

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022315Orig1s009

Trade Name: **Ozurdex**

Generic Name: **dexamethasone intravitreal implant**

Sponsor: **Allergan Inc.**

Approval Date: 06/28/2014

Indications: OZURDEX® (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
Summary Review	X
Officer/Employee List	
Office Director Memo	X
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	X
Administrative/Correspondence Document(s)	X

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22315/S-009

SUPPLEMENT APPROVAL

Allergan Inc.
Attention: Libette Luce, MA
Senior Manager, US Regulatory Affairs
200 Somerset Corporate Blvd.
Bldg. 200, #6001
Bridgewater, NJ 08807

Dear Ms. Luce:

Please refer to your Supplemental New Drug Application (sNDA) dated June 12, 2013, received June 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ozurdex (dexamethasone intravitreal implant) 0.7 mg.

We acknowledge receipt of your amendments dated August 14 and 28, October 4 and 11, November 8 and 20, and December 2 and 13, 2013, and March 11 and 31, April 7, May 16, and June 20 (two) and 27, 2014.

This "Prior Approval" supplemental new drug application provides for the use of Ozurdex (dexamethasone intravitreal implant) 0.7 mg, for the treatment of Diabetic Macular Edema.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the labeling submitted on June 27, 2014.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed package insert labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application since studies are impossible or highly impracticable because Diabetic Macular Edema rarely occurs in the pediatric population.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

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

/s/

RENATA ALBRECHT

06/28/2014

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OZURDEX® safely and effectively. See full prescribing information for OZURDEX®.

OZURDEX® (dexamethasone intravitreal implant)
Initial U.S. Approval: 1958

RECENT MAJOR CHANGES

- Indications and Usage (1.3) 06/2014

INDICATIONS AND USAGE

OZURDEX® is a corticosteroid indicated for:

- The treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.1)
- The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.2)
- The treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery (1.3)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection only. (2.1)
- The intravitreal injection procedure should be carried out under controlled aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the NOVADUR® solid polymer drug delivery system. (3)

CONTRAINDICATIONS

- Ocular or periocular infections (4.1)
- Advanced glaucoma (4.2)
- Non-intact posterior lens capsule (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. (5.2)
- The implant may migrate to the anterior chamber if the posterior lens capsule is not intact. (5.3)

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported by 20–70% of patients were cataract, increased intraocular pressure and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Retinal Vein Occlusion
- 1.2 Posterior Segment Uveitis
- 1.3 Diabetic Macular Edema

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Ocular or Periocular Infections
- 4.2 Advanced Glaucoma
- 4.3 Non-intact Posterior Lens Capsule
- 4.4 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Intravitreal Injection-related Effects
- 5.2 Steroid-related Effects
- 5.3 Risk of Implant Migration

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion

OZURDEX[®] (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

1.2 Posterior Segment Uveitis

OZURDEX[®] is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

1.3 Diabetic Macular Edema

OZURDEX[®] is indicated for the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection only.

2.2 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.

Remove the foil pouch from the carton and examine for damage. Then, open the foil pouch over a sterile field and gently drop the applicator on a sterile tray. Carefully remove the cap from the applicator. Hold the applicator in one hand and pull the safety tab straight off the applicator. **Do not twist or flex the tab.** The long axis of the applicator should be held parallel to the limbus, and the sclera should be engaged at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path. The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of the sclera is completed and the vitreous cavity is entered. The needle should not be advanced past the point where the sleeve touches the conjunctiva.

Slowly depress the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each applicator can only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new applicator must be used, and the sterile field, syringe, gloves, drapes, and eyelid speculum should be changed before **OZURDEX**[®] is administered to the other eye.

3 DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the **NOVADUR**[®] solid polymer drug delivery system.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

OZURDEX[®] (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Advanced Glaucoma

OZURDEX[®] is contraindicated in patients with advanced glaucoma.

4.3 Non-intact Posterior Lens Capsule

OZURDEX[®] is contraindicated in patients whose posterior lens capsule is not intact.

4.4 Hypersensitivity

OZURDEX[®] is contraindicated in patients with known hypersensitivity to any components of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Intravitreal Injection-related Effects

Intravitreal injections, including those with **OZURDEX**[®], have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection [*see Patient Counseling Information (17)*].

5.2 Steroid-related Effects

Use of corticosteroids including **OZURDEX**[®] may produce posterior subcapsular cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [*see Adverse Reactions (6.1)*].

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

5.3 Risk of Implant Migration

Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including **OZURDEX**[®] include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Table 1: Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX [®] N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with **OZURDEX**[®] peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received **OZURDEX**[®] required surgical procedures for management of elevated IOP.

Following a second injection of **OZURDEX**[®] in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in Table 2 were 3% in the **OZURDEX**[®] group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Table 2: Adverse Reactions Reported by $\geq 1\%$ of Patients

MedDRA Term	OZURDEX[®] N=324 (%)	Sham N=328 (%)
Ocular		
Cataract ¹	166/243 ² (68%)	49/230 (21%)
Intraocular pressure increased ³	115 (35%)	16 (5%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)

¹ Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of **OZURDEX[®]** subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

² 243 of the 324 **OZURDEX[®]** subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

³ Includes IOP increased and ocular hypertension.

Cataracts and Cataract Surgery

At baseline, 243 of the 324 **OZURDEX[®]** subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **OZURDEX[®]** group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the **OZURDEX[®]** group and 12 months in the Sham group. Among these patients, 61% of **OZURDEX[®]** subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for **OZURDEX[®]** group and 20 for Sham) of the studies.

Increased Intraocular Pressure

Table 3: Summary of Elevated IOP Related Adverse Reactions

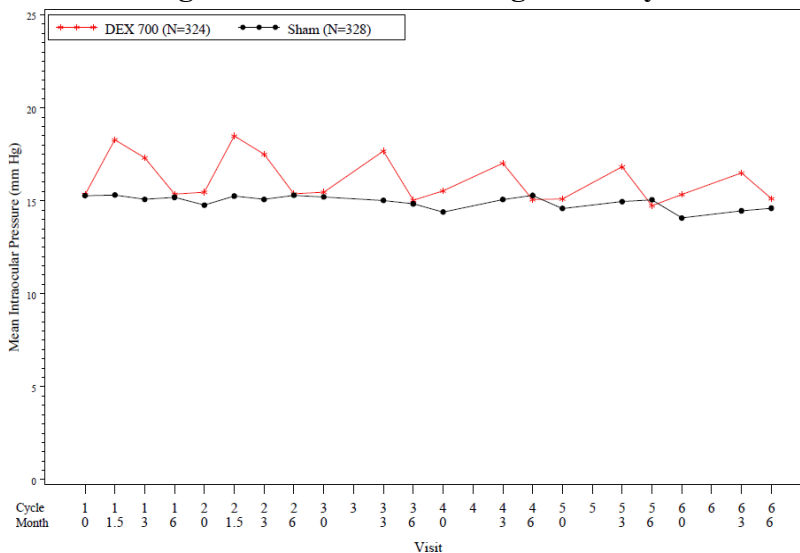
IOP	Treatment: N (%)	
	OZURDEX® N=324	Sham N=328
Any IOP Related AE	120 (37%)	18 (6%)
≥10 mm Hg IOP Change from Baseline at any visit	91 (28%)	13 (4%)
≥25 mm Hg IOP at any visit	106 (33%)	15 (5%)
≥35 mm Hg IOP at any visit	20 (6%)	3 (1%)
Glaucoma	4 (1.2%)	1 (0.3%)
IOP lowering procedure*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

Approximately 42% of the patients who received **OZURDEX®** were subsequently treated with IOP lowering medications during the study . In the sham control group, IOP lowering medications were used in approximately 10% of patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period) shown below:

Figure 1: Mean IOP during the study



6.2 Postmarketing Experience

The following reactions have been identified during post-marketing use of **OZURDEX**[®] in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **OZURDEX**[®], or a combination of these factors, include: complication of device insertion (implant misplacement), device dislocation with or without corneal edema, endophthalmitis, hypotony of the eye (associated with vitreous leakage due to injection), and retinal detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with **OZURDEX**[®] in pregnant women.

Animal reproduction

studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. **OZURDEX**[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an **OZURDEX**[®] injection in humans (0.7 mg dexamethasone) on a mg/m² basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an **OZURDEX**[®] injection in humans (0.7 mg dexamethasone) on a mg/m² basis.

8.3 Nursing Mothers

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

8.4 Pediatric Use

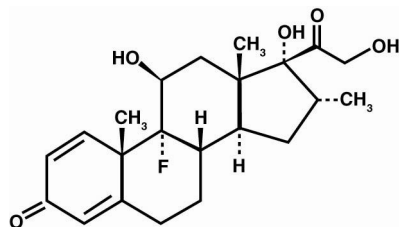
Safety and effectiveness of **OZURDEX**[®] in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

OZURDEX[®] is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR[®]** solid polymer sustained-release drug delivery system. **OZURDEX[®]** is preloaded into a single-use, **DDS[®]** applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The **NOVADUR[®]** system contains poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative. The chemical name for dexamethasone is Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11 β ,16 α)-. Its structural formula is:



MW 392.47; molecular formula: C₂₂H₂₉FO₅

Dexamethasone occurs as a white to cream-colored crystalline powder having not more than a slight odor, and is practically insoluble in water and very soluble in alcohol.

The PLGA matrix slowly degrades to lactic acid and glycolic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexamethasone, a corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.

12.3 Pharmacokinetics

Plasma concentrations were obtained from 21 patients with macular edema due to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and 21 patients with diabetic macular edema (DME) prior to dosing and at 4 to 5 additional post-dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In RVO and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In an *in vitro* metabolism study, following the incubation of [¹⁴C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours, no metabolites were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether **OZURDEX**[®] (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of **OZURDEX**[®], dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test.

Adequate fertility studies have not been conducted in animals.

14 CLINICAL STUDIES

Retinal Vein Occlusion

The efficacy of **OZURDEX**[®] for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) was assessed in two, multicenter, double-masked, randomized, parallel studies.

Following a single injection, **OZURDEX**[®] demonstrated the following clinical results for the percent of patients with ≥ 15 letters of improvement from baseline in best-corrected visual acuity (BCVA):

Table 4: Number (Percent) of Patients with ≥ 15 Letters Improvement from Baseline in BCVA

Study Day	Study 1			Study 2		
	OZURDEX [®] N=201	Sham N=202	p-value*	OZURDEX [®] N=226	Sham N=224	p-value*
Day 30	40 (20%)	15 (7%)	< 0.01	51 (23%)	17 (8%)	< 0.01
Day 60	58 (29%)	21 (10%)	< 0.01	67 (30%)	27 (12%)	< 0.01
Day 90	45 (22%)	25 (12%)	< 0.01	48 (21%)	31 (14%)	0.039
Day 180	39 (19%)	37 (18%)	0.780	53 (24%)	38 (17%)	0.087

*P-values were based on the Pearson's chi-square test.

In each individual study and in a pooled analysis, time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with **OZURDEX**[®] compared to sham ($p < 0.01$), with **OZURDEX**[®] treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a ≥ 15 letter (3-line) improvement in BCVA with **OZURDEX**[®] occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately one to three months after onset of this effect.

Posterior Segment Uveitis

The efficacy of **OZURDEX**[®] was assessed in a single, multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye.

After a single injection, the percent of patients reaching a vitreous haze score of 0 (where a score of 0 represents no inflammation) was statistically significantly greater for patients receiving **OZURDEX**[®] versus sham at week 8 (primary time point) (47% versus 12%). The percent of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving **OZURDEX**[®] versus 7% for sham at week 8.

Diabetic Macular Edema

The efficacy of **OZURDEX**[®] for the treatment of diabetic macular edema was assessed in two, multicenter, masked, randomized, sham-controlled studies. Subjects were to be evaluated for retreatment eligibility every three months starting from Month 6 but could only receive successive treatments at least 6 months apart. Retreatment was based on physician's discretion after examination including Optical Coherence Tomography. Patients in the **OZURDEX**[®] arm received an average of 4 treatments during the 36 months.

The primary endpoint was the proportion of patients with 15 or more letters improvement in BCVA from baseline at Month 39 or final visit for subjects who exited the study at or prior to Month 36. The Month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for subjects who received re-treatment at Month 36. Only fourteen percent of the study patients completed the Month 39 visit (16.8% from **OZURDEX**[®] and 12.2% from Sham).

Table 5: Visual Acuity outcomes at Month 39 (All randomized subjects with LOCF^c)

Study	Outcomes	Ozurdex [®]	Sham	Estimated Difference (95% CI)
1 ^a	Gain of ≥ 15 letters in BCVA (n(%))	34 (21%)	19 (12%)	9.3% (1.4%, 17.3%)
	Loss of ≥ 15 letters in BCVA (n(%))	15 (9%)	17 (10%)	-1.1% (-7.5%, 5.3%)
	Mean change in BCVA (SD)	4.1 (13.9)	0.9 (11.9)	3.2 (0.4%, 5.9%)
2 ^b	Gain of ≥ 15 letters in BCVA (n(%))	30 (18%)	16 (10%)	8.4% (0.9%, 15.8%)
	Loss of ≥ 15 letters in BCVA (n(%))	30 (18%)	18 (11%)	7.1% (-0.5%, 14.7%)
	Mean change in BCVA (SD)	0.4 (17.5)	0.8 (13.6)	-0.7 (-4.1, 2.6)

^aStudy 1: OZURDEX[®], N=163; Sham, N=165

^bStudy 2: OZURDEX[®], N=165; Sham, N=163

^c14% (16.8% from OZURDEX[®] and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 2 and Figure 3. The occurrence of cataracts impacted visual acuity during the study. The visual acuity improvement from baseline increases during a treatment cycle, peaks at approximately 3 Months posttreatment and diminishes thereafter. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the final study visit.

Figure 2 Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye

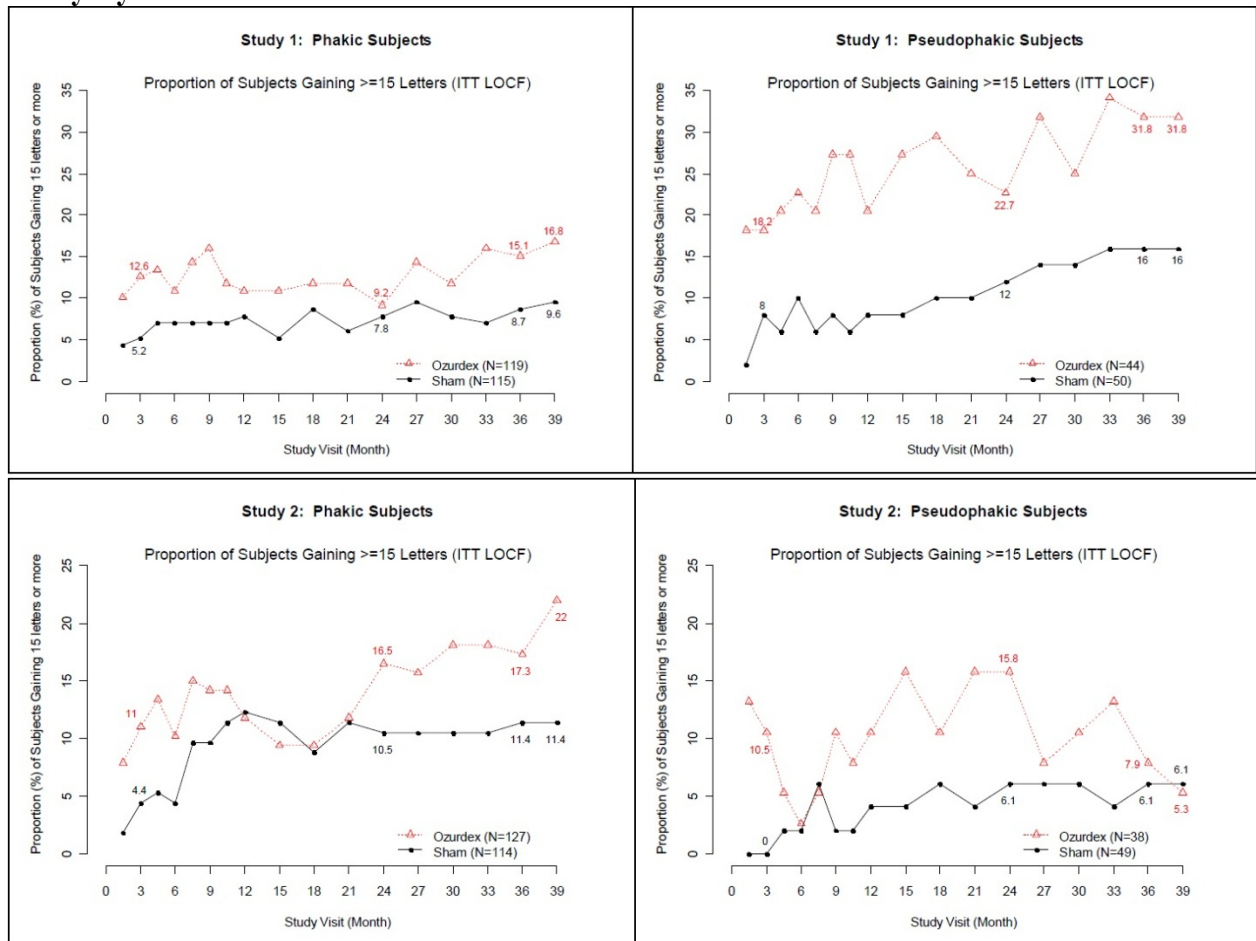
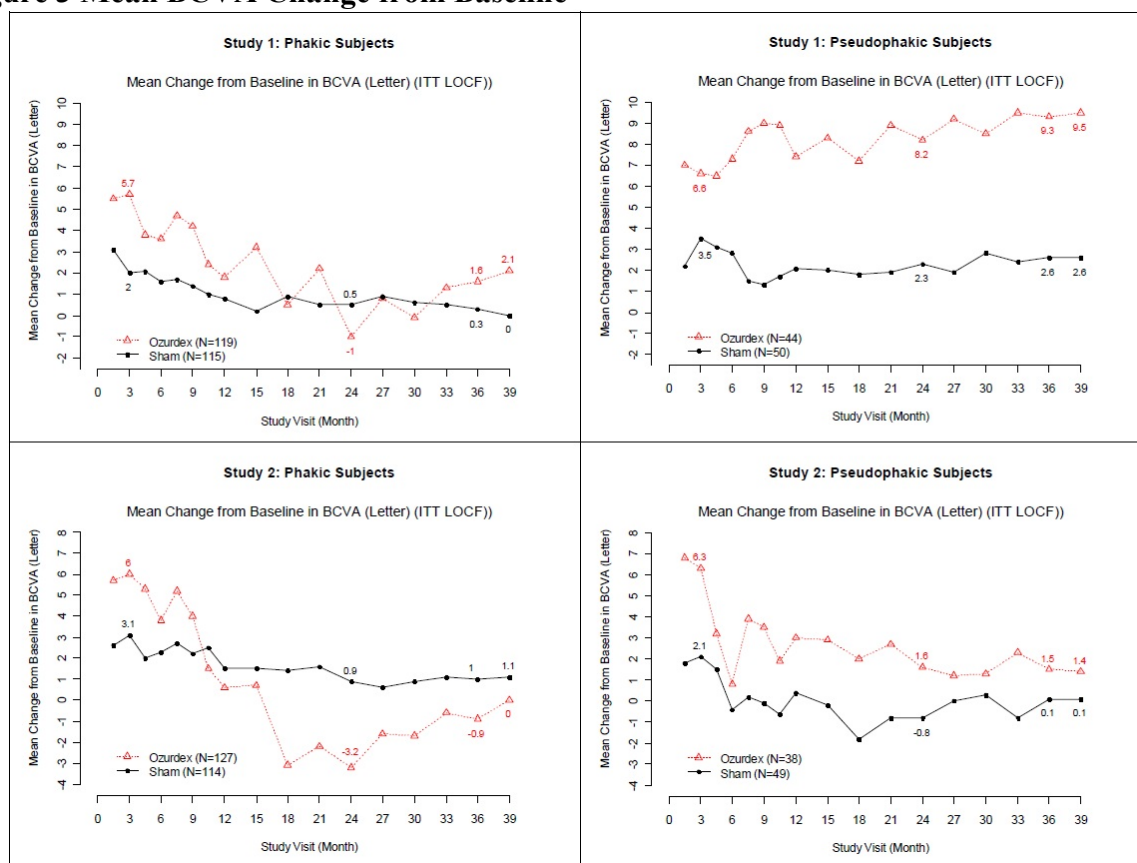


Figure 3 Mean BCVA Change from Baseline



The best corrected visual acuity outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 39 are presented in Table 6.

Table 6: Visual Acuity outcomes at Month 39 (Subgroup for pooled data with LOCF^c)

Subgroup (Pooled)	Outcomes	OZURDEX [®]	Sham	Estimated Difference (95% CI)
^a Pseudophakic	Gain of ≥ 15 letters in BCVA (n(%))	16 (20%)	11 (11%)	8.4% (-2.2%, 19.0%)
	Loss of ≥ 15 letters in BCVA (n(%))	4 (5%)	7 (7%)	-2.2% (-9.1%, 4.7%)
	Mean change in BCVA (SD)	5.8 (11.6)	1.4 (12.3)	4.2 (0.8%, 7.6%)
^b Phakic	Gain of ≥ 15 letters in BCVA (n(%))	48 (20%)	24 (11%)	9.0% (2.7%, 15.4%)
	Loss of ≥ 15 letters in BCVA (n(%))	41 (17%)	28 (12%)	4.4% (-1.9%, 10.7%)
	Mean change in BCVA (SD)	1.0 (16.9)	0.6 (12.9)	0.3 (-2.4, 3.0)

^a Pseudophakic: OZURDEX[®], N=82; Sham, N=99

^b Phakic: OZURDEX[®], N=246; Sham, N=229

^c 14% (16.8% from OZURDEX[®] and 12.2% from Sham,) of patients had BCVA outcome at Month 39, for the remaining patients the data at Month 36 or earlier was used in the analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

OZURDEX[®] (dexamethasone intravitreal implant) 0.7 mg is supplied in a foil pouch with 1 single-use plastic applicator, NDC 0023-3348-07.

Storage: Store at 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with **OZURDEX**[®]. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with **OZURDEX**[®] treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of **OZURDEX**[®], patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022315Orig1s009

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 22315/S-009
Related IND	IND 58633
Applicant Name	Allergan Inc
Date of Submission	June 13, 2013
Date of Amendment:	April 7, 2014
Review Type:	Standard
PDUFA Goal Date	July 13, 2014
Proprietary Name / Established (USAN) Name	Ozurdex Dexamethasone intravitreal implant 0.7 mg
Formulation Use	Implant Intravitreal dose
Proposed Indication	Treatment of diabetic macular edema
Action for Application	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	Lucious Lim, William Boyd 3/18/2014
CDTL Review	William Boyd 3/30/2014
Deputy Division Director Review	Wiley Chambers 4/7/2013, 6/19/2014
Statistical Review	Abel Eshete, Yan Wang 3/10/2014, 6/26/2014
Team Leader Review	Yan Wang, Dionne Price 6/28/2014
Pharmacology/Toxicology Review	Ilona Bebenek, Lori Kotch 3/12/2014
Clinical Pharmacology Review	Gerlie Gieser, Philip Colangelo 7/22/2013
Product Quality - EA	Balajee Shanmugam, Thomas Oliver 11/26/2013
CDER/ OC/Facilities Inspection	N/A
OSI/DGCPC	Susan Thompson, Kassa Ayalew 2/8/2014, 2/10/2014
OSE/DMEPA Labeling Review	N/A
OPDP/DPDP (formerly DDMAC)	Christine Corser 3/20/2014
Pediatric Review Committee	October 16, 2013 – full waiver
Maternal Health Consult	Melissa Tassinari 6/27/2014
Project Manager	Michael Puglisi

CDTL=Cross-Discipline Team Leader

OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
(formerly Division of Scientific Investigation (DSI))

OSE/DMEPA=Office of Surveillance and Epidemiology, Division of Medication Error
Prevention and Analysis

OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion;
formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

Table of Contents:

1.	Summary and Recommendations	3
1.1	Background DME Indication – Publicly Available Information	3
1.2	NDA 201923 Review Findings (NDA Under Review / Not for Public Disclosure)	7
1.3	Regulatory History of Ozurdex	9
1.4	Development of Ozurdex for Diabetic Macular Edema (DME)	10
1.5	Efficacy of Ozurdex	12
1.6	Safety of Ozurdex	16
1.7	Side-by-Side Presentation and Discussion of Ozurdex and Fluocinolone Acetonide Intravitreal Insert Studies	21
1.8	Benefit / Risk Assessment of Ozurdex	25
1.9	Ozurdex Efficacy Outcomes, Consideration for Labeling	26
1.10	Ozurdex Safety Outcomes, Consideration for Labeling	32
2.	Background	34
3.	CMC/Product Quality Microbiology	34
4.	Nonclinical Pharmacology/Toxicology	34
5.	Clinical Pharmacology/Biopharmaceutics	35
6.	Clinical Microbiology/Immunology	36
7.	Clinical/Statistical-Efficacy	36
8.	Safety	36
9.	Advisory Committee Meeting	37
10.	Pediatrics	37
11.	Other Relevant Regulatory Issues	38
11.1	Compliance Inspection	38
11.2	Office of Scientific Investigation (OSI) Audits	38
11.3	Debarment Certification	38
11.4	Financial Disclosure	38
11.5	Other Regulatory Issues	38
12.	Labeling	38
13.	Decision/Action/Risk Benefit Assessment	38
13.1	Regulatory Action	38
13.2	Risk Benefit Assessment	38
13.3	Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)	40

1. Summary and Recommendations

NDA 22315/S-009 is submitted for the indication of diabetic macular edema (DME), based on results from two adequate controlled studies (#206207-010 and #206207-011) in which 700 µg and 350 µg doses of dexamethasone intravitreal insert were compared to sham treatment, over the course of 3 years.

The efficacy supplement was reviewed by the clinical, statistical, pharmacology/toxicology, and product quality reviewers. Additional reviews were conducted by the Office of Scientific Investigations and labeling was reviewed by the Division of Prescription Drug Promotion.

The purpose of this review is to address the differences in scientific interpretations and recommendations by the clinical review team for this efficacy supplement and another corticosteroid insert for the proposed indication of DME (NDA 201923, Iluvien, fluocinolone acetonide). The recommendations made for the Ozurdex application are compared to the clinical and Agency recommendations for NDA 201923, Iluvien. To provide sufficient background, the publicly available information disclosed by the applicant, Alimera, for NDA 201923, Iluvien is provided in (Section 1.1) along with published efficacy and safety results of their clinical trials. Excerpts from FDA documents archived in DARRTS for the Iluvien NDA are described (Section 1.2); however, this information is not in the public domain. After providing the background on Iluvien, the review focuses on the history of Ozurdex (Section 1.3), the development of the DME indication (Section 1.4), the Ozurdex DME efficacy results (Section 1.5) the Ozurdex DME safety results (Section 1.6). A side-by-side presentation of the design and outcomes from the studies is provided (Section 1.7). Finally, consistent with the Division's recent recommendations for the Iluvien DME application, the benefits and risks of Ozurdex are discussed (Section 1.8), and information to communicate findings of efficacy (Section 1.9) and safety (1.10) in the labeling for Ozurdex are delineated.

The final recommendation is that Ozurdex be approved for use in patients with DME who are pseudophakic or scheduled for cataract surgery, given that the benefit for this group outweighs the risk of cataracts (these patients are no longer at risk for development of cataracts). This approach is consistent with handling of the Iluvien application and the risk/benefit discussions in late 2013 following the review of the Iluvien application for DME.

In addition, given the current recommendations from the clinical reviewers that Ozurdex can be approved for the indication of DME despite the findings of significant cataract formation and cataract surgery, the previous clinical perspectives about the risks vs. benefits of corticosteroids in DME patients may be evolving. An Advisory Committee (AC) meeting would provide an opportunity for a public discussion of the risks and benefits of these corticosteroids in the treatment of diabetic macular edema, but planning for that AC should not delay approval of this application.

1.1 Background DME Indication – Publicly Available Information

In the current application for NDA 22315/S-009, the Applicant provides some background on the indication of treatment of diabetic macular edema (DME). They include a summary of corticosteroid use in DME, and cite two publications by Campochiaro reporting on the results of

2 clinical trials of fluocinolone acetonide (FA) vitreous insert. The 2012 article states the studies were supported by Alimera Sciences. The applicant identifies the fluocinolone acetonide (FA) vitreous insert in the publications as Iluvien®.¹

¹ **2.5.1.3.3 Treatment of Diabetic Macular Edema**

The development and progression of DME is correlated with the type of diabetes (type 1 or type 2), duration of disease, patient's age at diagnosis, treatment with insulin, arterial hypertension, hyperlipidemia, and the degree of glycemic control achieved and maintained over the lifetime of the individual (Ding and Wong, 2012; Yau et al, 2012). It is widely recognized that the risk of vision loss due to DME can be reduced by effective control of serum glucose and blood pressure, and its early detection and timely treatments. Glycemic control along with management of blood pressure and lipid control remain crucial to controlling the rate of progression of diabetic retinopathy and preserving vision. The ideal treatment for DME is prevention by control of metabolic abnormalities of diabetes as evidenced by the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes (UKPD) Study (DCCT Research Group, 1993; UKPD Study Group, 1998). However, once DME has developed, therapeutic intervention is needed to halt or slow the progression of the disease and maintain visual acuity. Treatment is most successful when initiated in the early stage of the disease (Ciulla et al, 2003). The goals of treatment for patients with DME include reduction of inflammation, stopping or slowing fluid leakage into the retinal space (edema), halting vision loss, and potentially restoring vision (Cheung et al, 2010). Generally, the approach to DME management depends on the severity of underlying retinopathy and whether macular edema is clinically significant. Current therapies for DME can be divided into non-pharmacological and pharmacological interventions. Non-pharmacological therapies include laser photocoagulation and surgery (vitrectomy). Approved pharmacological treatments include an intravitreal corticosteroid (fluocinolone acetonide) and an anti-VEGF agent (ranibizumab).

Corticosteroids

Corticosteroids target multiple mediators in DME by possessing anti-inflammatory, antivascular permeability, and anti-angiogenic properties (Golan and Loewenstein, 2010). These agents act by decreasing the production of mediators such as interleukin-6 and VEGF, and may also directly stabilize the blood-retinal barrier (London et al, 2011). In contrast to anti-VEGF antibodies, which inhibit the actions of synthesized VEGF, corticosteroids act to directly decrease the synthesis of VEGF (Stewart, 2012). Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular edema (Enyedi et al, 1996; Leopold, 1985; Tennant, 1978).

