recurrence of uveitis in the study eye within 34 weeks following implantation compared to the proportion with recurrence of uveitis in the 34 weeks preceding implantation) for the 0.59 mg dose.

9.3 Recommendation on Postmarketing Actions

The clinical studies submitted in this NDA to support safety and efficacy, BLP 415-001 and 415-004, are ongoing and will not be completed until the enrolled subjects have completed 3 years of post-implantation follow-up. The applicant is expected to submit all data that are collected since submission of the original NDA as they become available.

In addition, the applicant should commit to a phase 4 post-marketing plan to adequately address concerns raised by the following: 1) the report of high incidence of cataract extraction and the potential for complications following cataract surgery in this population, 2) the recurrence of delamination after the manufacturing process had been modified, and 3) the lack of an assessment on the effect on the corneal endothelium for this drug product.

9.4 Labeling Review

See Section 10.2 for a line-by-line labeling review.

9.5 Comments to Applicant

- 1) The 34 Week post-implantation period was the pre-specified timepoint to evaluate efficacy. This cut-off-date does not apply to the safety evaluation of the drug product. The safety review should reflect the most up-to-date safety information.

10 APPENDICES

10.1 Review of Individual Study Reports

See section 6.1.3 for detailed information regarding the individual clinical trials BLP 415-001 and BLP 415-004.

10.2 Line-by-Line Labeling Review

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical-_____

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Wiley Chambers
4/4/05 01:50:27 PM
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CLINICAL REVIEW of NDA 21-737

M.O. Review Safety Update Proposal Review

Submitted: November 11, 2004
Received: November 12, 2004
Review completed: December 6, 2004
Reviewer: Lucious Lim, M.D., M.P.H.

Proposed Tradename: Retisert

Established Name: Fluocinolone acetonide

Sponsor: Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
(813) 866-2568
Contact: Yelen Concepcion

Pharmacologic Category: Corticosteroid

Proposed Indication: Treatment of non-infectious posterior uveitis

**Dosage Form and
Route of Administration:** Intravitreal implant

Submitted:

Submitted is a proposal for submission of the 4-month safety update. Sponsor proposes to provide the following in the safety update: 1) updated adverse event and exposure information from all clinical studies through June 30, 2004, 2) updated SAE Listings and Narratives through September 30, 2004, and 3) 1-year efficacy data from two Phase 3 posterior uveitis trials, BLP 415-001 and BLP 415-004. For the 4-month safety update, sponsor proposes to submit "Case Histories" in lieu of the Case Report Forms for patients who died or withdrew from the studies. Each "Case History" is a tabulation of the information contained in an individual patient's Case Report Form. A revised draft package insert updated with new safety and efficacy information will also be included.

Reviewer's Comments:

- 1) The substitution of "Case Histories" for Case Report Forms is not acceptable.*
- 2) A listing of all the AEs through January 2005 should be included.*

CLINICAL REVIEW of NDA 21-737

Recommended Regulatory Action:

The Reviewer's comments should be conveyed to the Sponsor.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 21-737
HFD-550/Div Files
HFD-550/CSO/Rodriguez
HFD-550/CTL/Boyd
HFD-550/Dep Div Director/Chambers

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