Corticosteroid-based intravitreal implants are being developed and investigated in the treatment of DME. These implants are meant to provide sustained release of the active drug, thereby reducing the frequency of repeated intravitreal injections. Complications from the use of corticosteroids may include increased IOP, cataract progression, development of glaucoma, and endophthalmitis (Boscia, 2010).

Fluocinolone acetonide (FA) vitreous insert (Iluvien®) is a non-biodegradable implant approved in several European countries for "the treatment of vision impairment associated with chronic DME considered insufficiently responsive to available therapies". Clinical studies have demonstrated improvements in BCVA following treatment with intravitreal FA at doses of 0.2 µg/day and 0.5 µg/day. However, adverse events such as cataract and increased IOP were observed. Almost all phakic patients treated with FA developed cataracts, and incisional surgery for glaucoma was necessary in 4.8% of low-dose patients and 8.1% of high-dose patients at month 36 (Campochiaro et al, 2011; **Campochiaro et al, 2012**). FA has the potential advantage of up to 36 months duration of effect; however, some of the patients may not require such a long-term exposure to the drug. In such cases, the insert may need to be surgically removed if treatment discontinuation is required before the current implant has ceased releasing the drug.

There continues to be a need for an effective and safe DME treatment that provides long-term treatment benefits including improvement in visual acuity and anatomical outcomes, has a reduced treatment burden compared with current anti-VEGF agents, is effective in treatment naïve patients and anti-VEGF non-responders, and can be used effectively to target the multifactorial pathology of DME beyond VEGF. Dexamethasone may provide benefits over currently available corticosteroids. However, the clinical use of dexamethasone intravitreal

The publicly available information is consistent with the information in the Iluvien NDA 201923, currently in its fourth review cycle.² The reviews of NDA 201923 are not publicly available; however, Campochiaro et al published the results of the fluocinolone acetonide (FA) vitreous insert studies supported by Alimera.³ As shown in the figures and table from the 2012 publication by Campochiaro, (and reflected in the Iluvien reviews) the net treatment efficacy of Iluvien® is about 10% for the ≥ 15 letter improvement in BCVA, net cataract formation is approximately 30%, net cataract extraction is approximately 50% and net IOP elevation is approximately 30%. The efficacy and safety information from the FA insert and the regulatory decisions are relevant when considering the results, interpretations and recommendations for the Ozurdex studies of DME submitted to this NDA 22315/S-009.

Table 2. Cataract- and Intraocular Pressure (IOP)-Related Adverse Events

Phakic Patients, % (Study Eye)	Control (n = 121)	0.2 µg/d FAc (n = 235)	0.5 µg/d FAc (n = 265)
Cataract-related events			
Cataract considered an AE	50.4	81.7	88.7
Cataract extraction	27.3	80.0	87.2
Subjects, % (Study Eye)	Control (n = 185)	0.2 µg/d FAc (n = 375)	0.5 µg/d FAc (n = 393)
IOP-related events			
AE of increased IOP	11.9	37.1	45.5
Any IOP-lowering meds*	14.1	38.4	47.3
Trabeculoplasty	0.0	1.3	2.5
Incisional glaucoma surgery	0.5	4.8	8.1

AE = adverse event; FAc = fluocinolone acetonide.
The percentage of patients in each treatment group with the listed adverse events is listed.
*For a minimum of 7 days.

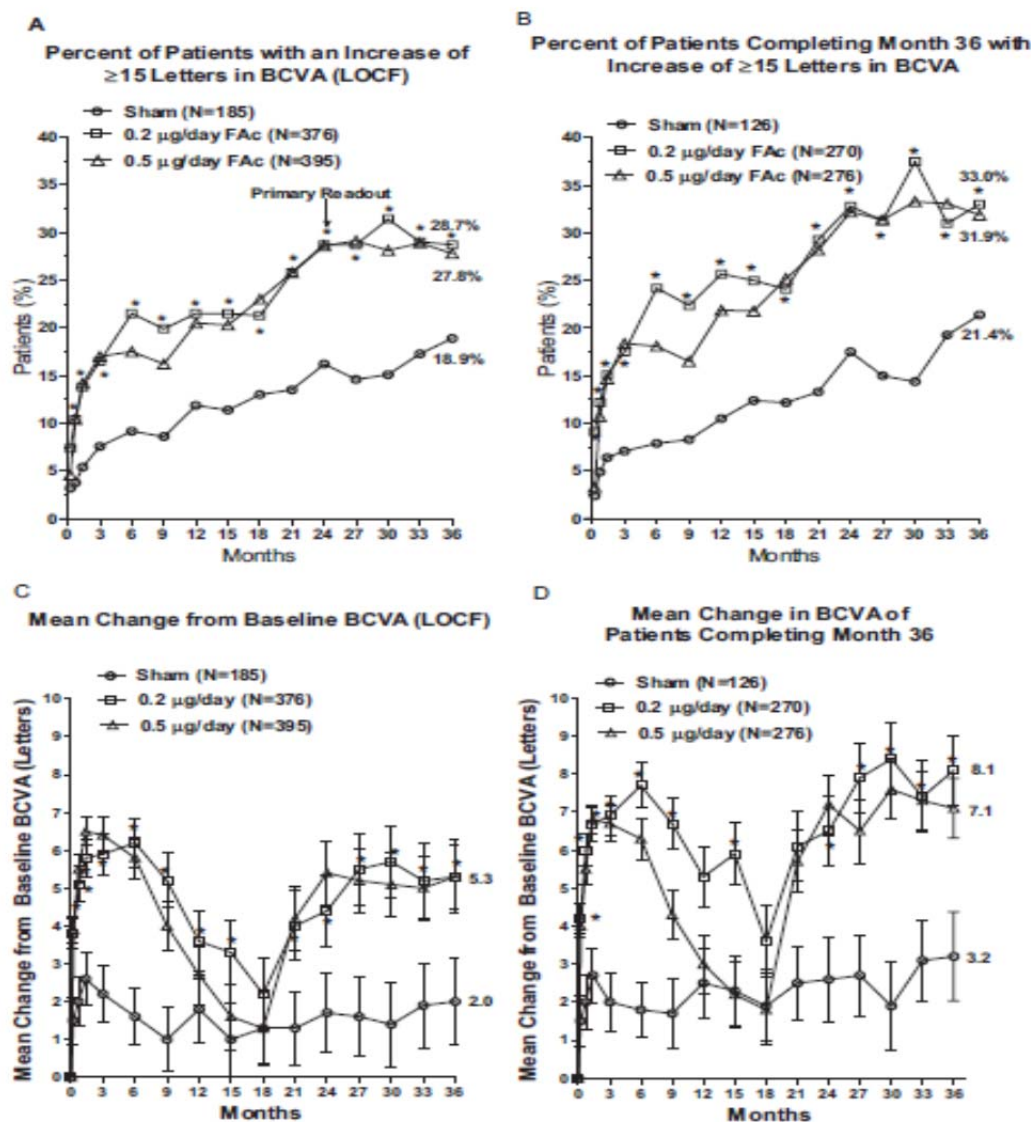
injections are limited by a short half-life of approximately 3 hours. Therefore, the biodegradable DEX PS DDS Applicator System has been developed by Allergan to enable sustained delivery of dexamethasone to the vitreous cavity and retina in the treatment of DME patients, including those without prior laser therapy (see Section 2.5.1.3.4). The duration of effect of this implant balances the need to reduce the number of intravitreal injections against the ability to discontinue treatment if necessary, leading to the minimization of surgical intervention to manage adverse events.

2.5.1.3.4.

The DEX PS DDS Applicator System is a sterile, single-use system intended to deliver one biodegradable implant into the vitreous which may offer a valuable new therapeutic option for the treatment of DME. It was designed to overcome ocular drug delivery barriers, and prolong the duration of the dexamethasone effect in the eye. **This biodegradable implant delivers a 700 µg or 350 µg total dose of dexamethasone to the vitreous with gradual release over time allowing for sustained drug levels to the target areas despite lower total daily dose.**

² March 27, 2014, Alimera Sciences Announces Resubmission of Iluvien New Drug Application to FDA, located at <http://investor.alimerasciences.com/releases.cfm>

³ Campochiaro PA et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119:2125-2132. The Acknowledgment section of the publication states that the study was supported by Alimera Sciences, Atlanta, Georgia.



Alimera has issued press releases about their product Iluvien, and disclosed publicly three Complete Response letters from FDA.⁴ The November 11, 2011 press release includes the statement that, “The FDA stated that the risks of adverse reactions shown for ILUVIEN in the FAME® Study were significant and were not offset by the benefits demonstrated by ILUVIEN in these clinical trials.” Alimera’s press release also stated that, “Based on extensive research with U.S. retinal physicians, we have learned that ILUVIEN's long-term sustained delivery treatment benefit is desired and that ILUVIEN has a manageable risk to benefit ratio.” In the October 18, 2013 press release, Alimera reports, “Identifying concerns regarding the benefit to

⁴ Alimera Sciences issued 3 press releases regarding Iluvien and FDA

- October 18, 2013 (Alimera Sciences Received Complete Response Letter for Iluvien),
- November 11, 2011 (Alimera Sciences Received Complete Response Letter from FDA for Iluvien),
- December 23, 2010 (FDA Issues Complete Response Letter to Alimera Sciences regarding New Drug Application for Iluvien, located at <http://investor.alimerasciences.com/releases.cfm>)

risk and safety profiles of ILUVIEN, the FDA stated that the NDA could not be approved in its present form.”

1.2 NDA 201923 Review Findings (NDA Under Review / Not for Public Disclosure)

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

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

“Cataract formation occurs in 46% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. Cataract operation occurs in 23% of the Sham group study eyes versus 75% in the 0.2 µg/day FA study eyes. Increased IOP occurs in 13% of the Sham group study eyes versus 35% of the 0.2 µg/day FA study eyes. The risk of increased IOP is nearly three times the rate in the 0.2 µg/day FA drug group.” [Review dated 12/22/2010]

“The risk of increased intraocular pressure (IOP) was nearly three times higher in the drug treatment groups compared to the Sham (control) group in the 36-month data. The drug’s potential benefits do not overcome this significant risk.” [Review dated 10/19/2011]

“Cataract formation (any type in phakic subjects) occurs in 50% of the Sham group study eyes versus 82% in the 0.2 µg/day FA study eyes. Cataract operations occurred in 27% of the Sham group study eyes versus 80% in the 0.2 µg/day FA study eyes. The drug’s potential benefits do not overcome this significant risk in the phakic population.” [Reviews dated 10/19/2011 and 10/17/2013]

“The rate of IOP elevation and glaucoma is unacceptable. The risk of increased intraocular pressure (IOP) is nearly three times higher in the drug treatment groups compared to the Sham (control) group. This adds additional risks to these patients from potential adverse drug reactions associated with the use of IOP lowering medications. The difference between Sham control and the 0.2µg/day FA in the percentage of patients requiring surgical intervention for the reduction of their IOP was 4-5%. The surgical risks in these patients and the potential endophthalmitis risks associated with filtering surgery are significant additional risks. The drug’s potential benefits do not overcome this significant risk.” [Review dated 10/17/2013]

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

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

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

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

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

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

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

During the October 23, 2013 teleconference, Alimera shared the following concerns, as recorded in the Meeting Minutes in DARRTS:

“Alimera stated that the company was struck by the tone of the October 18, 2013, Complete Response (CR) letter that clearly contained Dr. Chambers bias against long term use of Iluvien.”

“Alimera stated that in the October 16, 2013, meeting attended by Dr. Jenkins, Dr. Cox, and Dr. Albrecht, there was a more collegial environment than that experienced in prior meetings for Iluvien attended by Dr. Chambers.”

During the December 10, 2013 teleconference, one approach for a path forward was discussed, as recorded in the Meeting Minutes in DARRTS:

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

(b) (4)

“A discussion followed

(b) (4)

”

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

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

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

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

As noted above, based on NDA 201923 reviews and reflected in the 2012 publication by Campochiaro⁵, the net treatment efficacy of Iluvien ® is about 10% for the 15 or more letter improvement in BCVA, net cataract formation is approximately 30%, net cataract extraction is approximately 50% and net IOP elevation is approximately 30%. Based on the Agency discussions summarized above, it was concluded that these outcomes could not support an unrestricted indication for DME, but could support a limited indication.

How do the Iluvien efficacy and safety results and the risk/benefit considerations for Iluvien apply to the results and risk/benefit considerations for the current Ozurdex efficacy supplement for DME, NDA 22315/S-009?

The following sections address this issue of consistency:

1.3 Regulatory History of Ozurdex

Ozurdex was approved June 17, 2009, for treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Two phase 3 studies (206207-008 and 206207-009) were the basis of approval demonstrating safety and effectiveness in

⁵ Campochiaro PA et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119:2125-2132.

patients with macular edema following CRVO or BRVO. These Phase 3 studies were multicenter, masked, randomized, sham-controlled, safety and efficacy studies evaluating OZURDEX (dexamethasone intravitreal implant) for 6 months, followed by a 6-month open-label extension period. In these studies a single insert was administered and patients were seen at 6 months; the reported rates of cataract were 4% for Ozurdex and 2% for sham control, and increased IOP was reported in 25% Ozurdex versus 1% for sham control patients. When these patients were retreated and followed for an additional 6 months (total 12 months) the rate of cataracts increased to 11% and IOP elevations were reported in 32% of Ozurdex patients. Because the sham control arm had been crossed over to Ozurdex treatment, there was no sham control arm for comparison of adverse reactions rates.

Comment:

These studies evaluated administration of 1 to 2 Ozurdex inserts and followed patients for only 12 months; we do not have data on rates of cataracts that would have been seen if patients had been followed for 2 to 3 years whether with or without additional Ozurdex treatment vs. sham (this is relevant because the DME studies lasted for 3 years, and patients received from 1 to 7 inserts during that time).

On September 24, 2010, Ozurdex was approved for the treatment of non-infectious uveitis affecting the posterior segment of the eye; assessment of outcome was at 8 weeks. The duration of follow up for this indication was 26 weeks; rates of cataracts were 12% in the Ozurdex arm and 5% in the sham arm, IOP elevations were seen in 25% versus 7% of patients, respectively.

Comment:

This study evaluated administration of 1 insert and followed patients for 26 weeks (6 months); we do not have data on rates of cataracts that would have been seen if patients had been followed for 2 to 3 years whether with or without additional Ozurdex treatment vs. sham. Therefore, there was no information on the use of Ozurdex to treat a disease for 3 years until the DME studies of this duration were requested by the Division, as summarized below.

1.4 Development of Ozurdex for Diabetic Macular Edema (DME)

An end-of phase 2 meeting was held September 8, 2003 (IND 58,663) for the indication of persistent macular edema. On December 8, 2003 a meeting was held to discuss the development on non-diabetic macular edema and diabetic macular edema. The following statements are excerpted from the December 29, 2003 meeting minutes in DARRTS.

“FDA Response: See comments below regarding validation for diabetic macular edema trials. The persistent macular edema seen in diabetes mellitus is sufficiently different in nature from acute macular edema so as to require replication of efficacy in treatment in two adequate and well-controlled trials.

“FDA Response: Provided the validation plan is submitted and approved by the agency, a clinically significant difference in visual acuity at one year post-treatment could serve as a surrogate marker for a clinically significant difference in visual acuity at three years.

“If the conditions set forth in the validation plan are not met, the drug will be pulled from the market if it was approved on the surrogate endpoint. The validation plan needs to be submitted and reviewed before the agency can agree on a one year study endpoint.

“Please note that a one year endpoint for Diabetic Macular Edema is not acceptable without an acceptable validation plan, and a special protocol assessment cannot be reviewed without an acceptable validation plan.”

Comment:

Two studies were requested of the applicant, one was not considered sufficient. Three year data were requested, one year data were not considered sufficient. It is not clear whether the terms “persistent macular edema” and “acute macular edema” are referring to diabetic macular edema and macular edema following retinal vein occlusion, respectively. It is noted that the RVO trials were 6-12 months and the DME studies were 3 years in duration.

Allergan submitted amendment #4 in May of 2010 and proposed to re-treat patients at 36 months and revise the assessment of the primary endpoint from 24 months to 39 months.

Comment:

This topic is discussed in the FDA statistical reviews. Briefly, at the time the amendment was implemented, 52% of the patients had already exited the study. Only 16.5% of patients were evaluated and had data at 39 months, the majority of patients were imputed in this analysis using data from earlier visits.

It appears the choice of the 39 month endpoint 3 months after the last retreatment (instead of 42 month endpoint, 6 months after the last retreatment at the 36 visit, for example), was to capture the peak treatment effect of the insert, or greatest separation between the Ozurdex and the sham treatment response. [See Section 1.9 for a presentation of the “sinusoidal-like” pattern of the treatment response to Ozurdex, with 75% of patients receiving more than one Ozurdex insert, median 4 inserts, range 1-7 inserts.]

In September 2011, Allergan proposed to revise the primary endpoint to “BCVA average change from baseline during the study (AUC approach) in the study eye” for the ongoing phase 3 DME studies. The Agency responded on October 31, 2011 that the primary efficacy endpoint should remain “BCVA improvement of 15 or more letters from baseline at 3 years.” Additional comments from the October 31, 2011 communication are provided below. [The applicant requested the meeting be cancelled on November 2, 2011, the day before the meeting scheduled for November 3, 2011.]

“The primary endpoint is recommended to remain BCVA improvement of 15 or more letters from baseline at three years. The analysis that you propose, if it had been used in the Diabetic Control and Complications Trial (DCCT), would have incorrectly suggested that more intensive insulin therapy was inferior to less intensive insulin therapy.

“We do not agree with your proposal of the new primary efficacy endpoint because this endpoint does not differentiate the short term treatment effect (prior to 36-month) from the long term treatment effect. For the indication of DME, we recommend that the treatment

effect of a test product be demonstrated at a time point of at least 36 month or later because an earlier treatment success is not necessarily a good indicator of a later success.

“For an NDA filing it is expected that safety and efficacy be demonstrated in at least two adequate and well-controlled, multi-center, independent trials.

“Given this study is being proposed with potentially seven intravitreal steroid injections over a 3 year period for a class of drugs (steroids) that has significant risks of cataract formation (with subsequent cataract surgery) and elevated IOP as adverse events, there is significant concern the benefits of using this drug product may not outweigh its risks when treating DME. Additionally, this class of products (steroids) is also likely to impair healing and reduce the eye’s ability to recover from infections. This is potentially problematic for a diabetic population. The benefit over these risks needs to be demonstrated.

Comment:

In the above paragraph (text highlighted by underlining) there is a clear articulation of concerns about the risks and benefits of corticosteroid injections. Such concerns regarding the risks associated with corticosteroid use have been communicated to other sponsors investigating corticosteroids for DME, and are addressed in Sections 1.1 and 1.2.

In preparation for the August 14, 2012 pre-NDA efficacy supplement meeting, the applicant was sent preliminary comments August 8, 2012. The same risk/benefit paragraph (text underlined above) was repeated. [The applicant subsequently cancelled the meeting on August 9, 2012].

1.5 Efficacy of Ozurdex

Two adequate sham-controlled studies (#206207-010 and #206207-011) evaluated 700 µg and 350 µg doses of dexamethasone intravitreal insert over the course of 3 years. The primary efficacy endpoint for the Ozurdex studies was the same as for Iluvien: ≥ 15 letters improvement in best corrected visual acuity (BCVA) at 3 years. The protocol also pre-specified routine visits during which BCVA was assessed.

The patient disposition from the Statistical Review for the pooled population of the two studies is presented below. It is seen that 65% of DEX 700 and DEX 350 vs. 45% of sham patients completed the study. Adverse reactions accounted for most of the DEX discontinuations while lack of efficacy accounted for 6% to 7% of DEX patient discontinuations and 22% sham patient discontinuations.

Table 1: Patient Disposition

	DEX 700	DEX 350	Sham	Total
Study -010 and Study -011 Pooled				
Subjects Randomized	328 (100%)	324 (100%)	328 (100%)	980
Subjects Who completed the Study	212/328(64.6%)	212/324(65.4%)	146/328(44.5%)	
Completed the Study at Month 36	156/328(47.6%)	146/324(45.1%)	98/328(29.9%)	
Completed the Study at Month 39	56/328(17.1%)	66/324(20.4%)	48/328(14.6%)	
Reason for Discontinuation				
Adverse Events	45/328(13.7%)	47/324(14.5%)	39/328(11.9%)	
Lack of Efficacy	21/328(6.4%)	24/324(7.4%)	73/328(22.3%)	

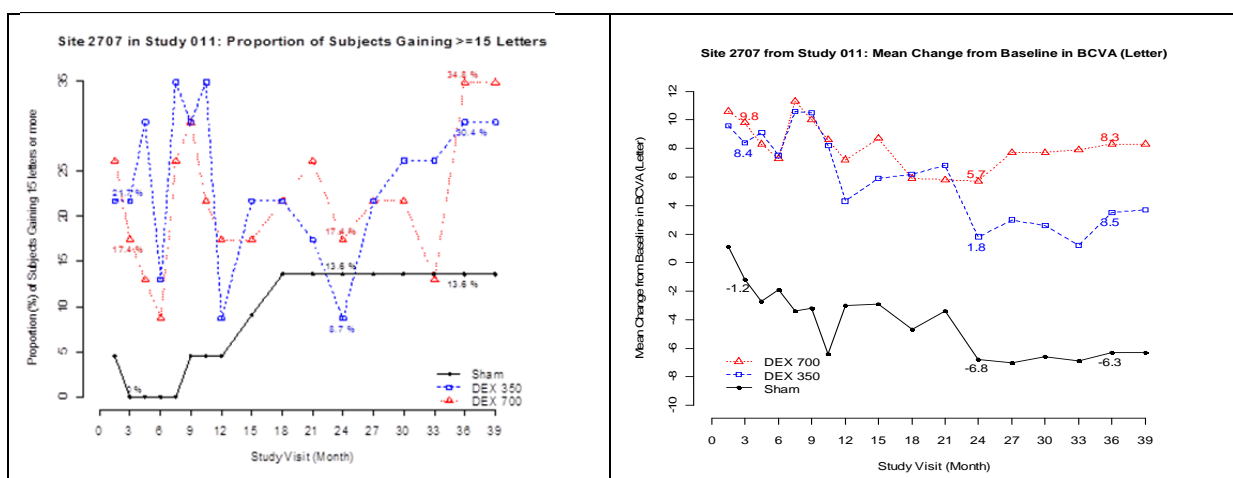
Lost-to-Follow-up	9/328(2.7%)	9/324(2.8%)	17/328(5.2%)	
Personal Reason	13/328(4%)	10/324(3.1%)	26/328(7.9%)	
Protocol Violations	3/328(0.9%)	3/324(0.9%)	1/328(0.3%)	
Other	25/328(7.6%)	19/324(5.9%)	26/328(7.9%)	

Source: Statistical Reviewer's Analysis.

The original analyses of the studies provided by Allergan and those performed by the FDA statistical reviewers differ in three ways:

- After OSI completed inspection of clinical study sites. OSI recommended that site 2707 in Study -011 be excluded from analysis of safety and efficacy (review dated February 10, 2014). This was because an employee who had since left the site was found in a previous inspection to have substituted OCT scans and falsified BCVA values. During the current inspection, the corrective measures taken by the investigator led to a classification of VAI. However, because the employee who falsified information was working at the site during the conduct of Study -011, it was not possible to ascertain that additional fraud did not occur; therefore, OSI could not vouch for the data integrity, and recommended exclusion of the data from the efficacy and safety review. In a separate document dated February 8, 2014, OSI also recommended excluding the data from the efficacy and safety analysis.

This investigator had the largest US enrollment of 68 patients: 23 patients in DEX 700 arm; 23 in DEX 350; and 22 in sham. In addition this center reported a net treatment effect of over 20% for DEX vs. sham, better than seen at other sites enrolling more than 10 patients, and greater than the net treatment effect of 8% to 9% for the two studies, as shown in the figure below. In addition, the mean change from baseline in BCVA is 8.3 - -6.3 letters = 14.6 letters, compared to approximately 0 to 3 letters in mean change from baseline in BCVA in Study 10 and rest of Study 11 sites (figure on right below). These reported outcomes added further concern about the reliability of the data.



- The applicant submitted a protocol amendment to change the primary endpoint from 24 months to 39 months (FDA had recommended 3 year trials), however at the time of the amendment most patients had already completed the study, and only 173/1048 (16.5%) patients had data at 39 months, others had data imputed from earlier visits. Changing the endpoint when most patients had 36 month data available initially raised questions of integrity of the analysis, since the majority of patient outcomes were based on LOCF and the minority based on observed BCVA. However, based on further discussion with staff and management in the Office of Biostatistics, and it is acceptable to present Month 39 data and explain the design and analysis of the study.
- The applicant counted some patients who received rescue therapy as successes; FDA counted patients who received rescue therapy as failure in the ITT analysis with LOCF at 3 years, (Month 36 and Month 39). There were 12 patients from both studies that fell into this category: 6 randomized to DEX 700, 2 randomized to DEX 350 and 4 randomized to sham. Thus, the numbers are relatively small, and have minimal impact on the results. For one DEX 750 and one sham patient the reason for rescue was actually listed as diabetic macular edema; reasons listed for other patients were diabetic retinopathy, macular edema, and retinal vascular changes.

The efficacy results for the two Phase 3 trials based on the FDA statistical review (excluding site 2707) are shown below (the treatment effect in the DEX 700 vs. sham arms are highlighted):

**Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years
(Excluding subjects from Study 206207-011, site 2707)**

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Month 36					
Study 010	32/163(19.6%)	33/166(19.9%)	18/165(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
Study 011	25/165(15.2%)	21/158(13.3%)	16/163(9.8%)	5.3%(-1.8%, 12.5%)	3.5%(-3.5%, 10.5%)
Month 39					
Study 010	34/163(20.9%)	31/166(18.7%)	19/165(11.5%)	9.3% (1.4%, 17.3%)	7.2%(-0.5%, 14.8%)
Study 011	30/165(18.2%)	24/158(15.2%)	16/163(9.8%)	8.4% (0.9%, 15.8%)	5.4% (-1.8%, 12.6%)

LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

The MO and Deputy Director's reviews report the applicant's analysis (with site 2707):

Study 206207-010: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	163	36 (22%)	166	31 (19%)	165	22 (13%)
% Difference (95% CI)	8.8 (0.5, 17.0)		5.3 (-2.5, 13.2)			
p-value	0.038 ^a		0.185 ^a			
PP with observed month 39 data only						
Final (36/39 months)	29	6 (21%)	34	8 (23%)	15	3 (20%)
% Difference (95% CI)	0.7 (-24.4, 25.7)		3.5 (-21.2, 28.3)			

p-value	> 0.999 ^b		> 0.999 ^b			
PP with LOCF						
Final (36/39 months)	144	35 (24%)	155	30 (19%)	143	21 (15%)
% Difference (95% CI)	9.6 (0.5, 18.7)		4.7 (-3.8, 13.2)			
p-value	0.040 ^a		0.285 ^a			

Study 206207-011: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	188	42 (22%)	188	42 (22%)	185	20 (11%)
% Difference (95% CI)	11.5 (4.1, 19.0)					
p-value	0.003 ^a		0.044 ^a			
PP with observed month 39 data only						
Final (36/39 months)	22	10 (45%)	25	6 (24%)	22	7 (32%)
% Difference (95% CI)	13.6 (-14.9, 42.1)		-7.8 (-33.5, 17.9)			
p-value	0.353 ^a		0.550 ^a			
PP with LOCF						
Final (36/39 months)	170	41 (24%)	159	31 (19%)	162	20 (12%)
% Difference (95% CI)	11.8 (3.6, 20.0)		7.2 (-0.8, 15.1)			
p-value	0.006 ^a		0.080 ^a			

Comparing the FDA statistical reviewer analysis and the applicant's analysis as reported in the medical officers' reviews, the amendment that added the Month 39 visit and counting rescue therapy as success has little impact on the results of Study 010. The treatment effect in the DEX 700 arm is 8.7% at Month 36 and 9.3% at Month 39 based on the FDA statistical analysis and 8.8% based on the applicant's analysis. These results are statistically significant.

This is not true for the analysis of Study -011, in which study site 2707 was found to have an employee who committed fraud and OSI recommended exclusion of data from both the efficacy and the safety analysis. When site 2707 was excluded from analysis, (and rescue therapy is analyzed as failure), the net treatment effect for DEX 700 in Study -011 is 5.3% at Month 36 and 8.4% at Month 39, compared to the applicant's original rate of 11.5%. The latter results at Month 39 are statistically significant.

The results support the efficacy of the DEX 700 dose. The results of DEX 350 also favor the active treatment but the results are not statistically significant for both studies.

Comment:

The review of the Ozurdex efficacy results shows that the net treatment effect in the proportion of patients whose best corrected visual acuity (BCVA) improved by 15 letters or more (3 lines) is approximately 10% for Ozurdex (9.3%, 8.4%) and similar to the approximately 10% net treatment effect seen in the Iluvien studies (Section 1.1). Therefore, these two products have modest efficacy of similar magnitude.

1.6 Safety of Ozurdex

The most frequently reported events in the two studies are cataract formation/cataract surgery and increased IOP; the rates of these events are highlighted in the table below. This table is provided in the FDA statistical review and has excluded site 2707 from the denominator, per OSI recommendations. The denominator exceeds 300 in each treatment arm (allowing assessment of adverse event rates of 1%).

An increase in IOP in the DEX 700 arm was reported in 37% of DEX patients and 5.5% of sham patients for a net difference is 31.5% (25.7%, 37.4%).

Of patients who were phakic at baseline, 60.9% in the DEX 700 arm and 7.8% in the sham arm underwent cataract surgery, for a difference of 53.1% (46%, 60.1%).

Table 2: Summary of Adverse Events (AE) (Pooled: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=324	DEX 350 N=320	Sham N=328	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	310(95.7%)	311(97.2%)	260(79.3%)	16.4%(11.5%,21.3%)	17.9%(13.2%,22.7%)
Any Ocular AE	274(84.6%)	282(88.1%)	190(57.9%)	26.6%(20%,33.3%)	30.2%(23.8%,36.6%)
Any Serious AE	110(34%)	113(35.3%)	79(24.1%)	9.9%(2.9%,16.8%)	11.2%(4.2%,18.2%)
Any Ocular Serious AE	24(7.4%)	14(4.4%)	4(1.2%)	6.2%(3.1%,9.3%)	3.2%(0.6%,5.7%)
Any Severe AE	151(46.6%)	149(46.6%)	100(30.5%)	16.1%(8.7%,23.5%)	16.1%(8.7%,23.5%)
Any Ocular Severe AE	91(28.1%)	71(22.2%)	34(10.4%)	17.7%(11.8%,23.6%)	11.8%(6.2%,17.4%)
Any IOP Related AE	120(37%)	107(33.4%)	18(5.5%)	31.5% (25.7%,37.4%)	27.9% (22.2%,33.7%)
≥10 mm Hg IOP Change from Baseline at any visit	91(28.1%)	79(24.7%)	13(4%)	24.1%(18.8%,29.5%)	20.7%(15.5%,25.9%)
≥25 mm Hg IOP at any visit	106(32.7%)	86(26.9%)	15(4.6%)	28.1%(22.6%,33.7%)	22.3%(16.9%,27.7%)
≥35 mm Hg IOP at any visit	20(6.2%)	16(5%)	3(0.9%)	5.3%(2.4%,8.1%)	4.1%(1.5%,6.7%)
Glaucoma	4(1.2%)	3(0.9%)	1(0.3%)	0.9%(-0.4%,2.3%)	0.6%(-0.6%,1.8%)
IOP Lowering Procedures	4(1.2%)	1(0.3%)	1(0.3%)	0.9%(-0.4%,2.3%)	0%(-0.8%,0.9%)
Cataract Surgery in Baseline Phakic Subjects	148(60.9%)	125(53%)	18(7.8%)	53.1% (46%,60.1%)	45.1% (37.9%,52.4%)
≥15 Letters Loss from Baseline	47(14.5%)	34(10.6%)	35(10.7%)	3.8%(-1.3%,8.9%)	0%(-4.8%,4.7%)
Death	9(2.8%)	14(4.4%)	5(1.5%)	1.3%(-1%,3.5%)	2.9%(0.2%,5.5%)
Escape Therapy	31(9.6%)	38(11.9%)	63(19.2%)	-9.6%(-15%,-4.3%)	-7.3%(-12.9%,-1.8%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Comment:

The Ozurdex safety results for the most frequently occurring adverse reactions show IOP elevations in approximately 30% more Ozurdex than sham patients; and cataract surgery in approximately 50% more Ozurdex than sham patients. The results seen with Iluvien were: IOP elevations in approximately 30% more Iluvien vs. sham patients, and cataract surgery in approximately 50% more Iluvien vs. sham patients. Therefore, it appears the attributable rates of these adverse reactions are similar for the two drugs.

For completeness, the following table from the Medical Officer and Deputy Director review of this Ozurdex submission is presented. It provides a comprehensive and extensive list of adverse events occurring during the clinical trials as tabulated by the applicant— this table includes study 2707 data. The information for this table is derived from the applicant's submission in the electronic document room, from the Integrated Summary of Safety (ISS), section 5.3.5.3, Table 2-2.1 (dated 23May2013).

The information in the **highlighted rows** is discussed in Section 1.7.

**Common Adverse Events Occurring at an incidence 1% or Greater
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	333 (96.0)	334 (97.4)	281 (80.3)
<u>Blood and lymphatic system disorders</u>			
Overall	18 (5.2)	21 (6.1)	15 (4.3)
Anemia	14 (4.0)	18 (5.2)	12 (3.4)
<u>Cardiac disorders</u>			
Overall	35 (10.1)	51 (14.9)	33 (9.4)
Atrial fibrillation	7 (2.0)	3 (0.9)	4 (1.1)
Coronary artery disease	6 (1.7)	9 (2.6)	8 (2.3)
Cardiac failure congestive	4 (1.2)	10 (2.9)	3 (0.9)
Angina pectoris	4 (1.2)	3 (0.9)	3 (0.9)
Myocardial infarction	2 (0.6)	11 (3.2)	5 (1.4)
Myocardial ischemia	1 (0.3)	3 (0.9)	5 (1.4)
<u>Ear and labyrinth disorders</u>			
Overall	10 (2.9)	10 (2.9)	4 (1.1)
Vertigo	4 (1.2)	6 (1.7)	2 (0.6)
<u>Endocrine disorders</u>			
Overall	8 (2.3)	6 (1.7)	2 (0.6)
Hypothyroidism	4 (1.2)	3 (0.9)	2 (0.6)
<u>Eye disorders</u>			
Overall	296 (85.3)	302 (88.0)	223 (63.7)
Cataract	141 (40.6)	125 (36.4)	44 (12.6)
Conjunctival hemorrhage	76 (21.9)	93 (27.1)	45 (12.9)
Macular edema	51 (14.7)	42 (12.2)	36 (10.3)
Cataract subcapsular	45 (13.0)	43 (12.5)	16 (4.6)
Vitreous hemorrhage	40 (11.5)	67 (19.5)	36 (10.3)
Visual acuity reduced	33 (9.5)	41 (12.0)	18 (5.1)
Macular fibrosis	30 (8.6)	43 (12.5)	18 (5.1)
Diabetic retinal edema	27 (7.8)	27 (7.8)	21 (6.0)
Dry eye	23 (6.6)	20 (5.8)	11 (3.1)
Ocular hypertension	23 (6.6)	17 (5.0)	6 (1.7)
Conjunctivitis	23 (6.6)	15 (4.4)	10 (2.9)
Retinal hemorrhage	22 (6.3)	28 (8.2)	16 (4.6)
Conjunctival hyperemia	21 (6.1)	30 (8.7)	20 (5.7)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Cataract nuclear	21 (6.1)	16 (4.7)	10 (2.9)
Retinal exudates	20 (5.8)	19 (5.5)	21 (6.0)
Diabetic retinopathy	20 (5.8)	19 (5.5)	13 (3.7)
Eye pain	19 (5.5)	25 (7.3)	16 (4.6)
Vitreous detachment	19 (5.5)	24 (7.0)	12 (3.4)
Posterior capsule opacification	17 (4.9)	18 (5.2)	8 (2.3)
Conjunctival edema	17 (4.9)	17 (5.0)	4 (1.1)
Vitreous floaters	17 (4.9)	12 (3.5)	10 (2.9)
Lenticular opacities	17 (4.9)	11 (3.2)	5 (1.4)
Punctate keratitis	14 (4.0)	11 (3.2)	11 (3.1)
Retinal aneurysm	13 (3.7)	16 (4.7)	7 (2.0)
Retinal neovascularization	12 (3.5)	23 (6.7)	21 (6.0)
Cataract cortical	11 (3.2)	17 (5.0)	11 (3.1)
Vitreous opacities	11 (3.2)	5 (1.5)	5 (1.4)
Blepharitis	10 (2.9)	6 (1.7)	20 (5.7)
Lacrimation increased	8 (2.3)	10 (2.9)	9 (2.6)
Foreign body sensation in eyes	8 (2.3)	7 (2.0)	5 (1.4)
Vitreous adhesions	7 (2.0)	6 (1.7)	5 (1.4)
Corneal erosion	7 (2.0)	4 (1.2)	3 (0.9)
Eyelid ptosis	7 (2.0)	3 (0.9)	2 (0.6)
Keratitis	6 (1.7)	7 (2.0)	3 (0.0)
Vision blurred	6 (1.7)	6 (1.7)	4 (1.1)
Anterior chamber inflammation	6 (1.7)	2 (0.6)	0 (0.0)
Eyelid edema	5 (1.4)	5 (1.5)	2 (0.6)
Macular hole	5 (1.4)	5 (1.5)	1 (0.3)
Eye irritation	5 (1.4)	4 (1.2)	7 (2.0)
Visual impairment	5 (1.4)	4 (1.2)	4 (1.1)
Retinal tear	5 (1.4)	3 (0.9)	3 (0.9)
Glaucoma	4 (1.2)	7 (2.0)	0 (0.0)
Iris neovascularization	4 (1.2)	5 (1.5)	4 (1.1)
Open angle glaucoma	4 (1.2)	3 (0.9)	2 (0.6)
Iritis	4 (1.2)	2 (0.6)	1 (0.3)
Blepharochalasis	4 (1.2)	1 (0.3)	2 (0.6)
Optic nerve cupping	3 (0.9)	6 (1.7)	1 (0.3)
Eye pruritus	3 (0.9)	4 (1.2)	8 (2.3)
Cystoid macular edema	3 (0.9)	4 (1.2)	1 (0.3)
Conjunctivitis allergic	3 (0.9)	1 (0.3)	4 (1.1)
Macular cyst	2 (0.6)	0 (0.0)	4 (1.1)
Gastrointestinal disorders			
Overall	50 (14.4)	57 (16.6)	42 (12.0)
Nausea	10 (2.9)	7 (2.0)	4 (1.1)
Diarrhea	7 (2.0)	9 (2.6)	3 (0.9)
Vomiting	6 (1.7)	8 (2.3)	3 (0.9)
Gastro-esophageal reflux disease	6 (1.7)	7 (2.0)	8 (2.3)
Gastritis	6 (1.7)	1 (0.3)	2 (0.6)
Constipation	5 (1.4)	8 (2.3)	5 (1.4)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Abdominal pain	4 (1.2)	2 (0.6)	3 (0.9)
Dyspepsia	3 (0.9)	2 (0.6)	4 (1.1)
Gastric ulcer	1 (0.3)	4 (1.2)	1 (0.3)
<u>General disorders and administration site conditions</u>			
Overall	30 (8.6)	34 (9.9)	25 (7.1)
Edema peripheral	9 (2.6)	13 (3.8)	8 (2.3)
Pyrexia	6 (1.7)	6 (1.7)	4 (1.1)
Non-cardiac chest pain	5 (1.4)	1 (0.3)	2 (0.6)
<u>Hepatobiliary disorders</u>			
Overall	4 (1.2)	7 (2.0)	7 (2.0)
Cholelithiasis	3 (0.9)	1 (0.3)	4 (1.1)
<u>Immune system disorders</u>			
Overall	8 (2.3)	19 (2.9)	3 (0.9)
Drug hypersensitivity	4 (1.2)	4 (1.2)	2 (0.6)
Seasonal allergy	1 (0.3)	4 (1.2)	1 (0.3)
<u>Infections and infestations</u>			
Overall	116 (33.4)	111 (32.4)	93 (26.6)
Nasopharyngitis	18 (5.2)	14 (4.1)	22 (6.3)
Bronchitis	15 (4.3)	10 (2.9)	10 (2.9)
Urinary tract infection	13 (3.7)	16 (4.7)	11 (3.1)
Influenza	13 (3.7)	12 (3.5)	11 (3.1)
Upper respiratory tract infection	10 (2.9)	19 (5.5)	17 (4.9)
Cellulitis	10 (2.9)	5 (1.5)	3 (0.9)
Sinusitis	7 (2.0)	4 (1.2)	1 (0.3)
Pneumonia	5 (1.4)	6 (1.7)	2 (0.6)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)
Gastroenteritis	4 (1.2)	4 (1.2)	2 (0.6)
Conjunctivitis viral	4 (1.2)	2 (0.6)	1 (0.3)
Hordeolum	2 (0.6)	6 (1.7)	1 (0.3)
Localized infection	2 (0.6)	1 (0.3)	5 (1.4)
Osteomyelitis	1 (0.3)	4 (1.2)	2 (0.6)
Tooth infection	0 (0.0)	5 (1.5)	0 (0.0)
<u>Injury, poisoning and procedural complications</u>			
Overall	62 (17.9)	55 (16.0)	29 (8.3)
Fall	11 (3.2)	14 (4.1)	7 (2.0)
Corneal abrasion	10 (2.9)	11 (3.2)	6 (1.7)
Ligament sprain	5 (1.4)	6 (1.7)	0 (0.0)
Foreign body in eye	5 (1.4)	1 (0.3)	0 (0.0)
Laceration	4 (1.2)	2 (0.6)	0 (0.0)
Procedural pain	4 (1.2)	1 (0.3)	2 (0.6)
Foot fracture	3 (0.9)	5 (1.5)	0 (0.0)
Contusion	0 (0.0)	5 (1.5)	1 (0.3)
<u>Investigations</u>			
Overall	142 (40.9)	136 (39.7)	46 (13.1)
Intraocular pressure increased	116 (33.4)	113 (32.9)	23 (6.6)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Blood creatinine increased	13 (3.7)	11 (3.2)	11 (3.1)
Glycosylated hemoglobin increased	11 (3.2)	10 (2.9)	6 (1.7)
Blood glucose increased	4 (1.2)	3 (0.9)	3 (0.9)
Blood pressure increased	4 (1.2)	2 (0.6)	2 (0.6)
<u>Metabolism and nutrition disorders</u>			
Overall	54 (15.6)	71 (20.7)	43 (12.3)
Hypercholesterolemia	16 (4.6)	11 (3.2)	12 (3.4)
Diabetes mellitus	11 (3.2)	5 (1.5)	8 (2.3)
Dyslipidemia	7 (2.0)	8 (2.3)	5 (1.4)
Diabetes mellitus inadequate control	6 (1.7)	9 (2.6)	6 (1.7)
Hypoglycemia	6 (1.7)	8 (2.3)	7 (2.0)
Hyperlipidemia	5 (1.4)	6 (1.7)	2 (0.6)
Type 2 diabetes mellitus	5 (1.4)	6 (1.7)	2 (0.6)
Gout	4 (1.2)	2 (0.6)	0 (0.0)
Hyperkalemia	2 (0.6)	6 (1.7)	1 (0.3)
Dehydration	1 (0.3)	6 (1.7)	3 (0.9)
Hyponatremia	0 (0.0)	5 (1.5)	0 (0.0)
<u>Musculoskeletal and connective tissue disorders</u>			
Overall	51 (14.7)	44 (12.8)	41 (11.7)
Osteoarthritis	9 (2.6)	3 (0.9)	4 (1.1)
Arthritis	8 (2.3)	5 (1.5)	2 (0.6)
Back pain	7 (2.0)	8 (2.3)	4 (1.1)
Pain in extremity	7 (2.0)	4 (1.2)	5 (1.4)
Musculoskeletal pain	4 (1.2)	4 (1.2)	3 (0.9)
Arthralgia	3 (0.9)	5 (1.5)	4 (1.1)
Muscle spasms	2 (0.6)	2 (0.6)	6 (1.7)
Spinal column stenosis	2 (0.6)	2 (0.6)	4 (1.1)
<u>Neoplasms benign, malignant and unspecified (includes cysts and polyps)</u>			
Overall	24 (6.9)	16 (4.7)	15 (4.3)
<u>Nervous system disorders</u>			
Overall	60 (17.3)	50 (14.6)	37 (10.6)
Headache	12 (3.5)	11 (3.2)	9 (2.6)
Dizziness	6 (1.7)	8 (2.3)	7 (2.0)
Transient ischemic attack	6 (1.7)	3 (0.9)	1 (0.3)
Cerebrovascular accident	5 (1.4)	3 (0.9)	4 (1.1)
Syncope	4 (1.2)	6 (1.7)	2 (0.6)
Carpal tunnel syndrome	4 (1.2)	3 (0.9)	1 (0.3)
Paraesthesia	4 (1.2)	1 (0.3)	2 (0.6)
Convulsion	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic neuropathy	1 (0.3)	5 (1.5)	2 (0.6)
Carotid artery stenosis	1 (0.3)	4 (1.2)	2 (0.6)
<u>Psychiatric disorders</u>			
Overall	22 (6.3)	19 (5.5)	15 (4.3)
Depression	8 (2.3)	12 (3.5)	8 (2.3)
Insomnia	8 (2.3)	3 (0.9)	2 (0.6)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Anxiety	7 (2.0)	4 (1.2)	3 (0.9)
<u>Renal and urinary disorders</u>			
Overall	31 (8.9)	41 (12.0)	14 (4.0)
Renal failure chronic	6 (1.7)	11 (3.2)	3 (0.9)
Renal failure acute	6 (1.7)	9 (2.6)	3 (0.9)
Renal failure	6 (1.7)	7 (2.0)	3 (0.9)
Renal impairment	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic nephropathy	0 (0.0)	4 (1.2)	1 (0.3)
<u>Reproductive system and breast disorders</u>			
Overall	12 (3.5)	6 (1.7)	4 (1.1)
Benign prostatic hyperplasia*	6 (2.9)	2 (1.0)	2 (0.9)
<u>Respiratory, thoracic and mediastinal disorders</u>			
Overall	28 (8.1)	49 (14.3)	16 (4.6)
Cough	4 (1.2)	13 (3.8)	2 (0.6)
Oropharyngeal pain	4 (1.2)	5 (1.5)	1 (0.3)
Sleep apnea syndrome	3 (0.9)	8 (2.3)	2 (0.6)
Dyspnea	3 (0.9)	5 (1.5)	4 (1.7)
Pleural effusion	0 (0.0)	4 (1.2)	3 (0.9)
<u>Skin and subcutaneous tissue disorders</u>			
Overall	24 (6.9)	22 (6.4)	20 (5.7)
Skin ulcer	4 (1.2)	4 (1.2)	2 (0.6)
<u>Surgical and medical procedures</u>			
Overall	5 (1.4)	3 (0.9)	1 (0.3)
<u>Vascular disorders</u>			
Overall	63 (18.2)	70 (20.4)	35 (10.0)
Hypertension	52 (15.0)	50 (14.6)	27 (7.7)
Hypotension	1 (0.3)	2 (0.6)	4 (1.1)

*Percentages based on the male population

During the April 1, 2014 labeling meeting with the applicant, the Division requested the table in Section 6.1 Adverse Reactions be revised and include all treatment-emergent adverse reactions that occur in $\geq 1\%$ of patients and include these in labeling, to help inform physicians about the potential adverse reactions associated with the use of Ozurdex in DME patients. See Section 1.10 for an updated table of treatment-emergent adverse reactions.

1.7 Side-by-Side Presentation and Discussion of Ozurdex and Fluocinolone Acetonide Intravitreal Insert Studies

The background and study results for NDA 201923 are summarized in Sections 1.1 and 1.2; the background and study results for the Ozurdex trials are summarized in Sections 1.3 – 1.6. In this section, information is presented side-by-side to see similarities and differences in main characteristics of the types and size of studies, as well as key outcome variables.

	Fluocinolone Acetonide Intravitreal Insert #	Ozurdex
STUDY OVERVIEW	Two randomized (2:2:1) double- masked Phase 3 trials	Two randomized (1:1:1) double-masked Phase 3 trials
Duration of trials	3 years	3 years
Number of planned study visits	>=16	>= 16
Number of patients receiving test drug – 2 doses tested	768	642
Number of patients receiving control	185	328
Location where studies conducted	US and outside US	US and outside US
OUTCOME		
Duration of Diabetes Mellitus	16.1-17.1 years	15.9-16.2 years
Duration of DME	3.5-3.9 years ##	15-17 months
Number of treatments, mean (range)	1 (range 1-3)	4 (range 1-7)
Rescue therapy given/discontinued due to lack of efficacy	~ 20%-25%	~20%-25%
Difference between test and control arms		
Primary endpoint: >=15 letter improvement in BCVA, difference between test drug arm and sham control arm	~ 10%	~ 10%
Cataract formation	~ 30%	~ 30%
Difference between test and control arms		
Cataract surgery	~ 50%	~ 50%
Difference between test and control arms		
Increased IOP	~ 30%	~ 30%
Difference between test and control arms		
IOP lowering medications	~ 30%	~ 30%
Difference between test and control arms		
Glaucoma surgery	~ 5%	~ 1%
Difference between test and control arms		
Mean change in BCVA from baseline (letters)	4 to 5 letters	0 to 3 letters
Difference between test and control arms		

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

Based on FDA review, the median duration is ~ 1.7 years

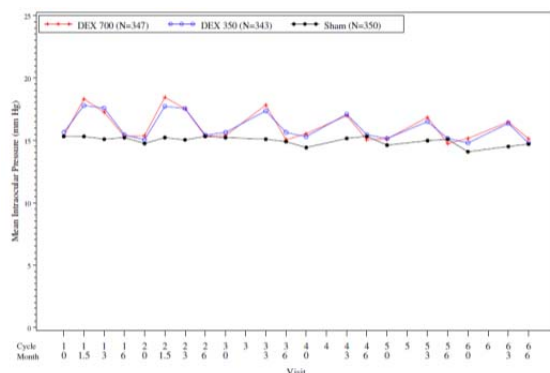
Comment:

As seen in the above table, there are many parallels in the studies and outcomes between the two corticosteroids; therefore it would seem reasonable to conclude that there would be consistency in the discussion of risk/benefit and recommendations regarding approval and labeling would be parallel. However,

- *Based on the results from the Iluvien trials and input from the Deputy Director and other ophthalmology reviewers, the recommendation was that the benefits of Iluvien could not overcome the risks, and Iluvien was not recommended for approval of the indication, treatment of diabetic macular edema during the previous review cycles.*
- *Based on the results from the Ozurdex trials, the input from the Deputy Director and other ophthalmology reviewers recommend approval of Ozurdex for the indication, (b) (4)*
(b) (4).

As summarized in Section 1.1 and Section 1.2, the Iluvien reviews for DME state the benefit of Iluvien cannot overcome the risk of cataracts and elevated IOP. By comparison, in the clinical reviews of the Ozurdex application there is a surprising absence of any concern about these events, even though they are seen at comparably high rates. There is no discussion about the inconsistency in recommendation, or any differences in the nature or severity of these adverse reactions which would make them acceptable in the setting of Ozurdex but not Iluvien. The Deputy Director's review of Ozurdex states:

“Corticosteroids are known to increase IOP, cause cataracts and decrease resistance to ocular infections. The graph below demonstrates the increase in IOP seen in some patients receiving the dexamethasone implants. The elevation in IOP is generally limited to a six month period. Repeat injections can be expected to contribute to repeat elevations in IOP.



“The development of cataracts, particularly posterior sub-capsular cataracts following corticosteroid use, topical or systemic, has been known since the 1960s. It is known to be dose dependent [Donshik PC *et al.* Posterior subcapsular cataracts induced by topical corticosteroids following keratoplasty for keratoconus. *Ann Ophthalmol.* 1981 Jan; 13(1):29-32.]

Cataract Surgery Rates

The Deputy Director's Review for Ozurdex does not report the rates of cataract surgery. There is no discussion of cataract surgery in the review and no comment about similarities/differences between the findings in the Ozurdex trials and Iluvien trials; this is particularly surprising given the focus and concern about cataracts and cataract surgery in the Iluvien review [Section 1.2].

The table of Common Adverse Events in the Deputy Director's Review includes the System Organ Class category for Surgical and Medical Procedures (copied below) but does not include an entry for "cataract surgery," even though this is a surgical procedure.

<u>Surgical and medical procedures</u>	DEX 700	DEX 350	Sham
Overall	5 (1.4)	3 (0.9)	1 (0.3)

The only mention of cataract removal in the Deputy Director's Ozurdex review is in the following sentence:

"The combination of cataract removal and treatment for macular edema contributes to the general improvement in vision in the dexamethasone groups as the trial progresses."

Following Iluvien treatment, there was a 3-fold increase in cataract extraction (from ~30% to ~80%) compared to a 7-fold increase with Ozurdex (~8% to ~61%) in cataract extraction. Therefore, it is not clear why one product (Iluvien) was not recommended for approval based on these adverse reactions while another is proposed for approval without any limitations or discussion to explain the conflicting recommendation. In fact, the rates of cataract surgery to manage the most frequent adverse reaction with Ozurdex are missing from the Deputy Director Review.

Cataract Rates

The Deputy Director Review for Ozurdex contains the Table of Common Adverse Events Occurring at an incidence 1% or Greater (Studies 206207-010 and 206207-011 Pooled, Safety Population) and displays the rates of individual events such as cataract, cataract subcapsular, cataract nuclear, cataract cortical. It is derived from the applicant's ISS table. Common adverse events include: "cataracts (68%), increased intraocular pressure/glaucoma (36%), conjunctival hemorrhage (22%), macular edema (15%), and vitreous hemorrhage (12%)." The Deputy Director Review of Ozurdex has no discussion of the cataract rates, including why the rates are or are not acceptable.

The second Deputy Director Review of Ozurdex dated June 19, 2014 discusses the rates of cataracts seen with the other two approved indications for Ozurdex. The rates [presented in Section 1.3] do not account for the fact that (1) there is an absence of 3-year follow up for patients who received one or two inserts and (2) approximately 75% of patients needed additional inserts to treat their DME as judged by the investigator based on clinical examination and OCT criteria, the average number was 4 inserts, and the range was 1-7 inserts. Both DME products were studied for a duration of 3 years as requested by the FDA; therefore, comparison to the other two Ozurdex indications does not provide the complete picture. When outcomes in patients with DME over the complete 3 years of the Ozurdex and Iluvien trials are compared, these separate trials have what appear fairly similar attributable net efficacy and safety findings.

The June 19, 2014 Ozurdex review also acknowledges that previously approved topical and systemic corticosteroids have not been limited to pseudophakic/aphakic patients, although specific indications, durations of treatment and cataract rates for these products are not discussed in the review. These prior approvals raise the question why the controlled clinical studies of

Iluvien, another intraocular insert, for the treatment of DME that showed corticosteroid related adverse events did not support approval of the DME indication.

Increased IOP Rates

The Deputy Director's Review for Ozurdex displays the rates of IOP elevation in the Table of Common Adverse Events. Increased IOP is also listed among the common ocular adverse events: "cataracts (68%), increased intraocular pressure/glaucoma (36%), conjunctival hemorrhage (22%), macular edema (15%), and vitreous hemorrhage (12%). The Deputy Director Review of Ozurdex has no discussion of the increased IOP rates, including why the rates are or are not acceptable.

Risk Benefit Consideration

For the Alimera product, Alimera's position, based on input from their consultants, was that the risks (adverse reactions) were manageable; but this position was not accepted by the ophthalmology reviewers. While there continued to be meetings and discussion of the scientific differences between the Division and Alimera, the Deputy Director Review for Iluvien dated 10/19/2011 states:

"9. Advisory Committee

No Advisory Committee Meeting was scheduled because 36 month data did not support the approval for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg and the safety profile suggested that the observed benefits did not outweigh the risks of the product."

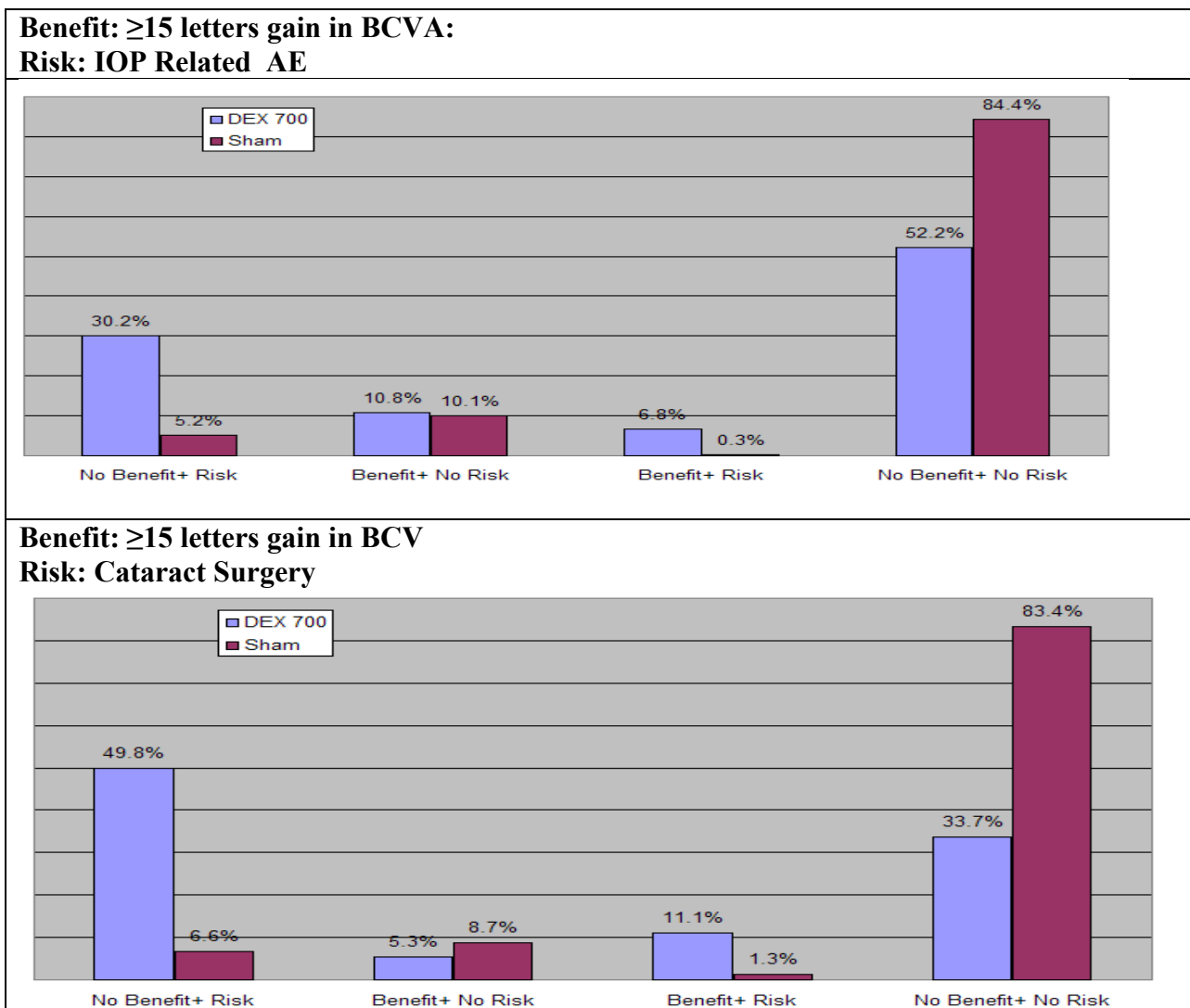
Generally, when there are scientific issues such as those articulated above, and there are differences in scientific viewpoint, the input of a scientific Advisory Committees is considered valuable. It appears that the decision not to discuss the Iluvien application at an Advisory Committee despite the differences in scientific opinion was based on the conviction that this safety profile was not acceptable, and the product's benefit did not outweigh the risks of the product.

Comment:

In summary, I find that the recommendations in the clinical review of Ozurdex recommending approval of the application for DME without any limitations is inconsistent with the previous recommendations for a product with a development program and clinical trial findings similar to those seen with Ozurdex. Therefore, in the following sections the benefits and risks of Ozurdex are reviewed, and a limited indication for DME is discussed, consistent with recommendations made for another corticosteroid, Iluvien.

1.8 Benefit / Risk Assessment of Ozurdex

The FDA statistical reviewer created a table graphically comparing patients who did or did not have benefit of ≥ 15 letters gain in BCVA, and did or did not have risk of IOP related events (top graph) and cataract surgery (bottom graph). The graphs show that there is a significantly larger proportion of patients who have the "worst case scenario" of no benefit plus risk in the DEX 700 arm compared to sham arm, and this group also has more benefit plus risk than the sham arm. On the other hand, there are about comparable rates of benefit plus no risk patients.



Therefore, excluding phakic patients is a strategy to mitigate the risk of the “worst case scenario” category for the cataract surgery risk. For the category of IOP elevation risk, the choice can be made whether or not to treat a patient with Ozurdex. This approach is also consistent with the planned approach for Iluvien [Section 1.2].

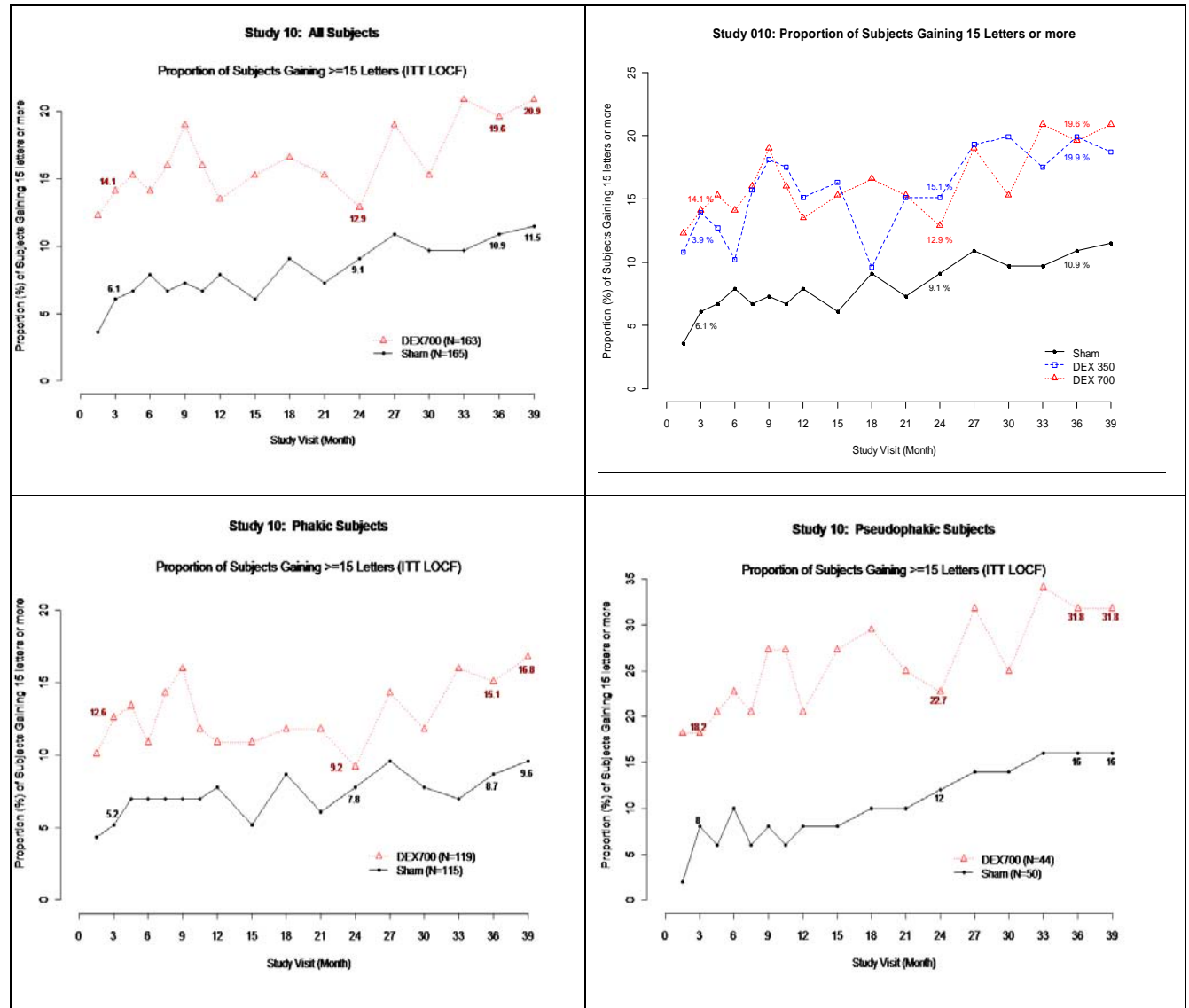
1.9 Ozurdex Efficacy Outcomes, Consideration for Labeling

I agree with the Deputy Director’s general description of the Ozurdex DME studies and efficacy based on BCVA.

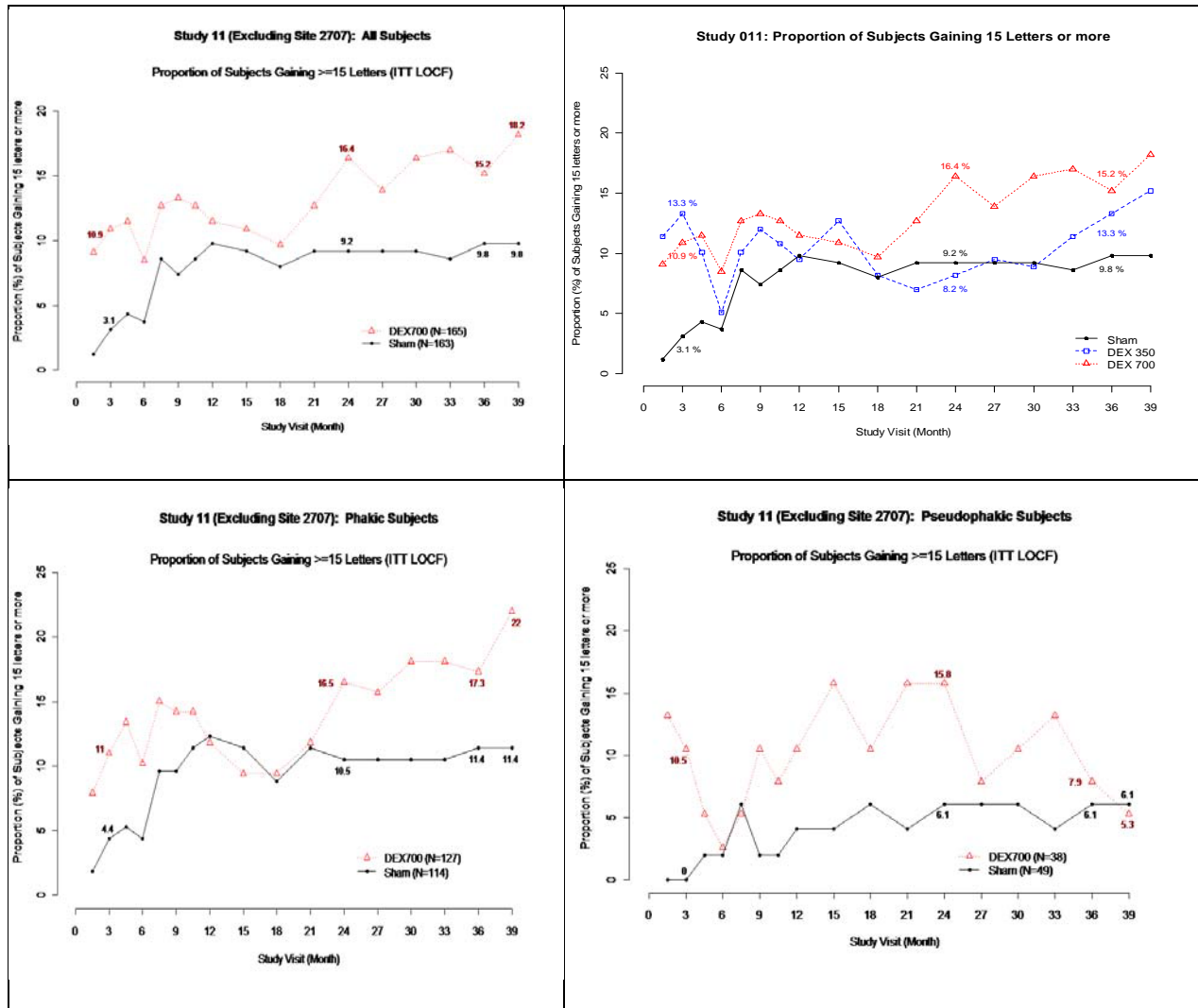
“These graphs demonstrate the initial effect of Ozurdex on Best Corrected Visual Acuity (BCVA). In many patients, there is a maximum effect 3 months after implantation and then the effect wanes. Repeat injections at 6 months improve vision; however, repeat injections increase the chances for cataract development. The effect of cataract development is seen from month 15 through month 30. The combination of cataract removal and treatment for macular edema contributes to the general improvement in vision in the dexamethasone groups as the trial progresses.”

The description helps put in perspective why the studies were amended to change the endpoint to Month 39, after retreatment at Month 36, since that approach would have the best likelihood of showing peak treatment effect.

The figures below show the outcome in Study -010 for the ≥ 15 letter improvement over time [source: FDA statistical reviews]. The DEX 700 arm (red triangles) is significantly better for the primary endpoint compared to the sham arm (black circles). The other figures show the response by lens status in phakic and pseudophakic patients.



In Study 11 there is an increase in proportion of patients with ≥ 15 letters improvement; however, at some of the timepoints the BCVA in the DEX arms dips below the sham arm (phakic DEX 700 patients, DEX 350 patients). The applicant reports this is due to cataract formation; their explanation seems reasonable, based on the pattern of response seen in pseudophakic patients.



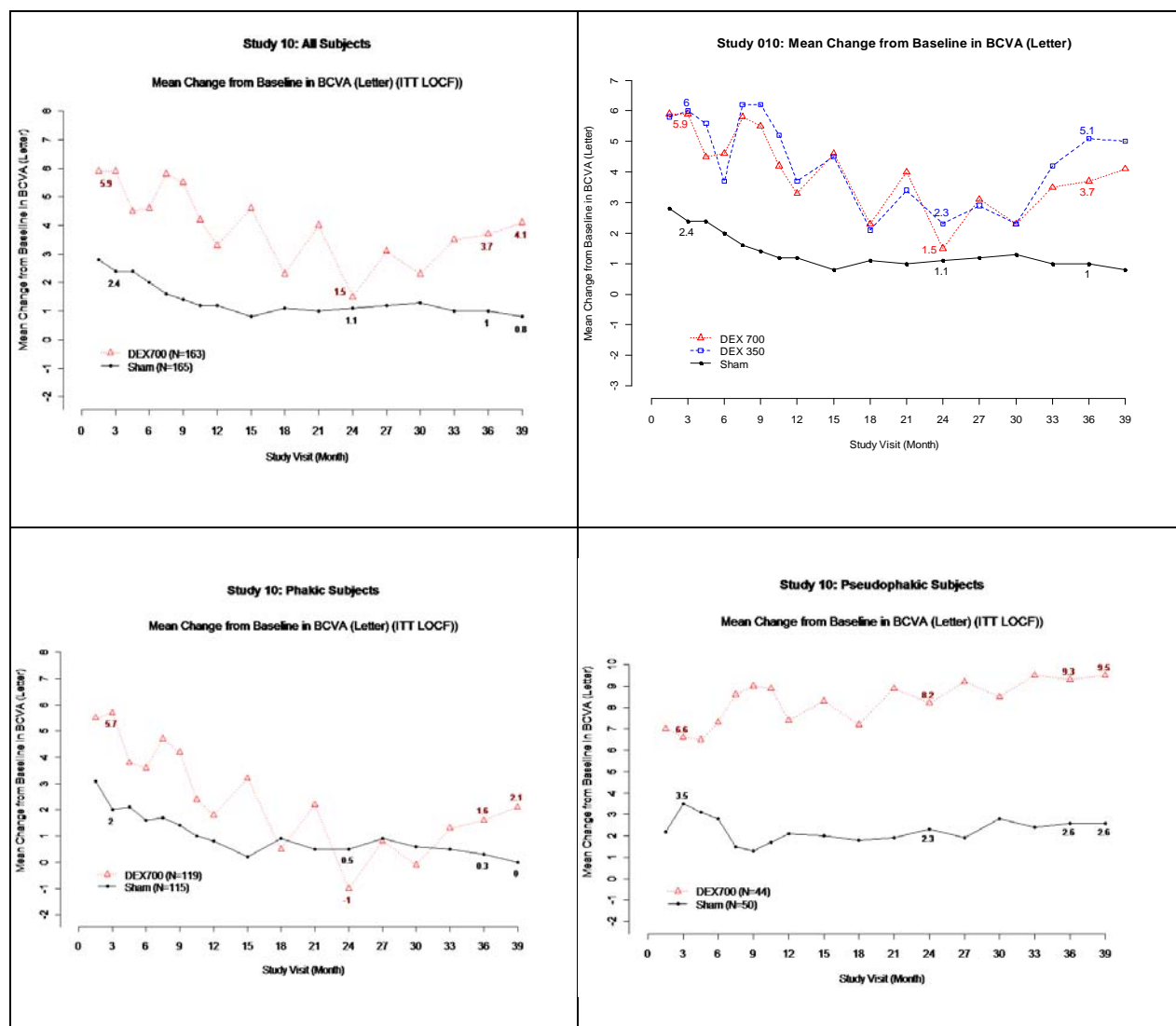
The table below titled, Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF), shows that while some patients benefited from treatment and had improvement of 1, 2 or 3 lines of BCVA, other patients had no change in BCVA or had a 1, 2, or 3 lines worsening in BCVA. The row showing ≥ 15 letter worsening is highlighted. The applicant's explanation that the worsening was associated with cataract formations is probably consistent with the study results, as shown in the figures of Mean Change in BCVA from Baseline. The worsening is seen mostly in the phakic patients compared to the pseudophakic patients, and this finding is more pronounced in Study -011 than in Study -010, as shown on the following pages.

Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF), revised

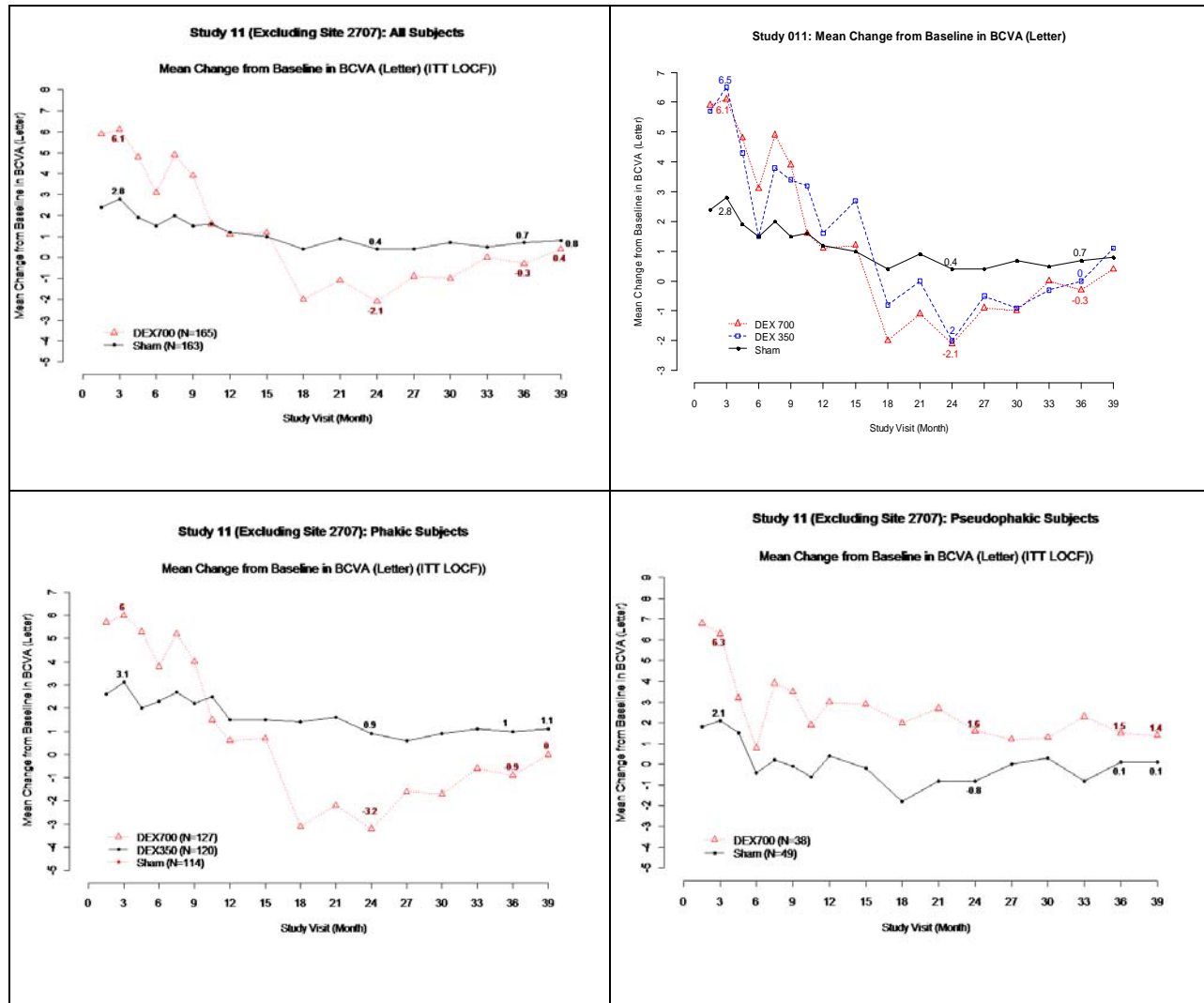
BCVA Change	Study 206207-010			Study 206207-011 (w/o 2707)		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163
≥ 15 Letters Improvement	32(19.6)	33(19.9)	18(10.9)	25(15.2)	21(13.3)	16(9.8)
≥ 10 and < 15 Letters Improvement	27(16.6)	21(12.7)	15(9.1)	18(10.9)	16(10.1)	19(11.7)
≥ 5 and < 10 Letters Improvement	27(16.6)	31(18.7)	20(12.1)	17(10.3)	31(19.6)	16(9.8)
No Change (-5 to +5 Letters)	45(27.6)	56(33.7)	75(45.5)	58(35.2)	42(26.6)	76(46.6)
≥ 5 and < 10 Letters Worsening	12(7.4)	12(7.2)	13(7.9)	10(6.1)	10(6.3)	13(8)
≥ 10 and < 15 Letters Worsening	5(3.1)	4(2.4)	7(4.2)	5(3.0)	13(8.2)	5(3.1)
≥ 15 Letters Worsening	15(9.2)	9(5.4)	17(10.3)	32(19.4)	25(15.8)	18(11.0)

Source: Statistical Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy but fell into one of the "improvement" categories were set to the "no change" category.

The following figures show the mean change in BCVA from baseline [source: FDA statistical reviews]. In Study 010 the DEX 700 arm (red triangles) is consistently above the sham control (black circles) for all patients. However, when plotted based on lens status, phakic patients show lower BCVA than sham patients between around Month 18 to Month 30. On the other hand, mean BCVA is consistently higher in the DEX 700 arm than the sham arm in pseudophakic patients.



In Study 011 (site 2707 excluded), the mean change in vision for all patients is lower in the DEX 700 arm compared to the sham control arm starting around Month 9 to Month 39. When looking at the outcome based on lens status, phakic patients show lower BCVA than sham patients between approximately Month 10 and Month 39. On the other hand, mean BCVA is consistently higher in the DEX 700 arm than the sham arm in pseudophakic patients.



In the second Deputy Director Review of Ozurdex dated June 19, 2014, it is suggested that the treatment effect of Ozurdex is greater in the first cycle and then less pronounced with subsequent injections, but the recommendations for approval do not suggest that patients should only receive one or two inserts of Ozurdex for DME. The results above from pseudophakic patients in Study 010 suggest that the retreatment is able to sustain the mean change from baseline compared to sham while Study 011 has more variability in the pattern of response. For phakic patients, the BCVA declines and dips below the sham curve for part of the study period in each of the two studies likely due to clinically-significant cataract formation.

Comment:

Based on the results of the mean change from baseline in BCVA the pseudophakic population had a consistently higher response to DEX treatment over the course of the 3-year trial compared to sham; however, the phakic population experienced a decrease in vision greater than the sham arm between Month 18 to 30 in Study 10 and as early as 9 months and extending through 39 in Study 11. Therefore, the benefit in phakic patients is inconsistent and confounded by the formation of cataracts. To be consistent with the previous discussion of how to handle risk/benefit for Iluvien, a similarly situated product, the DME indication will be limited to the population that has demonstrated consistent benefit compared to sham control over the course of the three years, that is, patients who are pseudophakic or already have a formed cataract and are scheduled for surgery.

1.10 Ozurdex Safety Outcomes, Consideration for Labeling

The following table from the FDA statistical review provides the safety data for the pseudophakic patients in the two studies combined. Overall there is a higher risk of ocular AEs mainly because of increased IOP with DEX treatment. The risk of most of the other frequently occurring adverse reactions is not significant; however, some of this may be due to the lower sample size, since approximately 25% were pseudophakic at baseline.

Table 3: Summary of Adverse Events (AE) (Pooled: Pseudophakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=81	DEX 350 N=84	Sham N=98	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	77(95.1%)	83(98.8%)	84(85.7%)	9.3%(1%,17.7%)	13.1%(5.8%,20.4%)
Any Ocular AE	59(72.8%)	70(83.3%)	60(61.2%)	11.6%(-2.1%,25.3%)	22.1%(9.6%,34.6%)
Any Serious AE	29(35.8%)	36(42.9%)	36(36.7%)	-0.9%(-15.1%,13.2%)	6.1%(-8.1%,20.4%)
Any Ocular Serious AE	2(2.5%)	0(0%)	0(0%)	2.5%(-0.9%,5.8%)	
Any Severe AE	35(43.2%)	40(47.6%)	37(37.8%)	5.5%(-9%,19.9%)	9.9%(-4.5%,24.2%)
Any Ocular Severe AE	10(12.3%)	15(17.9%)	8(8.2%)	4.2%(-4.8%,13.2%)	9.7%(-0.1%,19.5%)
Any IOP Related AE	25(30.9%)	29(34.5%)	9(9.2%)	21.7%(10.1%,33.3%)	25.3%(13.7%,37%)
≥10 mm Hg IOP Change from Baseline at any visit	20(24.7%)	24(28.6%)	2(2%)	22.7%(12.9%,32.4%)	26.5%(16.5%,36.6%)
≥25 mm Hg IOP at any visit	21(25.9%)	24(28.6%)	6(6.1%)	19.8%(9.1%,30.5%)	22.4%(11.7%,33.2%)
≥35 mm Hg IOP at any visit	6(7.4%)	4(4.8%)	1(1%)	6.4%(0.3%,12.4%)	3.7%(-1.2%,8.7%)
Glaucoma	1(1.2%)	1(1.2%)	0(0%)	1.2%(-1.2%,3.6%)	1.2%(-1.1%,3.5%)
IOP Lowering Procedures	1(1.2%)	0(0%)	0(0%)	1.2%(-1.2%,3.6%)	
≥15 Letters Loss from Baseline	5(6.2%)	4(4.8%)	7(7.1%)	-1%(-8.3%,6.3%)	-2.4%(-9.2%,4.5%)
Death	1(1.2%)	3(3.6%)	2(2%)	-0.8%(-4.5%,2.9%)	1.5%(-3.3%,6.4%)
Escape Therapy	7(8.6%)	9(10.7%)	12(12.2%)	-3.6%(-12.5%,5.3%)	-1.5%(-10.8%,7.7%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

The following table is derived from the data submitted by Allergan on May 16, 2014, for the combined treatment-related adverse reactions in the 2 clinical trials for patients with diabetic macular edema (excluding site 2707) as recommended by OSI. Discontinuation rates due to adverse reactions were 3% in the Ozurdex group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Table 2: Adverse Reactions Reported by $\geq 1\%$ of Patients

MedDRA Term	OZURDEX[®] N=324 (%)	Sham N=328 (%)
Ocular		
Cataract ¹	166/243 ² (68%)	49/230 (21%)
Intraocular pressure increased ³	115 (35%)	16 (5%)
Conjunctival Hemorrhage	76 (24%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry Eye	15 (5%)	7 (2%)
Vitreous Detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal Aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal Erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)

¹ Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX[®] subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

² 243 of the 324 OZURDEX[®] subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

³ Includes IOP increased and ocular hypertension.

Cataracts and Cataract Surgery

At baseline, 243 of the 324 Ozurdex subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the Ozurdex group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the Ozurdex group and 12 months in the Sham group. Among these patients, 61% of Ozurdex subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (median Month 21 for Ozurdex group and Month 20 for Sham group) of the studies.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

IOP	Treatment: N (%)	
	DEX 700 N=324	Sham N=328
Any IOP Related AE	120(37%)	18(6%)
≥ 10 mm Hg IOP Change from Baseline at any visit	91(28%)	13(4%)

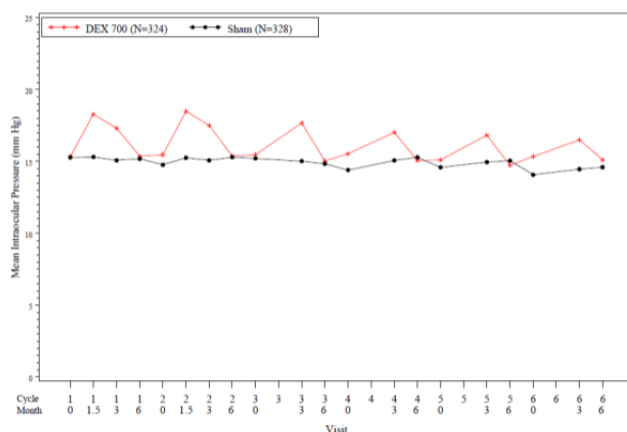
≥25 mm Hg IOP at any visit	106(33%)	15(5%)
≥35 mm Hg IOP at any visit	20(6%)	3(1%)
Glaucoma	4 (1.2%)	1 (0.3%)
IOP lowering surgical procedure *	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy

Sham: 1 laser iridotomy

Approximately 42% of the patients who received OZURDEX® were subsequently treated with IOP lowering medications during the study. In the sham control group, IOP lowering medications were used in approximately 10% of patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period) shown below:



2. Background

See above

3. CMC/Product Quality Microbiology

No new information was submitted in this efficacy supplement. The company claimed categorical exclusion from the requirement to prepare an environmental assessment which was deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/ toxicology studies were submitted. The text of Section 8 is being revised based on recommendations from the reviewers and Maternal Health Staff consult review:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX[®] in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed, OZURDEX[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX[®] injection in humans (0.7 mg dexamethasone) on a mg/m² basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX[®] injection in humans (0.7 mg dexamethasone) on a mg/m² basis.

8.3 Nursing Mothers

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

Comment: There are no outstanding issues preventing approval from the pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

As summarized in the Clinical Pharmacology review, a total of 21 DME patients were included in the PK substudies of Phase 3 Studies 206207-010 and 206207-011; 10 patients received Ozurdex[®] 700 mcg and 11 patients received 350 mcg. Plasma dexamethasone concentrations were measured at baseline (prior to dosing) and on days 1, 7, 21, 45, and 90 following the first Ozurdex[®] intravitreal injection. Ninety percent (47/52) of the samples obtained from those who received 700 mcg and 100% (60/60) of the samples obtained from those who received 350 mcg had plasma dexamethasone concentrations that were below the lower limit of quantitation (LLOQ = 50 pg/mL) of the HPLC/MS/MS assay. See complete review for further details. The first paragraph in Section 12.3 has been revised as follows:

12.3 Pharmacokinetics

Plasma concentrations were obtained from 21 patients with macular edema due to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and 21 patients with diabetic macular edema (DME) prior to dosing and at 4 to 5 additional post-

dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In RVO and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

Comment: There are no outstanding issues preventing approval from the Clinical Pharmacology perspective.

6. Clinical Microbiology/Immunology

N/A

7. Clinical/Statistical-Efficacy

The key scientific issues are summarized in Section 1. For details on other aspects of the efficacy supplement, see clinical reviews by Drs. Lim, Boyd and Chambers, and statistical reviews by Drs. Eshete and Wang.

(b) (4)

8. Safety

The key safety issues are discussed in Section 1. For additional information on other aspects, see clinical reviews by Drs. Lim, Boyd and Chambers and statistical reviews by Drs. Eshete and Wang.

Information on Endothelial Cell Density, as summarized from the Applicant's submission, is provided below:

Study -010

12.5.9 Endothelial Cell Density

Corneal endothelial cell density was measured at selected sites only (a total of 90 patients). At baseline, mean endothelial cell density was 2329.7 cells/mm² in the DEX 700 group, 2194.8 cells/mm² in the DEX 350 group, 2409.0 cells/mm² in the Sham group, and 2276.0 cells/mm² in the non-study eye (pooled across 89 nonstudy eyes from the 3 treatment groups) (Table 14.3-29). Within each treatment group, endothelial cell density decreased from baseline over time in the study eye. At month 36, mean decreases from baseline in endothelial cell density in the DEX 700, DEX 350, and Sham groups were 418.8, 367.4, and 182.3 cells/mm², respectively. In

the non-study eye, the mean decrease from baseline in endothelial cell density at month 36 was 164.7 cells/mm². The greater mean decrease in endothelial cell density from baseline in the DEX groups than Sham may have been due to the higher rates of cataract surgery in the DEX groups during the study period (61.5%, 61.0%, and 7.0% in the DEX 700, DEX 350, and Sham groups, respectively; see Table 12–21; Hugod et al, 2011).

Study -011 (analysis does not exclude site 2707)

12.5.9 Endothelial Cell Density

Corneal endothelial cell density was measured at selected sites only (a total of 117 patients, data from 116 study eyes and 117 non-study eyes). At baseline, mean endothelial cell density was 2469.4 cells/mm² in the DEX 700 group, 2531.6 cells/mm² in the DEX 350 group, 2485.0 cells/mm² in the Sham group, and 2452.0 cells/mm² in the non-study eye (pooled across 117 non-study eyes from the 3 treatment groups) (Table 14.3-29).

Within each treatment group, endothelial cell density decreased from baseline over time in the study eye. At month 36, mean decreases from baseline in endothelial cell density in the DEX 700, DEX 350, and Sham groups were 226.0, 298.7, and 24.5 cells/mm², respectively. In the non-study eye, the mean decrease from baseline in endothelial cell density at month 36 was 17.2 cells/mm². The greater mean decrease in endothelial cell density from baseline in the DEX groups than in the Sham group may have been due to the higher rates of cataract surgery in the DEX groups during the study period (57.2%, 44.9%, and 7.4% in the DEX 700, DEX 350, and Sham groups, respectively, see Table 12–21; Hugod et al, 2011).

The statistical review also includes figures showing outcomes in patients who developed cataracts during the studies, and these figures do not show clear separation among the three arms. However, such figures are difficult to interpret because the patients' BCVA is confounded by the presence of cataracts and cataract surgeries to remove the vision-impairing cataract for individual patients occurred at various times during the course of the studies. On the other hand, patients who are scheduled for cataract surgery around the time they begin treatment of DME are anticipated to enter the study pseudophakic, therefore they are no longer at risk of developing a vision-impairing cataract, and their BCVA is a measure of their response to treatment for their DME.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was initially planned for January 27, 2014 to discuss both the Ozurdex and Iluvien applications, but was cancelled because the scientific issues to be discussed at the AC were thought to have been addressed after discussing the Iluvien application with OND, OAP and Alimera. A path forward for the Iluvien application was identified during these discussions by proposing a limited indication to address the risks. Given the more recent recommendations for the Ozurdex application, an open public advisory committee discussion whether corticosteroids should be approved for treatment of diabetic macular edema without limiting the indication due to concern about risks such as cataract formation and cataract surgery would be valuable, but should not hold up approval of the current application.

10. Pediatrics

At a meeting of the Pediatric Review Committee (PeRC) on October 16, 2013, the committee agreed with the Division to grant a full waiver in all pediatric patients because studies would be impossible or highly impractical.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

Not applicable

11.2 Office of Scientific Investigation (OSI) Audits

OSI inspections were conducted on four sites. One of the sites in Study 011 (#2707) was chosen because the largest number of US patients was enrolled in that site and evidence of fraud was described. An employee was reported to have substituted OCT scans to ensure that subjects met inclusion criteria and falsified BCVA values during a previous inspection, and this employee also participated in Study 011. The employee has since left the firm, and the investigator took corrective action to prevent such occurrences in the future. However, OSI stated in the 2/10/2014 review that OSI cannot endorse data integrity and subject safety at site 2707. In the letter issued to the investigator on 2/8/2014, OSI includes a recommendation (on the internal cover page) to exclude the results from 2707 from the safety and efficacy analysis of the application (68 patients in total).

11.3 Debarment Certification

Allergan, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.4 Financial Disclosure

Financial disclosure forms were reviewed. There are financial interests or arrangements to disclose from one investigator that participated in the covered clinical trials (206-207-010 and 206207-011) and enrolled two patients; therefore it is reasonable to conclude these patients did not have substantial impact on the study results.

11.5 Other Regulatory Issues

12. Labeling

Labeling has been finalized.

- **Package insert (PI):** Revisions have been incorporated
- **Carton and Container Labels:** No change
- **Proprietary Name:** No change

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

Approval – treatment of diabetic macular edema in patients who are pseudophakic or scheduled for imminent cataract surgery.

13.2 Risk Benefit Assessment

Diabetic macular edema is a complication of diabetes mellitus (DM) and diabetic retinopathy. While the condition may generally occur after many years of DM and can then wax and wane over time, DME in the setting of diabetic retinopathy can also be progressive over time and ultimately result in significant loss in vision, including blindness.

Current treatment of DME includes maintaining excellent glycemic control and treatment with Lucentis (ranibizumab). Avastin (bevacizumab) is used off label and has been compared head-to-head to Lucentis in the United States⁶ and in the United Kingdom⁷ for a different indication, age-related macular degeneration. An efficacy supplement for Eylea, BLA 125387 and the NDA 201923 resubmission are currently under review for the DME indication.

Ozurdex was statistically significantly better compared to sham in improving BCVA by 15 or more letters, the primary endpoint of the studies. It was noted that the treatment effect peaks around month 3 after treatment and then declines. During the trials patients received an average of 4 inserts, range 1-7 inserts. Ozurdex inserts could be given to patients at approximately 6-month intervals based on OCT findings and physician assessment. Decisions for retreatment were based on OCT findings and examination by the physician.

Corticosteroids are associated with various adverse reactions, both ocular and systemic. The most common adverse reactions associated with ocular corticosteroids are cataract formation and increased IOP. These are generally managed surgically and with topical medications, respectively. Although there may be discussion whether the relatively low response rate in terms of improved BCVA (benefit) outweighs the high rate of cataracts/cataract surgery and increased IOP (risk), there is a way to mitigate the risk of significant cataract formation by limiting the indication to patients who are pseudophakic or are already scheduled for cataract surgery. Specifically, based on the results of the mean change from baseline in BCVA the pseudophakic population had a consistently higher response to treatment over the course of the 3-year trial compared to sham; however, the phakic population experienced a decrease in vision greater than the sham arm between Month 18 to 30 in Study 10 and as early as 9 months and extending through 39 in Study 11. Therefore, the benefit in phakic patients is inconsistent and confounded by the formation of cataracts. To be consistent with the recent discussions of how to handle risk/benefit for a similarly situated product, the DME indication is limited to the population that has demonstrated consistent benefit compared to sham over the course of the three year trials, that is, patients who are pseudophakic or already have a formed cataract and are scheduled for surgery.

Although the approval for use in patients who are not at risk of cataract formation is consistent with the data from the clinical trials [Section 1.9], it is reasonable to consider that after further experience with this product and other corticosteroid products, there may be further discussion of the benefits and risks of corticosteroids in the DME population. For example, it is also possible that individual physicians may choose to counsel phakic patients on the degree of anticipated benefit and the risks associated with corticosteroids, and informed patients may decide to accept

⁶ Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. The CATT Research Group. N Engl J Med 2011; 364:1897-1908 May 19, <http://www.nejm.org/doi/full/10.1056/NEJMoa1102673>

⁷ Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial [http://www.elsevier-usairforce.com/periodicals/ophtha/article/S0161-6420\(12\)00358-2/abstract](http://www.elsevier-usairforce.com/periodicals/ophtha/article/S0161-6420(12)00358-2/abstract)

NDA 22315/S-009, Ozurdex (dexamethasone posterior segment drug delivery system)
Proposed indication: treatment of diabetic macular edema

treatment with the hope of benefiting even at the risk of the adverse reactions and the procedures to manage them.

Based on the information provided in this application, Ozurdex will be approved for the treatment of diabetic macular edema in patients who are pseudophakic or scheduled for imminent cataract surgery as summarized in the labeling submitted June 27, 2014.

13.3 Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)

None

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

/s/

RENATA ALBRECHT

06/28/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

OFFICE DIRECTOR MEMO

**Deputy Division Director Review of NDA 22-315 S-009
Review #2**

Date	June 19, 2014
From	Wiley A. Chambers, M.D.
NDA #	22-315 SE1 009
Applicant	Allergan, Inc.
Date of Original Submission	June 17, 2013
Date of Amendment	May 16, 2014
Type of Application	505(b)(1) supplement to NDA
Name	Ozurdex (dexamethasone intravitreal implant)
Dosage forms / Strength	Intravitreal implant
Proposed Indication(s)	Treatment of diabetic macular edema
Recommended Action:	Approval

Introduction/Background

The original New Drug Application (NDA) for this product, Ozurdex (dexamethasone intravitreal implant), was approved on June 17, 2009, for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). An efficacy supplement for the additional use of Ozurdex in the treatment of non-infectious uveitis affecting the posterior segment of the eye (intermediate and/or posterior uveitis) was approved on September 24, 2010. This supplement, S-009, is for an additional indication for the treatment of diabetic macular edema.

On May 16, 2014, Allergan submitted a response to additional questions posed by the Agency on April 29, 2014. The Clinical Reviewer, Cross-Discipline Team Leader and Deputy Division Director have previously recommended that this supplemental application be approved.

Allergan Response: Allergan is hereby responding to FDA's comments of April 29, 2014. In addition to the responses (see attached), Allergan is providing the requested tables according to the FDA template, as well as the following updated labeling documents:

- Annotated Draft Labeling Text: PDF and WORD
- Draft Labeling Text (Track Changes): PDF and WORD
- Draft Labeling Text (Clean): PDF and WORD
- Labeling History: PDF

Reviewer's Comments: *The submission, while responding to the Agency's request, changes little to the previously known information about the drug product or its action in the treatment of diabetic macular edema. The additional tables and graphs provide re-analyses excluding Site 2707. This site was previously identified as having a staff member who potentially provided false information concerning the enrollment of patients at that site. The study results with and without the data from this site are very similar. In my opinion, the removal of adverse event reports from that site is not appropriate because the individual in question was not involved in reporting adverse events.*

Taken as a whole, I believe that the information available from studies 206207-010 and 206207-011 can be summarized as follows:

- 1. Administration of a single implant of Ozurdex in a patient with diabetic macular edema is expected to result in a reduction of the macular thickness and a modest improvement in visual acuity over the span of approximately 4 months. This effect is demonstrated in both phakic and pseudophakic patients in each of the two studies. The mean visual acuity shown on the graphs below.

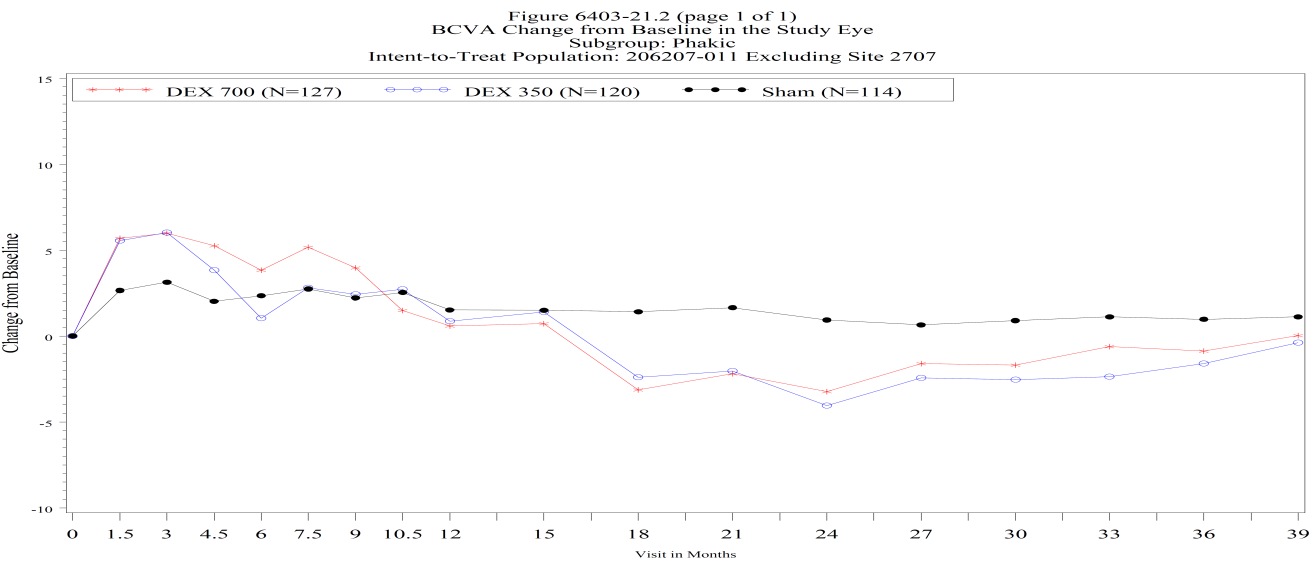
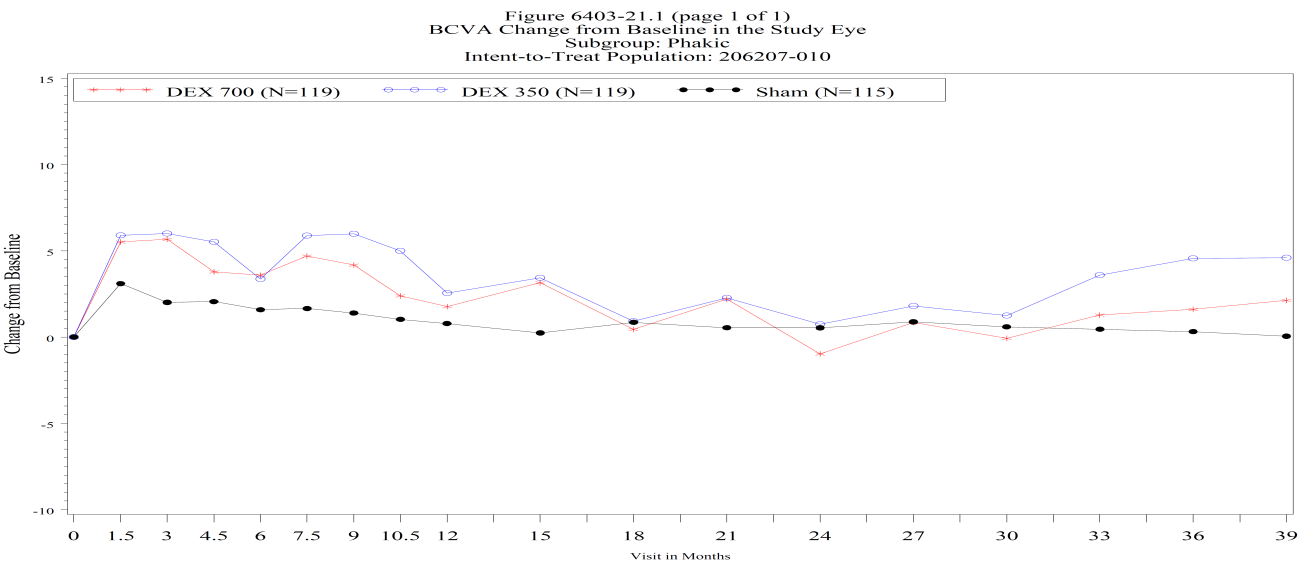


Figure 6403-22.1 (page 1 of 1)
BCVA Change from Baseline in the Study Eye
Subgroup: Pseudophakic
Intent-to-Treat Population: 206207-010

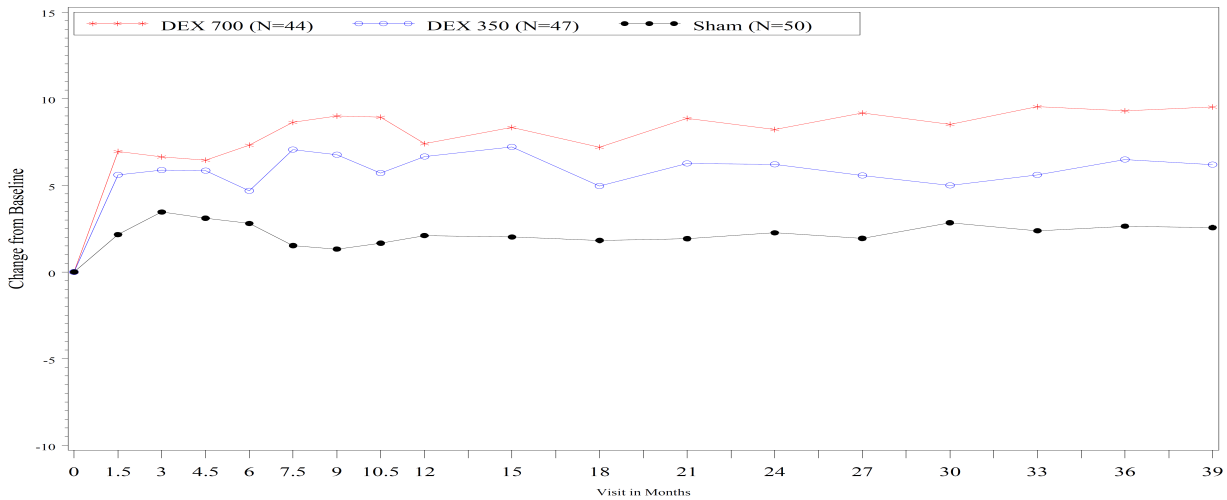
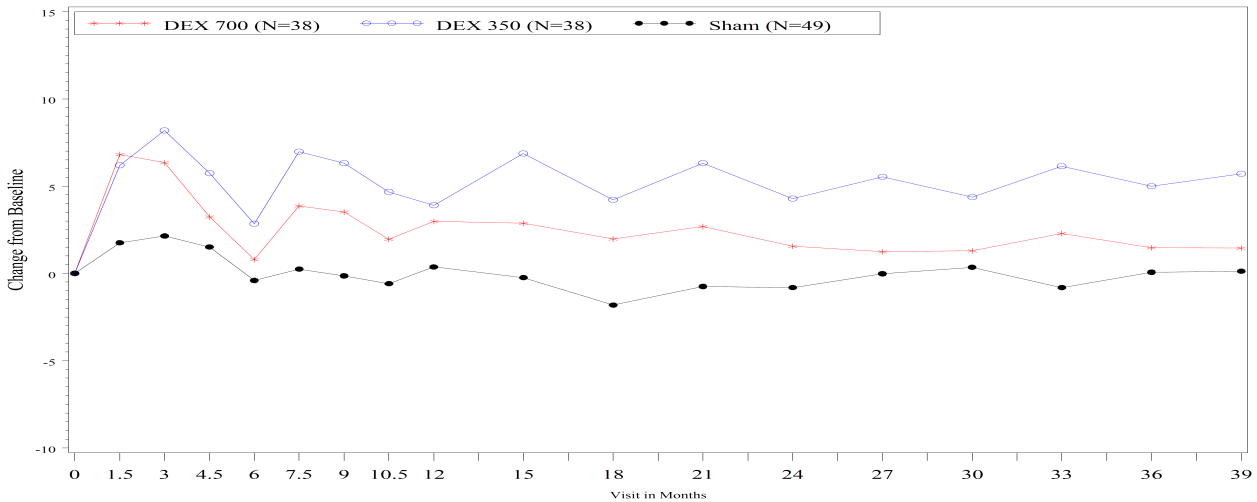


Figure 6403-22.2 (page 1 of 1)
BCVA Change from Baseline in the Study Eye
Subgroup: Pseudophakic
Intent-to-Treat Population: 206207-011 Excluding Site 2707

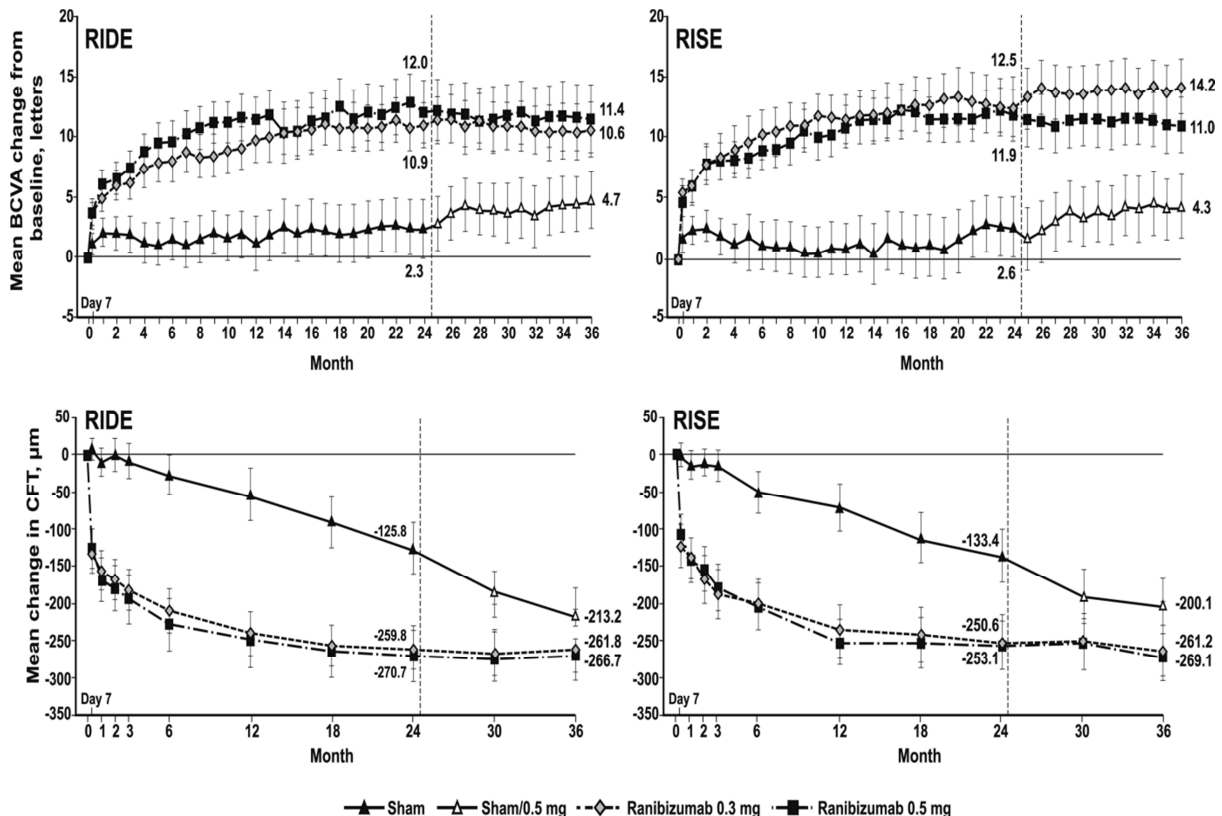


2. Administration of a second implant also results in an increase in visual acuity, but the effect is not as great as the first implant. Subsequent implants appear to result in continually less pronounced effects.
3. In phakic patients, corticosteroids such as dexamethasone accelerate the rate of cataract formation with a consequential decrease in visual acuity until the cataract is removed and replaced with an intraocular lens. Clinically significant cataract development is most commonly noted after 9-24 months of corticosteroid exposure.
4. The 36 month time point is not a critical evaluation time point in the treatment of diabetic macular edema for any product which does not affect hemoglobin A1c. Visual acuity

evaluations in phakic patients treated with one or more Ozurdex implants are generally expected to increase from month 24 through month 39 (and potentially beyond) due to the removal of cataracts and insertion of intraocular lenses.

Visual acuity evaluations in pseudophakic patients are generally expected to increase during the one to five month period following administration of an implant. Repeated administrations of Ozurdex are expected to improve visual acuity in pseudophakic patients during this four month window following each Ozurdex implantation, but as noted above, the amount of improvement often declines with each subsequent administration.

5. While pseudophakic patients may have a more rapid improvement in visual acuity compared to phakic patients, treatment of diabetic macular edema should not be delayed for patients to have cataract surgery. As noted in these trials, treatment with Ozurdex is more effective in improving visual acuity when it is administered earlier in the course of the disease. This was also true in studies where VEGF-F inhibitors were administered to patients with diabetic macular edema. As seen in the graphs below from studies of Lucentis, the delay in initiating VEGF therapy appears to have dampened the ultimate response to VEGF treatment.¹



¹ Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013 Oct;120(10):2013-22. doi: 10.1016/j.opht. 2013.02.034. Epub 2013 May 22.

Recommendations:

1. It is recommended that NDA 22-315 SE1 009, Ozurdex (dexamethasone intravitreal implant) be approved for the treatment of diabetic macular edema with labeling identified in this review but which differs from the labeling currently proposed by our Division.
2. Potential treatment with Ozurdex is not recommended to be limited to pseudophakic patients and is not recommended to be limited to patients scheduled for cataract surgery for the following reasons:
 - a. For some patients, corticosteroid treatment may be there best option for treating diabetic macular edema. Ozurdex, in particular the first implant is effective in reducing macular edema and improving visual acuity. Corticosteroids, administered by a variety of routes (topically, systemically, intraocularly) are well known to increase cataract development, but it should remain the medical judgment of physicians to decide whether the benefits outweigh the risk of cataract development for a particular patient. Since the 1960s² it has been reported that a fifth of children treated with systemic corticosteroids for more than one year and over half of children treated with systemic corticosteroids for more than two years will develop cataracts. It would be inconsistent with the Agency's previous decisions regarding the approval of corticosteroids to limit the use of Ozurdex to aphakic/pseudophakic patients (or patients scheduled for surgery). None of the approved systemically administered corticosteroids are restricted to aphakic patients for any of their approved indications in spite of the potential risk of cataract development. None of the previously approved topical corticosteroids is limited to aphakic patients. None of the previously approved corticosteroid intravitreal injections is limited to aphakic patients. The previously approved corticosteroid implant is not limited to aphakic patients. Neither of the previously approved indications for Ozurdex is limited to aphakic patients. It is my clinical judgment that the consequences of potential cataract development do not outweigh the potential benefit of treating macular edema.
 - b. The risk of cataract development is dependent on the number of Ozurdex implants administered. Because the number of patients treated with only one implant in the DME studies was small (Study 10, Dex 700, 14 patients, Dex 350, 7 patients; Study 11, Dex 700, 18 patients, Dex 350, 19 patients), the effect of multiple implants is best seen in the studies of other indications of Ozurdex.

Previous studies of macular edema due to vein occlusions evaluated the difference between one Ozurdex implant and two Ozurdex implants on the development of cataracts.

<u>Treatment</u>	<u>Cataract Adverse Events at 1 year</u>
Fellow Eye	5%
Single Sham	5%

2 Braver DA, Richards RD and Good TA. Posterior Subcapsular Cataracts in Steroid Treated Children. *Arch Ophthalmol.* 1967;77:161-162.

Single Dex 700	6%
Single Dex 350	7%
Sham followed by Dex 700	9%
Dex 350 followed by Dex 700	17%
Dex 700 followed by Dex 700	26%

As noted above, there is a significant difference between a single treatment with Ozurdex and continued treatment with Ozurdex.

- c. The consequences of delaying treatment of diabetic macular edema may be permanent visual loss. While a portion of patients with diabetic macular edema will have spontaneous resolution of their edema, for those patients who do not resolve (either on their own or with alternative treatments), treatment to reduce the edema is important in preserving visual function. A delay, waiting to become aphakic/pseudophakic or a delay until a cataract forms risks permanent visual loss while waiting for the very adverse event which has been suggested to avoid. While it may avoid the association of the corticosteroid causing a cataract, it is not necessarily in the patient's best interest and may lead to permanent visual loss.
3. The Pregnancy section of the labeling should be revised. The ratios of systemic absorption proposed in the labeling by both the applicant and earlier Agency reviews appear to be inconsistent with the original published studies and should be deleted for the following reasons:
 - a. The proposed Pregnancy section is based on studies^{3,4} conducted using topically applied dexamethasone ophthalmic solution and (b) (4).
 - b. Assay methods available at the time these studies were conducted were not capable of detecting the low level of systemic absorption which occurs following topical administration of dexamethasone ophthalmic solution.
 - c. In the study of mice³, dosing was 0.001 milliliters (mL) using an Eppendorf pipet, five times per day on gestation days 10 through 13. Dexamethasone concentrations were 1.5, 7.5 and 15 mg/mL resulting in doses of 0.0075 mg/day, 0.0375 mg/day and 0.075 mg/day on the assigned days. A common dose in humans would be one drop, 4 times per day of dexamethasone at a concentration of 1 mg/mL, equivalent to 0.2 mg/day. Resorptions and cleft palates were noted in all groups.
 - d. In the study of rabbits⁴, dosing was one drop every hour for six hours on day 6 of gestation followed by one drop four times per day on days 7 through 18 of gestation. The standard dexamethasone ophthalmic solution, 1 mg/mL was administered. The

³ Ballard PD, Hearney EF, Smith MB. Comparative Teratogenicity of Selected Glucocorticoids Applied Ocularly in Mice. *Teratology*. 1977; 16:175-180.

⁴ Kasirsky G, Lombardi L. Comparative Teratogenic Study of Various Corticoid Ophthalmics. *Toxicology and Applied Pharmacology*. 1970; 16:773-778.

dose on the first day would have been 0.3 mg, the dose on the following day would be the same as a common human dose of 0.2 mg/day. Fetal anomalies were noted in 25% of the embryos.

e.

(b) (4)

the systemic route of administration instead of ocular administration and the findings in the mice and rabbits suggest that this study information is not helpful in the understanding of the potential teratogenicity of the dexamethasone administered ocularly.

4. The Contraindications section of the labeling should be revised.

(b) (4)

The Contraindication section should be re-written to combine these two contraindications as: "OZURDEX® is contraindicated in patients whose posterior lens capsule is not intact."

5. The Warnings section of the labeling should be revised. Section 5.2 identifies a number of potential consequences of using corticosteroids. The text includes "Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. [see Adverse Reactions (6.1)]. Some of these events have been reported with Ozurdex (posterior subcapsular cataracts, increased intraocular pressure) and some of the events have not been reported (secondary ocular infections due to bacteria or fungi). The Heading should be titled "Potential Steroid-related Effects" so that it is not implied that all of the events have necessarily occurred.
6. The Adverse Reaction section of the labeling should be revised. The Division has proposed two subsections, "Cataract and Cataract Surgery" and "Increased Intraocular Pressure." While "Cataracts" were a reported adverse event, "Cataract Surgery" is not an adverse event. I recommend deleting the references to Cataract Surgery, particularly the percentages because the decision to perform cataract surgery is dependent on a number of medical, social and financial considerations, not the severity of the cataract. To the extent that the labeling includes the management of adverse events, the outcome following cataract surgery would have been more important than the number of cataract operations performed.

The subsection "Increased Intraocular Pressure" includes a Table, "Summary of Elevated IOP Related Adverse Reactions." This Table includes a line for "Glaucoma" and "IOP

lowering procedure.” Glaucoma is one of the optic neuropathies which can occur. Elevated intraocular pressure is one of the contributing factors, but it is not the only factor particularly in patients with diabetes. The diagnosis of glaucoma is made following an evaluation of a number of ocular parameters. To my knowledge, none of the patients developed glaucoma during the study. Some of the patients developed clinical signs which will put them at risk for developing glaucoma, such as iris neovascularization. The number of patients listed on this line appears to be inaccurate for the number of patients who developed glaucoma and an undefined subset of the patients who are at risk for developing glaucoma. The term “Glaucoma” in this table should be removed because it is inaccurate and misleading. The line “IOP lowering procedure” should also be removed because it is inaccurate, not an adverse event and is poorly defined. The decision to perform an ocular procedure, including those to lower intraocular pressure is dependent on a number of medical, social and financial considerations, not just the severity of the IOP. Cataract surgery routinely lowers intraocular pressure, yet it was not included in this line.

Recommended labeling is listed on the following pages:

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

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

/s/

WILEY A CHAMBERS
06/19/2014

Deputy Division Director Review of NDA 22-315 S-009

Date	April 7, 2014
From	Wiley A. Chambers, M.D.
NDA #	22-315 SE1 009
Applicant	Allergan, Inc.
Date of Submission	June 13, 2013
Type of Application	505(b)(1)
Name	Ozurdex (dexamethasone intravitreal implant)
Dosage forms / Strength	Intravitreal implant
Proposed Indication(s)	Treatment of diabetic macular edema
Recommended Action:	Approval

1. Introduction/Background

The original New Drug Application (NDA) for this product, Ozurdex (dexamethasone intravitreal implant), was approved on June 17, 2009, for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). An efficacy supplement for the additional use of Ozurdex in the treatment of non-infectious uveitis affecting the posterior segment of the eye (intermediate and/or posterior uveitis) was approved on September 24, 2010. This supplement, S-009, is for an additional indication for the treatment of diabetic macular edema.

2. CMC/Sterility Assurance

The Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System is an intraocular drug delivery system. The active ingredient, dexamethasone, is a corticosteroid with anti-inflammatory activity. Dexamethasone is combined with biodegradable polymers and extruded into a small implant for delivery into the posterior segment of the eye through a specifically designed applicator.

The 700 µg DEX PS DDS Applicator System contains an extruded dosage form of 700 µg dexamethasone in an inactive biodegradable polymer matrix of poly [lactic glycolic] acid (PLGA) (b)(4). The extruded DEX PS DDS is composed of a biodegradable copolymer (PLGA) containing (b)(4) dexamethasone that is slowly released from the polymer. The extruded 700 µg DEX PS DDS is loaded in the applicator during manufacturing and provided as a sterile finished product.

The CMC information for this supplement remains unchanged from the CMC information originally approved for this drug product.

3. Nonclinical Pharmacology/Toxicology

Although no new non-clinical studies were submitted and no additional studies were considered needed to support this supplemental application, the Pharm/Tox reviewer has reviewed published literature and revised the nonclinical sections of the current labeling. The cited published literature did not include any studies with the particular drug product which is the subject of this NDA. From my prospective, the Pharm/Tox labeling for Ozurdex (dexamethasone intravitreal implant) currently in use is acceptable. If modified, the dose multiple should be based on a systemic absorption comparison.

4. Clinical Pharmacology/Biopharmaceutics

Pharmacokinetic plasma samples were collected from selected patients in studies 206207-010 and 206207-011. The pharmacokinetic results show that the majority plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ) of 0.05 ng/mL.

5. Clinical/Statistical - Efficacy

Two, 3-year, randomized, multicenter, sham-controlled trials were conducted to assess the safety and efficacy of the 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the treatment of patients with diabetic macular edema. Patients were randomized in a 1:1:1 ratio to receive DEX 700, DEX 350, or Sham. Approximately 500 patients were enrolled in each study. Study visits occurred every 1.5 months during the first year and every 3 months during years 2 and 3. Starting from the month 6 visit, patients were evaluated for re-treatment eligibility every 3 months, but the study procedure was not to be performed more often than approximately every 6 months. Post-injection safety visits, required only when patients received a treatment or re-treatment, were scheduled 1, 7, and 21 days after the day of treatment or re-treatment.

The original endpoint was amended to 39 months prior to the completion of the trial. The effect of the product was observed to wear off by six months after implantation in each of the indications. The applicant added an additional endpoint to the protocol to capture a period when the peak effect was occurring, i.e., Month 39. However, only a small number of patients remained in the trial at the point that the change was made. There are too few patients with Month 39 data to evaluate data based only on Month 39. Month 36 results are available for most patients, although this represents a period of minimal steroid effect.

The statistical review used only the Month 36 endpoint and set patients who received rescue treatment as failures. This represents a conservative analysis since the drug product was effectively gone. The results are shown below:

Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
011	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)

Source: Statistical Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

The analyses from Primary Medical Officer Review are based on final protocol and are shown below.

Study 206207-010: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	163	36 (22%)	166	31 (19%)	165	22 (13%)
% Difference (95% CI)	8.8 (0.5, 17.0)		5.3 (-2.5, 13.2)			
p-value	0.038 ^a		0.185 ^a			
PP with observed month 39 data only						
Final (36/39 months)	29	6 (21%)	34	8 (23%)	15	3 (20%)
% Difference (95% CI)	0.7 (-24.4, 25.7)		3.5 (-21.2, 28.3)			
p-value	> 0.999 ^b		> 0.999 ^b			
PP with LOCF						
Final (36/39 months)	144	35 (24%)	155	30 (19%)	143	21 (15%)
% Difference (95% CI)	9.6 (0.5, 18.7)		4.7 (-3.8, 13.2)			
p-value	0.040 ^a		0.285 ^a			

^a P-value was from Chi-square test

^b Fisher's Exact test is used.

Study 206207-011: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

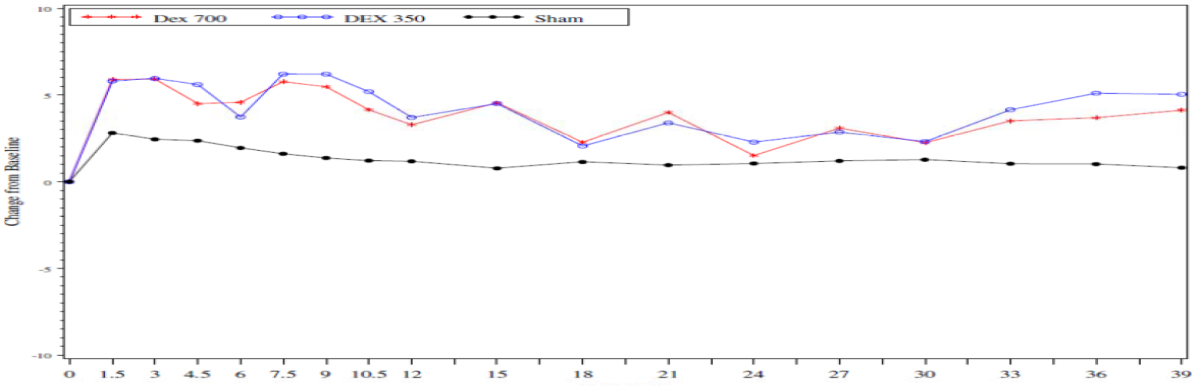
Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	188	42 (22%)	188	42 (22%)	185	20 (11%)
% Difference (95% CI)	11.5 (4.1, 19.0)		181			
p-value	0.003 ^a		0.044 ^a			
PP with observed month 39 data only						
Final (36/39 months)	22	10 (45%)	25	6 (24%)	22	7 (32%)
% Difference (95% CI)	13.6 (-14.9, 42.1)		-7.8 (-33.5, 17.9)			
p-value	0.353 ^a		0.550 ^a			
PP with LOCF						
Final (36/39 months)	170	41 (24%)	159	31 (19%)	162	20 (12%)
% Difference (95% CI)	11.8 (3.6, 20.0)		7.2 (-0.8, 15.1)			
p-value	0.006 ^a		0.080 ^a			

^a P-value was from Chi-square test.

These analyses demonstrate efficacy of the DEX 700 Treatment Group. As noted above, there were too few patients at Month 39, to evaluate the PP with observed month 39 data alone.

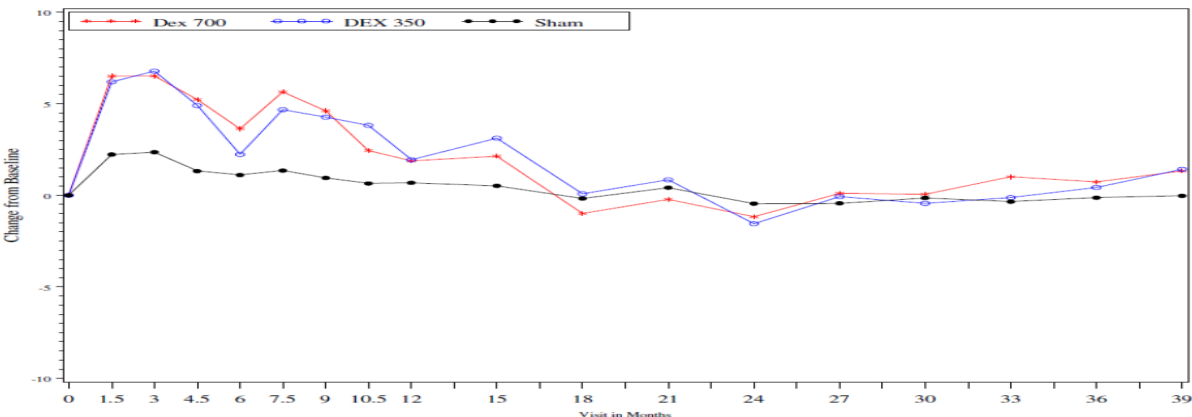
A better representation of the study results is shown in the graph displaying the mean visual acuity.

Plot of Mean Change from Baseline BCVA (Study 206207-010; ITT LOCF)



Source: Figure 11-1 of the applicant's submitted Study Reports. LOCF was used for imputing missing data.

Plot of Mean Change from Baseline BCVA (Study 206207-011; ITT LOCF)



Source:

Figure 11-1 of the applicant's submitted Study Reports. LOCF was used for imputing missing data.

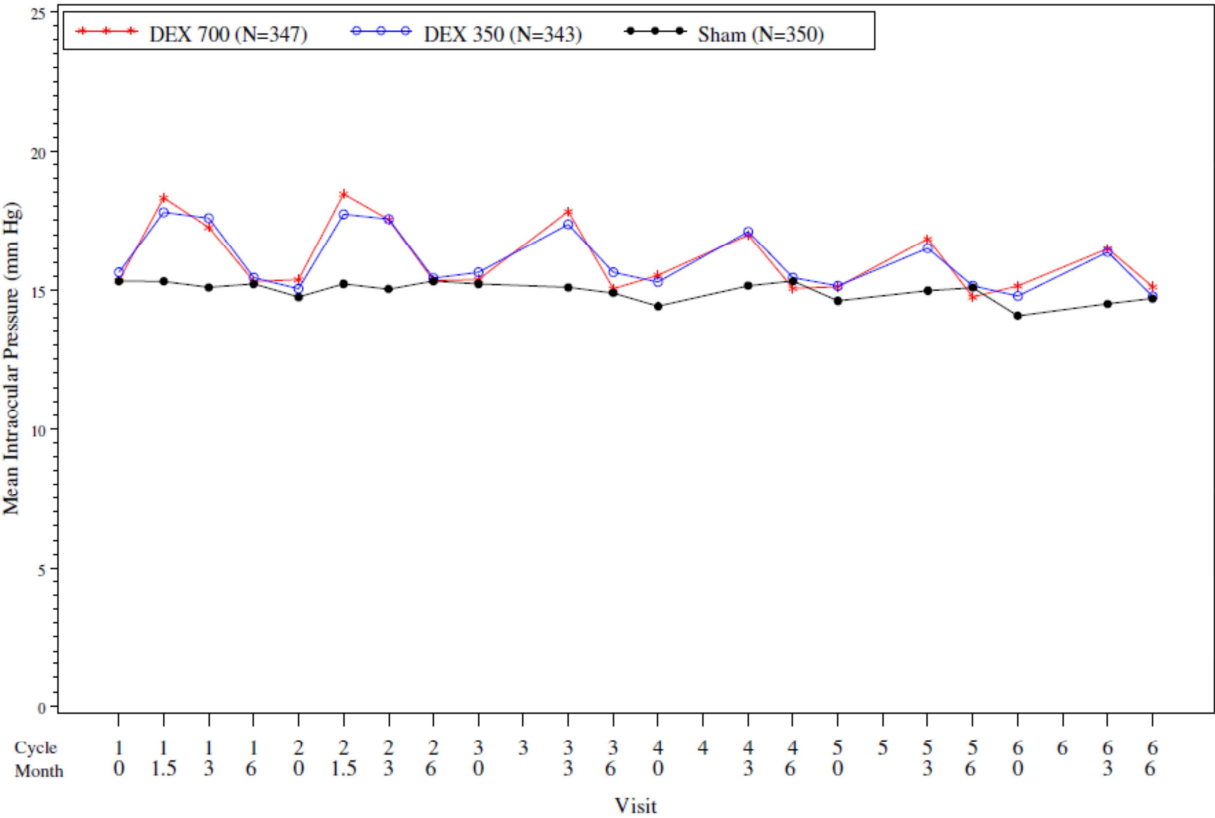
These graphs demonstrate the initial effect of Ozurdex on Best Corrected Visual Acuity (BCVA). In many patients, there is a maximum effect 3 months after implantation and then the effect wanes. Repeat injections at 6 months improve vision; however, repeat injections increase the chances for cataract development. The effect of cataract development is seen from month 15 through month 30. The combination of cataract removal and treatment for macular edema contributes to the general improvement in vision in the dexamethasone groups as the trial progresses.

One of the investigators (Dr. Sall) for one of the clinical trials (206207-11) employed an individual who could not be trusted. At the Agency's request, Allergan conducted an analysis of the primary efficacy variable for the 206207-011 study which excluded data from patients enrolled at Dr. Sall's site. The results as can be noted below were consistent with the results observed in the full ITT population. The p-values are slightly greater, the confidence intervals slightly wider, but this is to be expected with a reduced denominator.

	Dex 700	Dex 350	Sham	P value Dex 700 vs Sham	P-value Dex 350 vs Sham
Month 1.5	15/165 (9%)	18/158 (11%)	2/163 (1%)	0.001	<0.001
Month 3	18/165 (11%)	21/158 (13%)	5/163(3%)	0.005	<0.001
Month 4.5	19/165 (12%)	16/158 (10%)	7/163 (4%)	0.016	0.043
Month 6	14/165 (8%)	8/158 (5%)	6/163 (4%)	0.069	0.544
Month 7.5	21/165 (13%)	16/158 (10%)	14/163 (9%)	0.225	0.636
Month 9	22/165 (13%)	19/158 (12%)	12/163 (7%)	0.076	0.157
Month 10.5	21/165 (13%)	18/158 (11%)	15/163 (9%)	0.307	0.518
Month 12	20/165 (12%)	16/158 (10%)	17/163 (10%)	0.628	0.929
Month 15	20/165 (12%)	21/158 (13%)	16/163 (10%)	0.504	0.330
Month 18	18/165 (11%)	14/158 (9%)	14/163 (9%)	0.479	0.931
Month 21	23/165 (14%)	13/158 (8%)	16/163 (10%)	0.249	0.620
Month 24	30/165 (18%)	15/158 (10%)	16/163 (10%)	0.029	0.922
Month 27	26/165 (16%)	17/158 (11%)	16/163 (10%)	0.107	0.781
Month 30	30/165 (18%)	16/158 (10%)	16/163 (10%)	0.029	0.926
Month 33	32/165 (19%)	20/158 (13%)	15/163 (9%)	0.008	0.321
Month 36	29/165 (18%)	23/158 (15%)	17/163 (10%)	0.062	0.263
Month 39	34/165 (21%)	26/158 (16%)	17/163 (10%)	0.011	0.113

6. Safety

Corticosteroids are known to increase IOP, cause cataracts and decrease resistance to ocular infections. The graph below demonstrates the increase in IOP seen in some patients receiving the dexamethasone implants. The elevation in IOP is generally limited to a six month period. Repeat injections can be expected to contribute to repeat elevations in IOP.



The development of cataracts, particularly posterior sub-capsular cataracts following corticosteroid use, topical or systemic, has been known since the 1960s. It is known to be dose dependent [Donshik PC *et al.* Posterior subcapsular cataracts induced by topical corticosteroids following keratoplasty for keratoconus. *Ann Ophthalmol.* 1981 Jan; 13(1):29-32.]

**Common Adverse Events Occurring at an incidence 1% or Greater
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	333 (96.0)	334 (97.4)	281 (80.3)
<u>Blood and lymphatic system disorders</u>			
Overall	18 (5.2)	21 (6.1)	15 (4.3)
Anemia	14 (4.0)	18 (5.2)	12 (3.4)
<u>Cardiac disorders</u>			
Overall	35 (10.1)	51 (14.9)	33 (9.4)
Atrial fibrillation	7 (2.0)	3 (0.9)	4 (1.1)
Coronary artery disease	6 (1.7)	9 (2.6)	8 (2.3)
Cardiac failure congestive	4 (1.2)	10 (2.9)	3 (0.9)
Angina pectoris	4 (1.2)	3 (0.9)	3 (0.9)
Myocardial infarction	2 (0.6)	11 (3.2)	5 (1.4)
Myocardial ischemia	1 (0.3)	3 (0.9)	5 (1.4)
<u>Ear and labyrinth disorders</u>			
Overall	10 (2.9)	10 (2.9)	4 (1.1)
Vertigo	4 (1.2)	6 (1.7)	2 (0.6)
<u>Endocrine disorders</u>			
Overall	8 (2.3)	6 (1.7)	2 (0.6)
Hypothyroidism	4 (1.2)	3 (0.9)	2 (0.6)
<u>Eye disorders</u>			
Overall	296 (85.3)	302 (88.0)	223 (63.7)
Cataract	141 (40.6)	125 (36.4)	44 (12.6)
Conjunctival hemorrhage	76 (21.9)	93 (27.1)	45 (12.9)
Macular edema	51 (14.7)	42 (12.2)	36 (10.3)
Cataract subcapsular	45 (13.0)	43 (12.5)	16 (4.6)
Vitreous hemorrhage	40 (11.5)	67 (19.5)	36 (10.3)
Visual acuity reduced	33 (9.5)	41 (12.0)	18 (5.1)
Macular fibrosis	30 (8.6)	43 (12.5)	18 (5.1)
Diabetic retinal edema	27 (7.8)	27 (7.8)	21 (6.0)
Dry eye	23 (6.6)	20 (5.8)	11 (3.1)
Ocular hypertension	23 (6.6)	17 (5.0)	6 (1.7)
Conjunctivitis	23 (6.6)	15 (4.4)	10 (2.9)
Retinal hemorrhage	22 (6.3)	28 (8.2)	16 (4.6)
Conjunctival hyperemia	21 (6.1)	30 (8.7)	20 (5.7)
Cataract nuclear	21 (6.1)	16 (4.7)	10 (2.9)
Retinal exudates	20 (5.8)	19 (5.5)	21 (6.0)
Diabetic retinopathy	20 (5.8)	19 (5.5)	13 (3.7)
Eye pain	19 (5.5)	25 (7.3)	16 (4.6)
Vitreous detachment	19 (5.5)	24 (7.0)	12 (3.4)
Posterior capsule opacification	17 (4.9)	18 (5.2)	8 (2.3)
Conjunctival edema	17 (4.9)	17 (5.0)	4 (1.1)
Vitreous floaters	17 (4.9)	12 (3.5)	10 (2.9)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Lenticular opacities	17 (4.9)	11 (3.2)	5 (1.4)
Punctate keratitis	14 (4.0)	11 (3.2)	11 (3.1)
Retinal aneurysm	13 (3.7)	16 (4.7)	7 (2.0)
Retinal neovascularization	12 (3.5)	23 (6.7)	21 (6.0)
Cataract cortical	11 (3.2)	17 (5.0)	11 (3.1)
Vitreous opacities	11 (3.2)	5 (1.5)	5 (1.4)
Blepharitis	10 (2.9)	6 (1.7)	20 (5.7)
Lacrimation increased	8 (2.3)	10 (2.9)	9 (2.6)
Foreign body sensation in eyes	8 (2.3)	7 (2.0)	5 (1.4)
Vitreous adhesions	7 (2.0)	6 (1.7)	5 (1.4)
Corneal erosion	7 (2.0)	4 (1.2)	3 (0.9)
Eyelid ptosis	7 (2.0)	3 (0.9)	2 (0.6)
Keratitis	6 (1.7)	7 (2.0)	3 (0.0)
Vision blurred	6 (1.7)	6 (1.7)	4 (1.1)
Anterior chamber inflammation	6 (1.7)	2 (0.6)	0 (0.0)
Eyelid edema	5 (1.4)	5 (1.5)	2 (0.6)
Macular hole	5 (1.4)	5 (1.5)	1 (0.3)
Eye irritation	5 (1.4)	4 (1.2)	7 (2.0)
Visual impairment	5 (1.4)	4 (1.2)	4 (1.1)
Retinal tear	5 (1.4)	3 (0.9)	3 (0.9)
Glaucoma	4 (1.2)	7 (2.0)	0 (0.0)
Iris neovascularization	4 (1.2)	5 (1.5)	4 (1.1)
Open angle glaucoma	4 (1.2)	3 (0.9)	2 (0.6)
Iritis	4 (1.2)	2 (0.6)	1 (0.3)
Blepharochalasis	4 (1.2)	1 (0.3)	2 (0.6)
Optic nerve cupping	3 (0.9)	6 (1.7)	1 (0.3)
Eye pruritus	3 (0.9)	4 (1.2)	8 (2.3)
Cystoid macular edema	3 (0.9)	4 (1.2)	1 (0.3)
Conjunctivitis allergic	3 (0.9)	1 (0.3)	4 (1.1)
Macular cyst	2 (0.6)	0 (0.0)	4 (1.1)
<u>Gastrointestinal disorders</u>			
Overall	50 (14.4)	57 (16.6)	42 (12.0)
Nausea	10 (2.9)	7 (2.0)	4 (1.1)
Diarrhea	7 (2.0)	9 (2.6)	3 (0.9)
Vomiting	6 (1.7)	8 (2.3)	3 (0.9)
Gastro-esophageal reflux disease	6 (1.7)	7 (2.0)	8 (2.3)
Gastritis	6 (1.7)	1 (0.3)	2 (0.6)
Constipation	5 (1.4)	8 (2.3)	5 (1.4)
Abdominal pain	4 (1.2)	2 (0.6)	3 (0.9)
Dyspepsia	3 (0.9)	2 (0.6)	4 (1.1)
Gastric ulcer	1 (0.3)	4 (1.2)	1 (0.3)
<u>General disorders and administration site conditions</u>			
Overall	30 (8.6)	34 (9.9)	25 (7.1)
Edema peripheral	9 (2.6)	13 (3.8)	8 (2.3)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Pyrexia	6 (1.7)	6 (1.7)	4 (1.1)
Non-cardiac chest pain	5 (1.4)	1 (0.3)	2 (0.6)
<u>Hepatobiliary disorders</u>			
Overall	4 (1.2)	7 (2.0)	7 (2.0)
Cholelithiasis	3 (0.9)	1 (0.3)	4 (1.1)
<u>Immune system disorders</u>			
Overall	8 (2.3)	19 (2.9)	3 (0.9)
Drug hypersensitivity	4 (1.2)	4 (1.2)	2 (0.6)
Seasonal allergy	1 (0.3)	4 (1.2)	1 (0.3)
<u>Infections and infestations</u>			
Overall	116 (33.4)	111 (32.4)	93 (26.6)
Nasopharyngitis	18 (5.2)	14 (4.1)	22 (6.3)
Bronchitis	15 (4.3)	10 (2.9)	10 (2.9)
Urinary tract infection	13 (3.7)	16 (4.7)	11 (3.1)
Influenza	13 (3.7)	12 (3.5)	11 (3.1)
Upper respiratory tract infection	10 (2.9)	19 (5.5)	17 (4.9)
Cellulitis	10 (2.9)	5 (1.5)	3 (0.9)
Sinusitis	7 (2.0)	4 (1.2)	1 (0.3)
Pneumonia	5 (1.4)	6 (1.7)	2 (0.6)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)
Gastroenteritis	4 (1.2)	4 (1.2)	2 (0.6)
Conjunctivitis viral	4 (1.2)	2 (0.6)	1 (0.3)
Hordeolum	2 (0.6)	6 (1.7)	1 (0.3)
Localized infection	2 (0.6)	1 (0.3)	5 (1.4)
Osteomyelitis	1 (0.3)	4 (1.2)	2 (0.6)
Tooth infection	0 (0.0)	5 (1.5)	0 (0.0)
<u>Injury, poisoning and procedural complications</u>			
Overall	62 (17.9)	55 (16.0)	29 (8.3)
Fall	11 (3.2)	14 (4.1)	7 (2.0)
Corneal abrasion	10 (2.9)	11 (3.2)	6 (1.7)
Ligament sprain	5 (1.4)	6 (1.7)	0 (0.0)
Foreign body in eye	5 (1.4)	1 (0.3)	0 (0.0)
Laceration	4 (1.2)	2 (0.6)	0 (0.0)
Procedural pain	4 (1.2)	1 (0.3)	2 (0.6)
Foot fracture	3 (0.9)	5 (1.5)	0 (0.0)
Contusion	0 (0.0)	5 (1.5)	1 (0.3)
<u>Investigations</u>			
Overall	142 (40.9)	136 (39.7)	46 (13.1)
Intraocular pressure increased	116 (33.4)	113 (32.9)	23 (6.6)
Blood creatinine increased	13 (3.7)	11 (3.2)	11 (3.1)
Glycosylated hemoglobin increased	11 (3.2)	10 (2.9)	6 (1.7)
Blood glucose increased	4 (1.2)	3 (0.9)	3 (0.9)
Blood pressure increased	4 (1.2)	2 (0.6)	2 (0.6)
<u>Metabolism and nutrition disorders</u>			
Overall	54 (15.6)	71 (20.7)	43 (12.3)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Hypercholesterolemia	16 (4.6)	11 (3.2)	12 (3.4)
Diabetes mellitus	11 (3.2)	5 (1.5)	8 (2.3)
Dyslipidemia	7 (2.0)	8 (2.3)	5 (1.4)
Diabetes mellitus inadequate control	6 (1.7)	9 (2.6)	6 (1.7)
Hypoglycemia	6 (1.7)	8 (2.3)	7 (2.0)
Hyperlipidemia	5 (1.4)	6 (1.7)	2 (0.6)
Type 2 diabetes mellitus	5 (1.4)	6 (1.7)	2 (0.6)
Gout	4 (1.2)	2 (0.6)	0 (0.0)
Hyperkalemia	2 (0.6)	6 (1.7)	1 (0.3)
Dehydration	1 (0.3)	6 (1.7)	3 (0.9)
Hyponatremia	0 (0.0)	5 (1.5)	0 (0.0)
<u>Musculoskeletal and connective tissue disorders</u>			
Overall	51 (14.7)	44 (12.8)	41 (11.7)
Osteoarthritis	9 (2.6)	3 (0.9)	4 (1.1)
Arthritis	8 (2.3)	5 (1.5)	2 (0.6)
Back pain	7 (2.0)	8 (2.3)	4 (1.1)
Pain in extremity	7 (2.0)	4 (1.2)	5 (1.4)
Musculoskeletal pain	4 (1.2)	4 (1.2)	3 (0.9)
Arthralgia	3 (0.9)	5 (1.5)	4 (1.1)
Muscle spasms	2 (0.6)	2 (0.6)	6 (1.7)
Spinal column stenosis	2 (0.6)	2 (0.6)	4 (1.1)
<u>Neoplasms benign, malignant and unspecified (includes cysts and polyps)</u>			
Overall	24 (6.9)	16 (4.7)	15 (4.3)
<u>Nervous system disorders</u>			
Overall	60 (17.3)	50 (14.6)	37 (10.6)
Headache	12 (3.5)	11 (3.2)	9 (2.6)
Dizziness	6 (1.7)	8 (2.3)	7 (2.0)
Transient ischemic attack	6 (1.7)	3 (0.9)	1 (0.3)
Cerebrovascular accident	5 (1.4)	3 (0.9)	4 (1.1)
Syncope	4 (1.2)	6 (1.7)	2 (0.6)
Carpal tunnel syndrome	4 (1.2)	3 (0.9)	1 (0.3)
Paraesthesia	4 (1.2)	1 (0.3)	2 (0.6)
Convulsion	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic neuropathy	1 (0.3)	5 (1.5)	2 (0.6)
Carotid artery stenosis	1 (0.3)	4 (1.2)	2 (0.6)
<u>Psychiatric disorders</u>			
Overall	22 (6.3)	19 (5.5)	15 (4.3)
Depression	8 (2.3)	12 (3.5)	8 (2.3)
Insomnia	8 (2.3)	3 (0.9)	2 (0.6)
Anxiety	7 (2.0)	4 (1.2)	3 (0.9)
<u>Renal and urinary disorders</u>			
Overall	31 (8.9)	41 (12.0)	14 (4.0)
Renal failure chronic	6 (1.7)	11 (3.2)	3 (0.9)
Renal failure acute	6 (1.7)	9 (2.6)	3 (0.9)

System Organ Class Coded Adverse Event	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Renal failure	6 (1.7)	7 (2.0)	3 (0.9)
Renal impairment	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic nephropathy	0 (0.0)	4 (1.2)	1 (0.3)
<u>Reproductive system and breast disorders</u>			
Overall	12 (3.5)	6 (1.7)	4 (1.1)
Benign prostatic hyperplasia*	6 (2.9)	2 (1.0)	2 (0.9)
<u>Respiratory, thoracic and mediastinal disorders</u>			
Overall	28 (8.1)	49 (14.3)	16 (4.6)
Cough	4 (1.2)	13 (3.8)	2 (0.6)
Oropharyngeal pain	4 (1.2)	5 (1.5)	1 (0.3)
Sleep apnea syndrome	3 (0.9)	8 (2.3)	2 (0.6)
Dyspnea	3 (0.9)	5 (1.5)	4 (1.7)
Pleural effusion	0 (0.0)	4 (1.2)	3 (0.9)
<u>Skin and subcutaneous tissue disorders</u>			
Overall	24 (6.9)	22 (6.4)	20 (5.7)
Skin ulcer	4 (1.2)	4 (1.2)	2 (0.6)
<u>Surgical and medical procedures</u>			
Overall	5 (1.4)	3 (0.9)	1 (0.3)
<u>Vascular disorders</u>			
Overall	63 (18.2)	70 (20.4)	35 (10.0)
Hypertension	52 (15.0)	50 (14.6)	27 (7.7)
Hypotension	1 (0.3)	2 (0.6)	4 (1.1)

*Percentages based on the male population

The most common ocular adverse events were cataracts (68%), increased intraocular pressure/glaucoma (36%), conjunctival hemorrhage (22%), macular edema (15%), and vitreous hemorrhage (12%).

The most common non-ocular adverse events were hypertension (15%), hypercholesterolemia (5%), nasopharyngitis (5%), anemia (4%), bronchitis (4%), headache (4%), increased blood creatinine (4%), influenza (4%), and urinary tract infection (4%).

7. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

8. Pediatrics

In their June 13, 2013, submission, Allergan requested a full waiver of the pediatric assessment requirement of OZURDEX in patients (16 years of age or less) based on the fact that diabetic macular edema (DME) rarely occurs in this population. Because the pediatric patient population is so small, conducting the necessary studies would be impossible or highly impractical. The application was

reviewed by the clinical group and the Pediatric Review Committee, and a full waiver was granted for the diabetic macular edema indication.

Safety and effectiveness of Ozurdex in pediatric patients have not been established.

9. Other Relevant Regulatory Issues

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

10. Labeling

There is disagreement between members of the review team concerning the proposed labeling. The labeling included in this review has been sent to the applicant at the request of the Division Director of DTOP. I disagree with the proposed labeling. Specifically, I disagree with limiting the indication to patients who are pseudophakic or are phakic and scheduled for cataract surgery. The increased risk of developing cataracts is a known complication of using corticosteroid. The risk is known to increase with the duration of corticosteroid use. This risk was not considered to outweigh the potential benefits of using Ozurdex in the treatment of uveitis, nor was it considered to outweigh the potential benefits of using Ozurdex in the treatment of macular edema due to a vein occlusion. The risk of cataract development should not preclude using Ozurdex to treat diabetic macular edema. If multiple Ozurdex implants are implanted, patients can expect to develop cataracts, but that should be an informed choice.

I also disagree with the revised non-clinical sections. The review supporting the changes appears to be based on published reports which are not included in the submission. I believe that the comparison with Ozurdex should be based on a comparing the systemic absorption of the doses tested in animals and human systemic absorption. For example, the ocular dosing in rabbits would have been expected to produce a systemic level of approximately 6 ng/mL [*Drug Metabolism and Disposition*. 2011;39:1181–1187]. The maximal human plasma level measured was usually less than the minimal level of quantitation of 0.05 ng/mL. Even if the maximal systemic level measured in humans (0.1 ng/mL) is used for the calculation, the ratio is 60 fold instead of the 4 fold proposed.

11. Regulatory Action

I recommend that NDA 22-315 SE1 009, Ozurdex (dexamethasone intravitreal implant) be approved for the treatment of diabetic macular edema with labeling which differs from the labeling currently proposed by our Division.

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

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/s/

WILEY A CHAMBERS
04/07/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 22-315 SE1 009

Date	March 27, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-315 SE1 009
Applicant	Allergan, Inc.
Date of Submission	June 13, 2013
PDUFA Goal Date	April 13, 2013
Type of Application	505(b)(1)
Name	Ozurdex (dexamethasone intravitreal implant)
Dosage forms / Strength	Intravitreal implant
Proposed Indication(s)	Treatment of diabetic macular edema
Recommended:	Recommended for Approval

1. Introduction

The original New Drug Application (NDA) for this product, Ozurdex (dexamethasone intravitreal implant), was approved on June 17, 2009, for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Subsequently, Ozurdex was approved on September 24, 2010, for the treatment of non-infectious uveitis affecting the posterior segment of the eye (NDA 22-315/S-003).

Throughout this review, Ozurdex (dexamethasone intravitreal implant) may alternately be referred to as Dexamethasone intravitreal implant, Dexamethasone Posterior Segment Drug Delivery System, or DEX PS DDS Applicator System.

2. Background

This is a 505(b)(1) application.

The Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System is an intraocular drug delivery system. The active ingredient, dexamethasone, is a corticosteroid with anti-inflammatory activity. Dexamethasone is combined with biodegradable polymers and extruded into a small implant for delivery into the posterior segment of the eye through a specifically designed applicator.

The 700 µg DEX PS DDS Applicator System contains an extruded dosage form of 700 µg dexamethasone in an inactive biodegradable polymer matrix of poly [lactic glycolic] acid (PLGA) (b)(4). The extruded DEX PS DDS is composed of a biodegradable copolymer

(PLGA) containing (b) (4) dexamethasone that is slowly released from the polymer. The extruded 700 µg DEX PS DDS is loaded in the applicator during manufacturing and provided as a sterile finished product.

An End-of-Phase 2 (IND 58,663) was conducted on September 18, 2003, with Oculex, the original IND sponsor (the IND was transferred to Allergan on November 24, 2003) to discuss the development of Ozurdex for the treatment of persistent diabetic macular edema (DME). The Agency made the following key recommendations:

- The Agency prefers the use of the vehicle or an alternate dose in clinical trials. Despite the use of masked and unmasked investigators, the potential exists for the introduction of significant bias with sham injection alone. While not preferred, a sham was strongly discouraged unless there was more than one dose included.
- The macular edema seen in diabetes mellitus is sufficiently different in nature from acute macular edema so as to require replication of efficacy in 2 adequate and well-controlled trials.
- The primary efficacy endpoint should be the proportion of patients with BCVA improvement of 15 or more letters from baseline in the study eye at 36 months.
- Intent-to-treat (ITT) with last observation carried forward (LOCF) and the per-protocol with observed cases analyses for each protocol should be provided in the final study report.

On December 6, 2004, the initial protocols for the Phase 3 studies in DME were submitted to the IND, and then initiated in February 2005.

Fast Track status for the diabetic macular edema indication was granted by the Agency on January 10, 2005. Per the Agency letter: DEX PS DDS is intended for the treatment of a serious or life-threatening condition, namely persistent Diabetic Macular Edema; DEX PS DDS demonstrates the potential to address medical needs unmet by available treatments for Diabetic Macular Edema.

On September 30, 2011, in a briefing package submitted to the Agency in preparation for a Type-C meeting, Allergan proposed to change the primary efficacy endpoint to “BCVA average change from baseline during the study (AUC approach) in the study eye” for the 2 ongoing Phase 3 DME studies. The Agency responded on October 31, 2011, that the primary efficacy endpoint should remain “BCVA improvement of 15 or more letters from baseline at 3 years.”

Allergan submitted a pre-NDA briefing package on July 13, 2013. Responses to the pre-NDA meeting questions were provided to Allergan on August 8, 2013.

3. CMC

From the CMC Review finalized 11/26/2013:

This efficacy supplement provides for inclusion of an additional indication, treatment of diabetic macular edema. The company, per 21 CFR 25.31 (b) claims categorical exclusion from the requirement to prepare an Environmental Assessment for Ozurdex™ (dexamethasone intravitreal

implant). Per their request, approval of a supplemental NDA, will not increase the use of the active moiety and no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action. The applicant's request for categorical exclusion from environmental assessment is acceptable. There are no CMC changes in this supplement.

The reviewer recommended approval of this supplemental application from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical sections of the proposed label submitted by the applicant remained the same as those of the label for Ozurdex (dexamethasone intravitreal implant) currently in use. The non-clinical issues for DEX PS DDS were properly addressed and discussed in the original NDA 22-315. No new non-clinical information is submitted in the supplemental application.

From the Pharmacology/Toxicology Review finalized 3/12/2014:

PharmTox has recommended changes for sections 8 and 13 of Ozurdex label. Following are their revisions to these sections for NDA 22-315/S-009. As of the date of this review, discussion continues amongst the review team regarding dose/exposure multiples and communication of risk in Section 8.1.

(b) (4)



(b) (4)



5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 7/22/2013:

The applicant submitted this efficacy supplement to seek approval of Ozurdex 700 mcg for the treatment of diabetic macular edema (DME), based mainly on the clinical efficacy and safety findings of two multicenter, blinded, randomized, sham-controlled Phase 3 trials involving 1,048 DME patients who received up to 7 Ozurdex intravitreal injections during the 3-year study period. In a subset of DME patients in these two trials, plasma dexamethasone concentrations were measured up to 90 days following the administration of the first Ozurdex intravitreal injection. The applicant proposes to update *Section 12.3 Pharmacokinetics* of the Ozurdex® USPI with plasma PK data obtained from DME patients.

(b) (4)



6. Sterility Assurance

The CMC information for this supplement remains unchanged from the CMC information originally approved for this drug product.

7. Clinical/Statistical - Efficacy

The primary support for efficacy for DEX 700 comes from Studies 206207-0110 and 206207-011

From the original Medical Officer Review dated 3/18/2014:

The primary efficacy endpoint was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at the year 3 final assessment with missing values imputed by LOCF.

Analyses of Primary Endpoint:

Study 206207-010: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	163	36 (22.1)	166	31 (18.7)	165	22 (13.3)
% Difference (95% CI)	8.8 (0.5, 17.0)		5.3 (-2.5, 13.2)			
p-value	0.038 ^a		0.185 ^a			
PP with observed data only						
Final (36/39 months)	29	6 (20.7)	34	8 (23.5)	15	3 (20.0)
% Difference (95% CI)	0.7 (-24.4, 25.7)		3.5 (-21.2, 28.3)			
p-value	> 0.999 ^b		> 0.999 ^b			
PP with LOCF						
Final (36/39 months)	144	35 (24.3)	155	30 (19.4)	143	21 (14.7)
% Difference (95% CI)	9.6 (0.5, 18.7)		4.7 (-3.8, 13.2)			
p-value	0.040 ^a		0.285 ^a			

^a P-value was from Chi-square test.

^b Fisher's Exact test is used.

There was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months)¹ in patients treated with DEX 700 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.038$) and PP with LOCF population ($p=0.040$). Statistical difference was not seen in the PP with observed data only population due to the small sample size. A statistically significant difference was not seen in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 350 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.185$) and PP with LOCF population ($p=0.285$).

Study 206207-011: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	188	42 (22.3)	188	42 (22.3)	185	20 (10.8)
% Difference (95% CI)	11.5 (4.1, 19.0)		181			
p-value	0.003 ^a		0.044 ^a			
PP with observed data only						
Final (36/39 months)	22	10 (45.5)	25	6 (24.0)	22	7 (31.8)
% Difference (95% CI)	13.6 (-14.9, 42.1)		-7.8 (-33.5, 17.9)			
p-value	0.353 ^a		0.550 ^a			
PP with LOCF						
Final (36/39 months)	170	41 (24.1)	159	31 (19.5)	162	20 (12.3)
% Difference (95% CI)	11.8 (3.6, 20.0)		7.2 (-0.8, 15.1)			
p-value	0.006 ^a		0.080 ^a			

^a P-value was from Chi-square test.

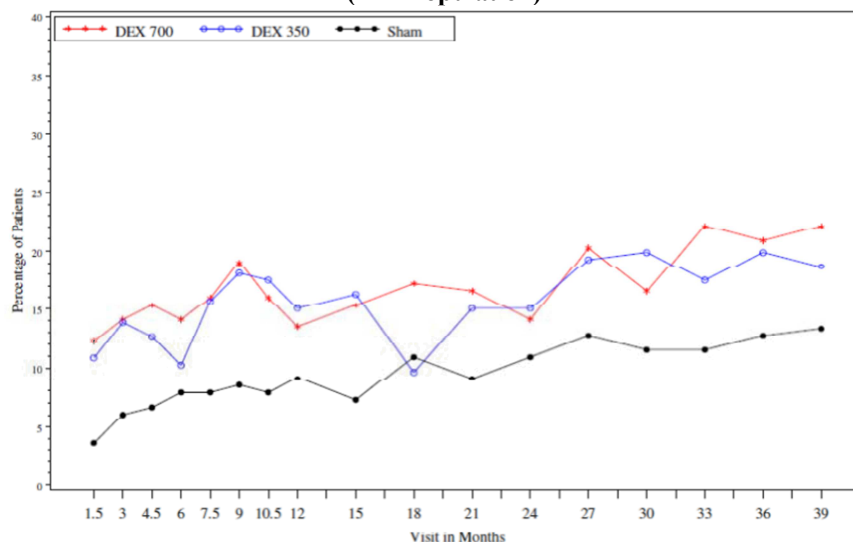
There was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 700 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.003$) and PP with LOCF population ($p=0.006$). Statistical difference was not seen in the PP with observed data only population due to the small sample size. There was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit

¹ In Amendment 4 (May 8, 2010) to Studies 206207-0110 and 206207-011, the primary analysis was changed to month 36 from month 24 to ensure that the cumulative risks and benefits to patients with diabetic macular edema would be best evaluated over a period of 3 years. Also, as per the Amendment 4, patients were allowed to receive a study treatment at month 36 as needed by retreatment criteria, and a month 39 visit was added to provide an assessment of efficacy and safety from any month 36 retreatment. By the time all sites received ethics committee approval to initiate Amendment 4, 52% (549/1048) of patients had either prematurely exited the study or completed the month 36 visit and exited the study. Only patients who were continued in the study and received injections at month 36 (following Amendment 4) continued to month 39. Thus the sample sizes for the month 39 timepoint are lower than those for the month 36 timepoint for the overall population.

The Statistical group has chosen not to utilize the primary efficacy variable specified in the Amendment 4 protocol revision which provided for re-treatment at Month 36 and follow-up at Month 39. Clinical disagrees with this approach. The amendment was not ad hoc and was consistent with Agency advice given at the September 30, 2011, Type C meeting.

(36/39 months) in patients treated with DEX 350 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.044$) but not in the PP with LOCF population ($p=0.080$).

Study 206207010: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye (ITT Population)

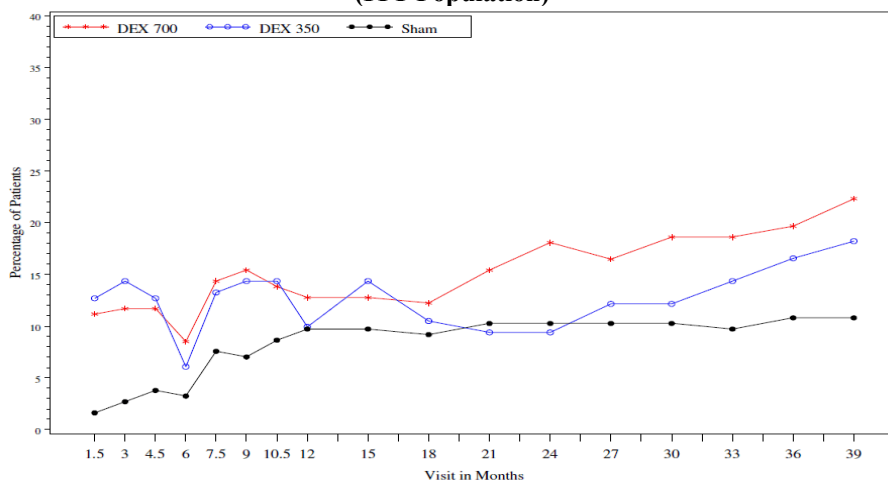


BCVA = best-corrected visual acuity; ITT = intent-to-treat

Note: Missing values are imputed by last observation carried forward at the follow-up visits

For Study 206207-010, the percentage of patients with ≥ 15 letters improvement from baseline generally increases at the beginning of each treatment cycle, peaks at 3 months post-treatment, and returns to baseline by month 6. The peak percentage of patients with ≥ 15 letters improvement from baseline appears to increase with each additional treatment cycle.

Study 206207011: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye (ITT Population)



BCVA = best-corrected visual acuity; ITT = intent-to-treat

Note: Missing values are imputed by last observation carried forward at the follow-up visits

The results for Study 206207-011 are similar to that of Study 206207-010.

Analyses of Primary Endpoint: Study 206207-011 w/o Investigator Sall

An information request dated November 12, 2013, was transmitted to the applicant. The applicant responded in an amendment dated November 20, 2013.

FDA Inquiry: Regarding Study 206207-011 and Investigator Kenneth Sall, M.D. (Site #100221 Investigator # 2707): We request an analysis of the primary efficacy variable for this trial with the subjects enrolled by Dr. Sall excluded. If there is a difference between the results of this analysis and analyses where Dr. Sall's subjects are included, we request that you provide an explanation.

Allergan Response: Allergan has conducted an analysis of the primary efficacy variable for the 206207-011 study which excluded data from patients enrolled at Dr. Sall's site. The primary efficacy analysis (proportion of patients with a BCVA improvement of 15 or more letters from baseline at final visit with missing value imputed by LOCF) showed a greater proportion of patients in the DEX 700 group experienced a BCVA improvement of ≥ 15 letters compared to Sham (20.6% vs. 10.4%). The results were statistically significant ($p=0.011$) and were consistent with the results observed in the full ITT population.

Table 2016.2 (page 1 of 3) BCVA 15 or More Letters Improvement from Baseline (ITT) LOCF Analysis (Intent-to-Treat Population: Study 206207-011 Excluding 68 Patients from Site 2707, Kenneth Sall)						
	DEX 700 (N=165)	DEX 350 (N=158)	Sham (N=163)	DEX 700 vs Sham P-value, Difference, (95% CI) [a]	DEX 350 vs Sham P-value, Difference, (95% CI) [a]	DEX 700 vs DEX 350 P-value, Difference, (95% CI) [a]
Month 1.5						
Yes	15/165 (9.1%)	18/158 (11.4%)	2/163 (1.2%)	0.001	<0.001	0.495
No	150/165 (90.9%)	140/158 (88.6%)	161/163 (98.8%)	7.9%	10.2%	-2.3%
				(3.2%, 12.6%)	(4.9%, 15.4%)	(-8.9%, 4.3%)
Month 3						
Yes	18/165 (10.9%)	21/158 (13.3%)	5/163 (3.1%)	0.005	<0.001	0.511
No	147/165 (89.1%)	137/158 (86.7%)	158/163 (96.9%)	7.8%	10.2%	-2.4%
				(2.4%, 13.3%)	(4.3%, 16.1%)	(-9.5%, 4.7%)
Month 4.5						
Yes	19/165 (11.5%)	16/158 (10.1%)	7/163 (4.3%)	0.016	0.043	0.688
No	146/165 (88.5%)	142/158 (89.9%)	156/163 (95.7%)	7.2%	5.8%	1.4%
				(1.4%, 13.0%)	(0.2%, 11.5%)	(-5.4%, 8.2%)
Month 6						
Yes	14/165 (8.5%)	8/158 (5.1%)	6/163 (3.7%)	0.069	0.544	0.222
No	151/165 (91.5%)	150/158 (94.9%)	157/163 (96.3%)	4.8%	1.4%	3.4%
				(-0.3%, 9.9%)	(-3.1%, 5.9%)	(-2.0%, 8.9%)
Month 7.5						
Yes	21/165 (12.7%)	16/158 (10.1%)	14/163 (8.6%)	0.225	0.636	0.463
No	144/165 (87.3%)	142/158 (89.9%)	149/163 (91.4%)	4.1%	1.5%	2.6%
				(-2.5%, 10.8%)	(-4.8%, 7.9%)	(-4.3%, 9.5%)
Month 9						
Yes	22/165 (13.3%)	19/158 (12.0%)	12/163 (7.4%)	0.076	0.157	0.724
No	143/165 (86.7%)	139/158 (88.0%)	151/163 (92.6%)	6.0%	4.7%	1.3%
				(-0.6%, 12.5%)	(-1.8%, 11.1%)	(-5.9%, 8.6%)

CDTL Review
William M. Boyd, M.D.
NDA 22-315 SE1 009
Ozurdex (dexamethasone intravitreal implant)

Table 2016.2 (page 2 of 3)
BCVA 15 or More Letters Improvement from Baseline (ITT)
LOCF Analysis
(Intent-to-Treat Population: Study 206207-011 Excluding 68 Patients from Site 2707, Kenneth Sall)

	DEX 700 (N=165)	DEX 350 (N=158)	Sham (N=163)	DEX 700 vs Sham P-value, Difference, (95% CI) [a]	DEX 350 vs Sham P-value, Difference, (95% CI) [a]	DEX 700 vs DEX 350 P-value, Difference, (95% CI) [a]
Month 10.5						
Yes	21/165 (12.7%)	18/158 (11.4%)	15/163 (9.2%)	0.307	0.518	0.713
No	144/165 (87.3%)	140/158 (88.6%)	148/163 (90.8%)	3.5%	2.2%	1.3%
				(-3.2%, 10.3%)	(-4.5%, 8.8%)	(-5.8%, 8.4%)
Month 12						
Yes	20/165 (12.1%)	16/158 (10.1%)	17/163 (10.4%)	0.628	0.929	0.569
No	145/165 (87.9%)	142/158 (89.9%)	146/163 (89.6%)	1.7%	-0.3%	2.0%
				(-5.2%, 8.5%)	(-6.9%, 6.3%)	(-4.9%, 8.8%)
Month 15						
Yes	20/165 (12.1%)	21/158 (13.3%)	16/163 (9.8%)	0.504	0.330	0.752
No	145/165 (87.9%)	137/158 (86.7%)	147/163 (90.2%)	2.3%	3.5%	-1.2%
				(-4.5%, 9.1%)	(-3.5%, 10.5%)	(-8.4%, 6.1%)
Month 18						
Yes	18/165 (10.9%)	14/158 (8.9%)	14/163 (8.6%)	0.479	0.931	0.538
No	147/165 (89.1%)	144/158 (91.1%)	149/163 (91.4%)	2.3%	0.3%	2.0%
				(-4.1%, 8.7%)	(-5.9%, 6.4%)	(-4.5%, 8.5%)
Month 21						
Yes	23/165 (13.9%)	13/158 (8.2%)	16/163 (9.8%)	0.249	0.620	0.103
No	142/165 (86.1%)	145/158 (91.8%)	147/163 (90.2%)	4.1%	-1.6%	5.7%
				(-2.9%, 11.1%)	(-7.9%, 4.7%)	(-1.1%, 12.5%)
Month 24						
Yes	30/165 (18.2%)	15/158 (9.5%)	16/163 (9.8%)	0.029	0.922	0.024
No	135/165 (81.8%)	143/158 (90.5%)	147/163 (90.2%)	8.4%	-0.3%	8.7%
				(0.9%, 15.8%)	(-6.8%, 6.1%)	(1.2%, 16.1%)

Table 2016.2 (page 3 of 3)
BCVA 15 or More Letters Improvement from Baseline (ITT)
LOCF Analysis
(Intent-to-Treat Population: Study 206207-011 Excluding 68 Patients from Site 2707, Kenneth Sall)

	DEX 700 (N=165)	DEX 350 (N=158)	Sham (N=163)	DEX 700 vs Sham P-value, Difference, (95% CI) [a]	DEX 350 vs Sham P-value, Difference, (95% CI) [a]	DEX 700 vs DEX 350 P-value, Difference, (95% CI) [a]
Month 27						
Yes	26/165 (15.8%)	17/158 (10.8%)	16/163 (9.8%)	0.107	0.781	0.186
No	139/165 (84.2%)	141/158 (89.2%)	147/163 (90.2%)	5.9%	0.9%	5.0%
				(-1.3%, 13.1%)	(-5.7%, 7.6%)	(-2.4%, 12.4%)
Month 30						
Yes	30/165 (18.2%)	16/158 (10.1%)	16/163 (9.8%)	0.029	0.926	0.038
No	135/165 (81.8%)	142/158 (89.9%)	147/163 (90.2%)	8.4%	0.3%	8.1%
				(0.9%, 15.8%)	(-6.2%, 6.9%)	(0.5%, 15.6%)
Month 33						
Yes	32/165 (19.4%)	20/158 (12.7%)	15/163 (9.2%)	0.008	0.321	0.100
No	133/165 (80.6%)	138/158 (87.3%)	148/163 (90.8%)	10.2%	3.5%	6.7%
				(2.7%, 17.7%)	(-3.4%, 10.3%)	(-1.2%, 14.7%)
Month 36						
Yes	29/165 (17.6%)	23/158 (14.6%)	17/163 (10.4%)	0.062	0.263	0.461
No	136/165 (82.4%)	135/158 (85.4%)	146/163 (89.6%)	7.1%	4.1%	3.0%
				(-0.3%, 14.6%)	(-3.1%, 11.4%)	(-5.0%, 11.0%)
Month 39/Final						
Yes	34/165 (20.6%)	26/158 (16.5%)	17/163 (10.4%)	0.011	0.113	0.338
No	131/165 (79.4%)	132/158 (83.5%)	146/163 (89.6%)	10.2%	6.0%	4.2%
				(2.4%, 17.9%)	(-1.4%, 13.5%)	(-4.3%, 12.6%)

Note: Missing values are imputed by last observation carried forward at the follow-up visits.

[a] P-value was from Chi-square test. Treatment group difference: DEX 700 - Sham, DEX 350 - Sham, DEX 700 - DEX 350. The 95% confidence intervals were constructed using normal approximation for binary variables.

After removal of Investigator Sall from the 206207-011 study, the results are still statistically significant.

Analyses of Primary Endpoint: Pseudophakic Patients

Analyses of the pooled subgroup of subjects with a pseudophakic study eye at baseline were performed for the primary efficacy endpoint, secondary and other endpoints.

Efficacy Results in the Study Eye of Pseudophakic Patients (Studies 206207-010 and 206207-011 Pooled, ITT Population)

Variable/timepoint	DEX 700 (N = 86)	DEX 350 (N = 88)	Sham (N = 101)	P-value ^a	
				DEX 700 vs Sham	DEX 350 vs Sham
Mean BCVA average change from baseline (AUC) during the study (letters)	6.5	5.9	1.7	< 0.001	< 0.001
BCVA \geq 15 letters improvement from baseline at year 3/final visit(%)	23.3	15.9	10.9	0.024	0.329
Mean percent of visits with BCVA \geq 15 letters improvement during the study (%)	21.2	17.1	7.6	< 0.001	< 0.001
Time to BCVA \geq 15 letters improvement (cumulative rate at year 3/final visit [%])	57.4	43.7	26.3	< 0.001	0.005
Mean OCT retinal thickness at center subfield average change from baseline (AUC) during the study (μ m)	-131.8	-117.1	-50.8	< 0.001	< 0.001

μ m = microns; AUC = area under the curve; BCVA = best-corrected visual acuity; OCT = optical coherence tomography

^a P-value is based on ANCOVA with treatment and study as factors and baseline as covariate for the analyses of mean average change; CMH general association test stratified by study for mean percent of patients with BCVA \geq 15 letters improvement; Wilcoxon rank-sum test for analyses of mean percent of visits; and log-rank test for time to event analysis.

For the pooled pseudophakic subpopulation (N=275) from Studies 206207-010 and 206207-011, there was a statistically significant difference in the proportion of patients with \geq 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in the patients treated with DEX 700 (p=0.024), but not in the patients treated with DEX 350 (p=0.329) as compared to patients treated with Sham in the ITT population.

Efficacy Summary Statement

The adequate and well controlled studies 206207-0110 and 206207-011 support the efficacy of Ozurdex (dexamethasone intravitreal implant) in the treatment of diabetic macular edema. There was a statistically significant difference in the proportion of patients with \geq 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 700 as compared to patients treated with Sham in the ITT with LOCF population.

After removal of Investigator Sall from the 206207-011 study, the results are still statistically significant.

8. Safety

From the original Medical Officer Review dated 3/18/2014:

The safety data from the two phase 3 studies (Studies 206207-010 and 206207-011) and the two phase 2 studies (Studies 206207-012 and 206207-018) were evaluated to assess safety. The safety data from studies 206207-010 and 206207-011 was pooled into the Integrated Safety Analysis Population to provide overall incidence of adverse events for each treatment group.

Overall Exposure at Appropriate Doses/Durations

A total of 527 patients were exposed to DEX 700 during the conduct of studies 206207-010 (160 patients), 206207-011 (187 patients), 206207-012 (125 patients), and 206207-018 (55).

Exposure in Study Treatment (Studies 206207-010 and 206207-011, Safety Population)

Study Treatment	DEX 700 (N=347)	DEX 350 (N=343)	Sham (N=350)
Cumulative Number (%) of Patients Receiving Study Treatment(s)			
≥ 1 Treatment	347 (100.0)	343 (100.0)	350 (100.0)
≥ 2 Treatments	303 (87.3)	309 (90.1)	244 (69.7)
≥ 3 Treatments	249 (71.8)	264 (77.0)	181 (51.7)
≥ 4 Treatments	210 (60.5)	223 (65.0)	140 (40.0)
≥ 5 Treatments	168 (48.4)	183 (53.4)	114 (32.6)
≥ 6 Treatments	119 (34.3)	142 (41.4)	85 (24.3)
7 Treatments	31 (8.9)	37 (10.8)	35 (10.0)
Number (%) of Patients Who Received 1-7 Treatments			
1 Treatment	44 (12.7)	34 (9.9)	106 (40.3)
2 Treatment	54 (15.6)	45 (13.1)	63 (18.0)
3 Treatment	39 (11.2)	41 (12.0)	41 (11.7)
4 Treatment	42 (12.1)	40 (11.7)	26 (7.4)
5 Treatment	49 (14.1)	41 (12.0)	29 (8.3)
6 Treatment	88 (25.4)	105 (30.6)	50 (14.3)
7 Treatment	31 (8.9)	37 (10.8)	35 (10.0)
Cumulative (Number of Patients [%]) and Average Study Duration of Exposure			
≥ 6 months	339 (97.7)	335 (97.7)	304 (86.9)
≥ 12 months	304 (87.6)	314 (91.5)	242 (69.1)
≥ 18 months	278 (80.1)	295 (86.0)	199 (56.9)
≥ 24 months	261 (75.2)	269 (78.4)	176 (50.3)
≥ 30 months	252 (69.7)	253 (73.8)	164 (46.9)
≥ 36 months	139 (40.1)	145 (42.3)	93 (26.6)
≥ 39 months	18 (5.2)	16 (4.7)	11 (3.1)
Mean Number of Treatments/Patient	4.1	4.4	3.3

There was adequate study drug exposure to assess the safety of this drug.

Subject Disposition

Study 206207-010: Subject Disposition and Primary Reason for Discontinuation (ITT Population)

Disposition and Discontinuation	DEX 700 n (%)	DEX 350 n (%)	Sham n (%)	Total n (%)
Total Randomized	163 ^a	166 ^b	165 ^c	494
Treated	160	165	164	489
As randomized	160 (98.2)	165 (99.4)	164 (99.4)	489 (99.0)
Never received treatment	3 (1.8)	1 (0.6)	1 (0.6)	5 (1.0)
ITT Population	163	166	165	494
Completed	107 (65.6)	118 (71.1)	70 (42.4)	295 (59.7)
Discontinued	56 (34.4)	48 (28.9)	95 (57.6)	199 (40.3)
Primary reason for Discontinuation (ITT Population)				
Adverse event	20 (12.3)	18 (10.8)	16 (9.7)	54 (10.9)
Ocular	10 (6.1)	10 (6.0)	13 (7.9)	33 (6.7)
Non-ocular	10 (6.1)	8 (4.8)	3 (1.8)	21 (4.3)
Lack of efficacy	9 (5.5)	14 (8.4)	37 (22.4)	60 (12.1)
Lost to follow-up	5 (3.1)	5 (3.0)	10 (6.1)	20 (4.0)
Personal reasons	7 (4.3)	4 (2.4)	16 (9.7)	27 (5.5)
Protocol violation	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.4)
Other ^d	13 (8.0)	7 (4.2)	16 (9.7)	36 (7.3)
Per Protocol (PP) Population	144	155	143	442
Completed	98 (68.1)	112 (72.3)	61 (42.7)	271 (61.3)
Discontinued	46 (31.9)	43 (27.7)	82 (57.3)	171 (38.7)
Safety Population	160	165	164	489
Completed	107 (66.9)	118 (71.5)	70 (42.7)	295 (60.3)
Discontinued	53 (33.1)	47 (28.5)	94 (57.3)	194 (39.7)

ITT=intent-to-treat

^a Three patients were randomized to DEX 700 but never received treatment.

^b One patient was randomized to DEX 350 but never received treatment.

^c One patient was randomized to Sham but never received treatment.

^d "Other" reasons for discontinuation included site closure, patient withdrawal of consent, poor compliance from patient, sponsor request, patient participation in other trial, etc.

**Study 206207-011: Subject Disposition and Primary Reason for Discontinuation
(ITT Population)**

Disposition and Discontinuation	DEX 700 n (%)	DEX 350 n (%)	Sham n (%)	Total n (%)
Total Randomized	188 ^a	181 ^{b,c}	185 ^c	554
Treated	187	178	186	551
As randomized	187 (99.5)	178 (99.4)	185 (100.0)	550 (99.3)
Never received treatment	1 (0.5)	3 (1.6)	0 (0.0)	4 (0.7)
ITT Population	188	181	185	554
Completed	118 (62.8)	112 (61.9)	82 (44.3)	312 (56.3)
Discontinued	70 (37.2)	69 (38.1)	103 (55.7)	242 (43.7)
Primary reason for Discontinuation (ITT Population)				
Adverse event	25 (13.3)	30 (16.6)	23 (12.4)	78 (14.1)
Ocular	18 (9.6)	18 (9.9)	14 (7.6)	50 (9.0)
Non-ocular	7 (3.7)	12 (6.6)	9 (4.9)	28 (5.1)
Lack of efficacy	14 (7.4)	11 (6.1)	47 (25.4)	72 (13.0)
Lost to follow-up	6 (3.2)	7 (3.9)	8 (4.3)	21 (3.8)
Personal reasons	7 (3.7)	6 (3.3)	10 (5.4)	23 (4.2)
Protocol violation	1 (0.5)	3 (1.7)	1 (0.5)	5 (0.9)
Other ^d	17 (9.0)	12 (6.6)	14 (7.6)	43 (7.8)
Per Protocol (PP) Population	170	159	162	491
Completed	114 (67.1)	106 (66.7)	76 (46.9)	296 (60.3)
Discontinued	56 (32.9)	53 (33.3)	86 (53.1)	195 (39.7)
Safety Population	187	178	186	551
Completed	118 (63.1)	112 (62.9)	82 (44.1)	312 (56.6)
Discontinued	69 (36.9)	66 (37.1)	104 (55.9)	239 (43.4)

ITT=intent-to-treat

^a One patient was randomized to DEX 700 but never received treatment.

^b Two patient were randomized to DEX 350 but never received treatment.

^c One patient was randomized to DEX 350 but actually received Sham. This patient discontinued the study due to a serious AE of macular fibrosis after Sham treatment. The patient is counted in the DEX 350 group for analyses based on the ITT population and in the Sham group for analyses based on the safety population.

^d "Other" reasons for discontinuation included site closure, patient withdrawal of consent, patient relocation, etc.

Adverse Events

Common Adverse Events Occurring at an incidence 1% or Greater (Studies 206207-010 and 206207-011 Pooled, Safety Population)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	333 (96.0)	334 (97.4)	281 (80.3)
<u>Blood and lymphatic system disorders</u>			
Overall	18 (5.2)	21 (6.1)	15 (4.3)
Anemia	14 (4.0)	18 (5.2)	12 (3.4)
<u>Cardiac disorders</u>			
Overall	35 (10.1)	51 (14.9)	33 (9.4)
Atrial fibrillation	7 (2.0)	3 (0.9)	4 (1.1)
Coronary artery disease	6 (1.7)	9 (2.6)	8 (2.3)
Cardiac failure congestive	4 (1.2)	10 (2.9)	3 (0.9)
Angina pectoris	4 (1.2)	3 (0.9)	3 (0.9)
Myocardial infarction	2 (0.6)	11 (3.2)	5 (1.4)
Myocardial ischemia	1 (0.3)	3 (0.9)	5 (1.4)
<u>Ear and labyrinth disorders</u>			
Overall	10 (2.9)	10 (2.9)	4 (1.1)
Vertigo	4 (1.2)	6 (1.7)	2 (0.6)
<u>Endocrine disorders</u>			
Overall	8 (2.3)	6 (1.7)	2 (0.6)
Hypothyroidism	4 (1.2)	3 (0.9)	2 (0.6)
<u>Eye disorders</u>			
Overall	296 (85.3)	302 (88.0)	223 (63.7)
Cataract	141 (40.6)	125 (36.4)	44 (12.6)
Conjunctival hemorrhage	76 (21.9)	93 (27.1)	45 (12.9)
Macular edema	51 (14.7)	42 (12.2)	36 (10.3)
Cataract subcapsular	45 (13.0)	43 (12.5)	16 (4.6)
Vitreous hemorrhage	40 (11.5)	67 (19.5)	36 (10.3)
Visual acuity reduced	33 (9.5)	41 (12.0)	18 (5.1)
Macular fibrosis	30 (8.6)	43 (12.5)	18 (5.1)
Diabetic retinal edema	27 (7.8)	27 (7.8)	21 (6.0)
Dry eye	23 (6.6)	20 (5.8)	11 (3.1)
Ocular hypertension	23 (6.6)	17 (5.0)	6 (1.7)
Conjunctivitis	23 (6.6)	15 (4.4)	10 (2.9)
Retinal hemorrhage	22 (6.3)	28 (8.2)	16 (4.6)
Conjunctival hyperemia	21 (6.1)	30 (8.7)	20 (5.7)
Cataract nuclear	21 (6.1)	16 (4.7)	10 (2.9)
Retinal exudates	20 (5.8)	19 (5.5)	21 (6.0)
Diabetic retinopathy	20 (5.8)	19 (5.5)	13 (3.7)
Eye pain	19 (5.5)	25 (7.3)	16 (4.6)
Vitreous detachment	19 (5.5)	24 (7.0)	12 (3.4)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Posterior capsule opacification	17 (4.9)	18 (5.2)	8 (2.3)
Conjunctival edema	17 (4.9)	17 (5.0)	4 (1.1)
Vitreous floaters	17 (4.9)	12 (3.5)	10 (2.9)
Lenticular opacities	17 (4.9)	11 (3.2)	5 (1.4)
Punctate keratitis	14 (4.0)	11 (3.2)	11 (3.1)
Retinal aneurysm	13 (3.7)	16 (4.7)	7 (2.0)
Retinal neovascularization	12 (3.5)	23 (6.7)	21 (6.0)
Cataract cortical	11 (3.2)	17 (5.0)	11 (3.1)
Vitreous opacities	11 (3.2)	5 (1.5)	5 (1.4)
Blepharitis	10 (2.9)	6 (1.7)	20 (5.7)
Lacrimation increased	8 (2.3)	10 (2.9)	9 (2.6)
Foreign body sensation in eyes	8 (2.3)	7 (2.0)	5 (1.4)
Vitreous adhesions	7 (2.0)	6 (1.7)	5 (1.4)
Corneal erosion	7 (2.0)	4 (1.2)	3 (0.9)
Eyelid ptosis	7 (2.0)	3 (0.9)	2 (0.6)
Keratitis	6 (1.7)	7 (2.0)	3 (0.0)
Vision blurred	6 (1.7)	6 (1.7)	4 (1.1)
Anterior chamber inflammation	6 (1.7)	2 (0.6)	0 (0.0)
Eyelid edema	5 (1.4)	5 (1.5)	2 (0.6)
Macular hole	5 (1.4)	5 (1.5)	1 (0.3)
Eye irritation	5 (1.4)	4 (1.2)	7 (2.0)
Visual impairment	5 (1.4)	4 (1.2)	4 (1.1)
Retinal tear	5 (1.4)	3 (0.9)	3 (0.9)
Glaucoma	4 (1.2)	7 (2.0)	0 (0.0)
Iris neovascularization	4 (1.2)	5 (1.5)	4 (1.1)
Open angle glaucoma	4 (1.2)	3 (0.9)	2 (0.6)
Iritis	4 (1.2)	2 (0.6)	1 (0.3)
Blepharochalasis	4 (1.2)	1 (0.3)	2 (0.6)
Optic nerve cupping	3 (0.9)	6 (1.7)	1 (0.3)
Eye pruritus	3 (0.9)	4 (1.2)	8 (2.3)
Cystoid macular edema	3 (0.9)	4 (1.2)	1 (0.3)
Conjunctivitis allergic	3 (0.9)	1 (0.3)	4 (1.1)
Macular cyst	2 (0.6)	0 (0.0)	4 (1.1)
<u>Gastrointestinal disorders</u>			
Overall	50 (14.4)	57 (16.6)	42 (12.0)
Nausea	10 (2.9)	7 (2.0)	4 (1.1)
Diarrhea	7 (2.0)	9 (2.6)	3 (0.9)
Vomiting	6 (1.7)	8 (2.3)	3 (0.9)
Gastro-esophageal reflux disease	6 (1.7)	7 (2.0)	8 (2.3)
Gastritis	6 (1.7)	1 (0.3)	2 (0.6)
Constipation	5 (1.4)	8 (2.3)	5 (1.4)
Abdominal pain	4 (1.2)	2 (0.6)	3 (0.9)
Dyspepsia	3 (0.9)	2 (0.6)	4 (1.1)
Gastric ulcer	1 (0.3)	4 (1.2)	1 (0.3)
<u>General disorders and administration site</u>			

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
<u>conditions</u>			
Overall	30 (8.6)	34 (9.9)	25 (7.1)
Edema peripheral	9 (2.6)	13 (3.8)	8 (2.3)
Pyrexia	6 (1.7)	6 (1.7)	4 (1.1)
Non-cardiac chest pain	5 (1.4)	1 (0.3)	2 (0.6)
<u>Hepatobiliary disorders</u>			
Overall	4 (1.2)	7 (2.0)	7 (2.0)
Cholelithiasis	3 (0.9)	1 (0.3)	4 (1.1)
<u>Immune system disorders</u>			
Overall	8 (2.3)	19 (2.9)	3 (0.9)
Drug hypersensitivity	4 (1.2)	4 (1.2)	2 (0.6)
Seasonal allergy	1 (0.3)	4 (1.2)	1 (0.3)
<u>Infections and infestations</u>			
Overall	116 (33.4)	111 (32.4)	93 (26.6)
Nasopharyngitis	18 (5.2)	14 (4.1)	22 (6.3)
Bronchitis	15 (4.3)	10 (2.9)	10 (2.9)
Urinary tract infection	13 (3.7)	16 (4.7)	11 (3.1)
Influenza	13 (3.7)	12 (3.5)	11 (3.1)
Upper respiratory tract infection	10 (2.9)	19 (5.5)	17 (4.9)
Cellulitis	10 (2.9)	5 (1.5)	3 (0.9)
Sinusitis	7 (2.0)	4 (1.2)	1 (0.3)
Pneumonia	5 (1.4)	6 (1.7)	2 (0.6)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)
Gastroenteritis	4 (1.2)	4 (1.2)	2 (0.6)
Conjunctivitis viral	4 (1.2)	2 (0.6)	1 (0.3)
Hordeolum	2 (0.6)	6 (1.7)	1 (0.3)
Localized infection	2 (0.6)	1 (0.3)	5 (1.4)
Osteomyelitis	1 (0.3)	4 (1.2)	2 (0.6)
Tooth infection	0 (0.0)	5 (1.5)	0 (0.0)
<u>Injury, poisoning and procedural complications</u>			
Overall	62 (17.9)	55 (16.0)	29 (8.3)
Fall	11 (3.2)	14 (4.1)	7 (2.0)
Corneal abrasion	10 (2.9)	11 (3.2)	6 (1.7)
Ligament sprain	5 (1.4)	6 (1.7)	0 (0.0)
Foreign body in eye	5 (1.4)	1 (0.3)	0 (0.0)
Laceration	4 (1.2)	2 (0.6)	0 (0.0)
Procedural pain	4 (1.2)	1 (0.3)	2 (0.6)
Foot fracture	3 (0.9)	5 (1.5)	0 (0.0)
Contusion	0 (0.0)	5 (1.5)	1 (0.3)
<u>Investigations</u>			
Overall	142 (40.9)	136 (39.7)	46 (13.1)
Intraocular pressure increased	116 (33.4)	113 (32.9)	23 (6.6)
Blood creatinine increased	13 (3.7)	11 (3.2)	11 (3.1)
Glycosylated hemoglobin increased	11 (3.2)	10 (2.9)	6 (1.7)
Blood glucose increased	4 (1.2)	3 (0.9)	3 (0.9)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Blood pressure increased	4 (1.2)	2 (0.6)	2 (0.6)
<u>Metabolism and nutrition disorders</u>			
Overall	54 (15.6)	71 (20.7)	43 (12.3)
Hypercholesterolemia	16 (4.6)	11 (3.2)	12 (3.4)
Diabetes mellitus	11 (3.2)	5 (1.5)	8 (2.3)
Dyslipidemia	7 (2.0)	8 (2.3)	5 (1.4)
Diabetes mellitus inadequate control	6 (1.7)	9 (2.6)	6 (1.7)
Hypoglycemia	6 (1.7)	8 (2.3)	7 (2.0)
Hyperlipidemia	5 (1.4)	6 (1.7)	2 (0.6)
Type 2 diabetes mellitus	5 (1.4)	6 (1.7)	2 (0.6)
Gout	4 (1.2)	2 (0.6)	0 (0.0)
Hyperkalemia	2 (0.6)	6 (1.7)	1 (0.3)
Dehydration	1 (0.3)	6 (1.7)	3 (0.9)
Hyponatremia	0 (0.0)	5 (1.5)	0 (0.0)
<u>Musculoskeletal and connective tissue disorders</u>			
Overall	51 (14.7)	44 (12.8)	41 (11.7)
Osteoarthritis	9 (2.6)	3 (0.9)	4 (1.1)
Arthritis	8 (2.3)	5 (1.5)	2 (0.6)
Back pain	7 (2.0)	8 (2.3)	4 (1.1)
Pain in extremity	7 (2.0)	4 (1.2)	5 (1.4)
Musculoskeletal pain	4 (1.2)	4 (1.2)	3 (0.9)
Arthralgia	3 (0.9)	5 (1.5)	4 (1.1)
Muscle spasms	2 (0.6)	2 (0.6)	6 (1.7)
Spinal column stenosis	2 (0.6)	2 (0.6)	4 (1.1)
<u>Neoplasms benign, malignant and unspecified (includes cysts and polyps)</u>			
Overall	24 (6.9)	16 (4.7)	15 (4.3)
<u>Nervous system disorders</u>			
Overall	60 (17.3)	50 (14.6)	37 (10.6)
Headache	12 (3.5)	11 (3.2)	9 (2.6)
Dizziness	6 (1.7)	8 (2.3)	7 (2.0)
Transient ischemic attack	6 (1.7)	3 (0.9)	1 (0.3)
Cerebrovascular accident	5 (1.4)	3 (0.9)	4 (1.1)
Syncope	4 (1.2)	6 (1.7)	2 (0.6)
Carpal tunnel syndrome	4 (1.2)	3 (0.9)	1 (0.3)
Paraesthesia	4 (1.2)	1 (0.3)	2 (0.6)
Convulsion	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic neuropathy	1 (0.3)	5 (1.5)	2 (0.6)
Carotid artery stenosis	1 (0.3)	4 (1.2)	2 (0.6)
<u>Psychiatric disorders</u>			
Overall	22 (6.3)	19 (5.5)	15 (4.3)
Depression	8 (2.3)	12 (3.5)	8 (2.3)
Insomnia	8 (2.3)	3 (0.9)	2 (0.6)
Anxiety	7 (2.0)	4 (1.2)	3 (0.9)
<u>Renal and urinary disorders</u>			

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	31 (8.9)	41 (12.0)	14 (4.0)
Renal failure chronic	6 (1.7)	11 (3.2)	3 (0.9)
Renal failure acute	6 (1.7)	9 (2.6)	3 (0.9)
Renal failure	6 (1.7)	7 (2.0)	3 (0.9)
Renal impairment	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic nephropathy	0 (0.0)	4 (1.2)	1 (0.3)
<u>Reproductive system and breast disorders</u>			
Overall	12 (3.5)	6 (1.7)	4 (1.1)
Benign prostatic hyperplasia ^b	6 (2.9)	2 (1.0)	2 (0.9)
<u>Respiratory, thoracic and mediastinal disorders</u>			
Overall	28 (8.1)	49 (14.3)	16 (4.6)
Cough	4 (1.2)	13 (3.8)	2 (0.6)
Oropharyngeal pain	4 (1.2)	5 (1.5)	1 (0.3)
Sleep apnea syndrome	3 (0.9)	8 (2.3)	2 (0.6)
Dyspnea	3 (0.9)	5 (1.5)	4 (1.7)
Pleural effusion	0 (0.0)	4 (1.2)	3 (0.9)
<u>Skin and subcutaneous tissue disorders</u>			
Overall	24 (6.9)	22 (6.4)	20 (5.7)
Skin ulcer	4 (1.2)	4 (1.2)	2 (0.6)
<u>Surgical and medical procedures</u>			
Overall	5 (1.4)	3 (0.9)	1 (0.3)
<u>Vascular disorders</u>			
Overall	63 (18.2)	70 (20.4)	35 (10.0)
Hypertension	52 (15.0)	50 (14.6)	27 (7.7)
Hypotension	1 (0.3)	2 (0.6)	4 (1.1)

^aBased on MEDRA, version 15.0

^bPercentages based on the male population

The most common ocular adverse events were cataracts (68%), increased intraocular pressure/glaucoma (36%), conjunctival hemorrhage (22%), macular edema (15%), and vitreous hemorrhage (12%).

The most common non-ocular adverse events were hypertension (15%), hypercholesterolemia (5%), nasopharyngitis (5%), anemia (4%), bronchitis (4%), headache (4%), increased blood creatinine (4%), influenza (4%), and urinary tract infection (4%).

Deaths

There were six deaths during the conduct of study 206207-012, one death in study 206207-018, twelve deaths in study 206207-010, and seventeen deaths in study 206207-011.

In study 206207-012, two subjects treated with DEX 700 died due to 1) respiratory failure and 2.) malignant lung neoplasm. Four subjects treated with Sham DEX died due to 1) cardio-respiratory

arrest, 2) myocardial infarction, 3) malignant lung neoplasm, and 4) Alzheimer's type dementia with failure to thrive.

In study 206207-018, one subject treated with DEX 700 died due to anoxic encephalopathy after experiencing a thrombosis in an arteriovenous fistula.

In study 206207-010, four of the deaths were in the DEX 700 group, five of the deaths were in the DEX 350 group, and three of the deaths were in the Sham group.

In study 206207-011, five of the deaths were in the DEX 700 group, ten of the deaths were in the DEX 350 group, and two were in the Sham group.

Summary of Death
(Studies 206207-010 and 206207-011 Pooled)

Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	9 (2.6)	15 (4.4)	5 (1.4)
Multi-organ failure	2 (0.6)		
Acute respiratory failure	1 (0.3)	1 (0.3)	
Renal failure acute	1 (0.3)	1 (0.3)	
Adenocarcinoma pancreas	1 (0.3)		
Coma	1 (0.3)		
Hemorrhage intracranial	1 (0.3)		
Hemorrhagic stroke	1 (0.3)		
Hepatic failure	1 (0.3)		
Pancreatic carcinoma metastatic	1 (0.3)		
Pneumonia	1 (0.3)		
Road traffic accident	1 (0.3)		
Sepsis	1 (0.3)		
Victim of homicide	1 (0.3)		
Myocardial infarction		4 (1.2)	1 (0.3)
Cardiac arrest		3 (0.9)	1 (0.3)
Diabetic nephropathy		2 (0.6)	
Acute respiratory distress syndrome		1 (0.3)	
Arrhythmia		1 (0.3)	
Azotemia		1 (0.3)	
Cardiac failure congestive		1 (0.3)	
Gastric cancer		1 (0.3)	
H1N1 influenza		1 (0.3)	
Hyperkalemia		1 (0.3)	
Hypotension		1 (0.3)	
Hypovolemic shock		1 (0.3)	
Pleural effusion		1 (0.3)	

Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Pneumonia pneumococcal		1 (0.3)	
Pneumonia streptococcal		1 (0.3)	
Pulseless electrical activity		1 (0.3)	
Respiratory distress		1 (0.3)	
Sudden death		1 (0.3)	
Tuberculosis		1 (0.3)	
Ventricular fibrillation		1 (0.3)	
Cardiomyopathy			1 (0.3)
Myocardial ischemia			1 (0.3)
Subdural hematoma			1 (0.3)

^aBased on MEDRA, version 15.0

The reported deaths are not unexpected for an elderly diabetic population followed over a study period of more than 3 years.

Submission Specific Primary Safety Concerns: IOP and Cataract

Corticosteroids as a class are known to increase the risk of increased intraocular pressure in those patients who are steroid responders and of cataract development. Analyses of these risks are presented below.

Number of Subjects with Elevated IOP Adverse Events in the Study Eye (Studies 206207-010 and 206207-011 Pooled, Safety Population)

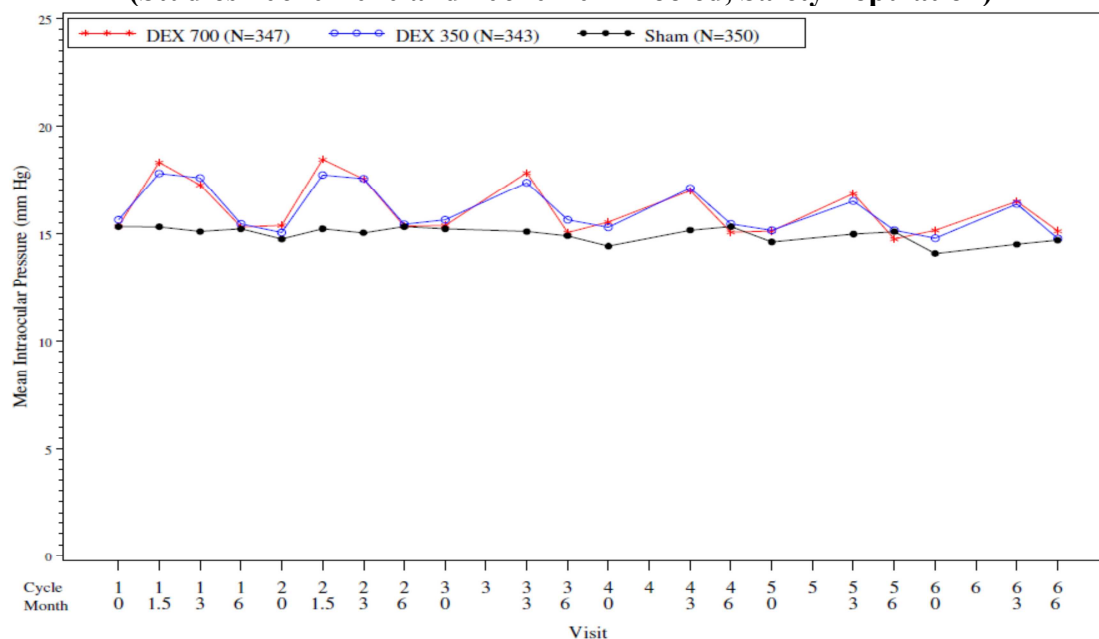
Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	125 (36.0)	117 (34.1)	18 (5.1)
Intraocular pressure increased	107 (30.8)	103 (30.0)	12 (3.4)
Ocular hypertension	21 (6.1)	17 (5.0)	5 (1.4)
Open angle glaucoma	3 (0.9)	3 (0.9)	2 (0.6)
Glaucoma	3 (0.9)	3 (0.9)	0 (0.0)
Angle closure glaucoma	1 (0.3)	0 (0.0)	0 (0.0)
Borderline glaucoma	0 (0.0)	1 (0.3)	0 (0.0)
Glaucomatous optic disc atrophy	0 (0.0)	1 (0.3)	0 (0.0)

Note: Includes all adverse events with a MEDRA preferred term associated with elevated intraocular pressure which includes intraocular pressure increased, intraocular pressure fluctuation, ocular hypertension, angle closure glaucoma, borderline glaucoma, diabetic glaucoma, glaucoma, glaucoma traumatic, glaucomatous optic disc atrophy, open angle glaucoma, pigmentary glaucoma or normal tension glaucoma.

^aBased on MEDRA, version 15.0

Approximately 36% of patients treated with DEX 700 and 34% of patients treated with DEX 350 reported experiencing an elevated IOP adverse event as compared to 5% of patients treated with Sham.

Mean Intraocular Pressure by Visit within Each Treatment Cycle (Studies 206207-010 and 206207-011 Pooled, Safety Population)



Note: "Month" represents the number of months after each treatment.

For pooled Studies 206207-010 and 206207-011, the mean IOP increases at the beginning of each treatment cycle, peaks at 3 months post-treatment, and returns to baseline by month 6. The peak mean IOP appears to be higher in the earlier treatment cycles than in the later treatment cycles.

Number (%) of Subjects Using IOP-lowering Medications in the Study Eye (Studies 206207-010 and 206207-011 Pooled, Safety Population)

Visit	DEX 700 (N = 347)	DEX 350 (N = 343)	Sham (N = 350)	Total (N = 1040)
Baseline ^a	12/347 (3.5)	26/343 (7.6)	14/350 (4.0)	52/1040 (5.0)
Baseline to Month 12	114/347 (32.9)	99/343 (28.9)	23/350 (6.6)	236/1040 (22.7)
Month 12 to Month 24	90/305 (29.5)	89/314 (28.3)	11/241 (4.6)	190/860 (22.1)
Month 24 to Month 39/Final	75/261 (28.7)	75/269 (27.9)	12/176 (6.8)	162/706 (22.9)
Year 3/Final Visit ^b	56/261 (21.5)	49/269 (18.2)	6/176 (3.4)	111/706 (15.7)
Ever Used During the Study ^c	144/347 (41.5)	129/343 (37.6)	32/350 (9.1)	305/1040 (29.3)

IOP = intraocular pressure

Note: IOP-lowering medications included beta blocking agents, sympathomimetics, prostaglandins, carbonic anhydrase inhibitors, brimonidine, and combination agents.

^a Baseline refers to medications used prior to the first treatment.

^b Year 3/Final Visit includes only those medications marked as "ongoing" on the year 3 case report form.

^c Ever Used includes those who ever used IOP-lowering medications in the study eye at any time during the study.

Approximately 40% of patients in the DEX 700 and DEX 350 treatment group required IOP-lowering medications during the study as compared to 9% in the Sham treatment group.

Eight subjects (4 in the DEX 700 group, 3 in the DEX 350 group, and 1 in the Sham group) underwent a procedure for the treatment of IOP elevation.

In the DEX 700 group:

Subject 4341-4469 underwent a trabeculectomy in the study eye for worsening of elevated IOP on study day 476

Subject 4449-4759 underwent a trabeculectomy in the study eye for high IOP on study day 714 and an iridotomy on study day 719.

Subject 6654-4750 underwent an iridectomy in the study eye as part of cataract surgery (for worsening cataract) on study day 549.

Subject 4533-7318 underwent an iridotomy in both the study eye and non-study eye for narrow angle glaucoma on study day 322.

In the DEX 350 group:

Patient 7871-4970 underwent a trabeculectomy in the study eye on study day 857.

Patient 4353-4744 underwent trabeculoplasty in the study eye for increased IOP on study day 688.

Patient 9095-7742 underwent a trabeculoplasty in the study eye for ocular hypertension on study day 279.

**Number of Phakic Subjects at Baseline with Cataract Adverse Events
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

Coded Adverse Event^a	DEX 700 (N=262) n (%)	DEX 350 (N=256) n (%)	Sham (N=250) n (%)
Any cataract AE	178 (67.9)	164 (64.1)	51 (20.4)
Cataract	126 (48.1)	109 (42.6)	32 (12.8)
Cataract subcapsular	41 (15.6)	41 (16.0)	12 (4.8)
Cataract nuclear	18 (6.9)	15 (5.9)	8 (3.2)
Lenticular opacities	16 (6.1)	11 (4.3)	3 (1.2)
Cataract cortical	7 (2.7)	13 (5.1)	9 (3.6)

Note: Includes terms cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, lenticular opacities.

^aBased on MEDRA, version 15.0

Approximately 68% of patients who were phakic at baseline in the DEX 700 treatment group and 64% of phakic patients at baseline in the DEX 350 treatment group reported a cataract adverse event as compared to 20% of patients in the Sham treatment group.

**Number (%) of Phakic Subjects at Baseline Who Had Cataract Surgery
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

Study visit	DEX 700 (N = 262)	DEX 350 (N = 256)	Sham (N = 250)
Month 6	9 (3.4)	8 (3.1)	5 (2.0)
Month 12	22 (8.4)	15 (5.9)	0 (0.0)
Month 18	41 (15.6)	31 (12.1)	5 (2.0)
Month 24	46 (17.6)	43 (16.8)	4 (1.6)
Month 30	32 (12.2)	29 (11.3)	1 (0.4)
Month 36	6 (2.3)	8 (3.1)	3 (1.2)
Month 39	1 (0.4)	0 (0.0)	0 (0.0)
Ever Had ^a	155 (59.2)	134 (52.3)	18 (7.2)

Note: Cataract surgery include: cataract operation, lens extraction, intraocular lens implant, lenticular operation, and phacocystectomy.

^a “Ever Had” includes those patients who had cataract surgery in the study eye at any time during the study.

Approximately 59% of the patients treated with DEX 700 and 52% of the patients treated with DEX 350 had a cataract surgery performed during the study as compared to 7% for the patients treated with Sham. For the patients treated with DEX, the majority of the cataract surgeries were performed in the second and third years of the trial.

Safety Summary Statement

The adequate and well controlled studies 206207-0110 and 206207-011 support the safety of Ozurdex (dexamethasone intravitreal implant) in the treatment of diabetic macular edema.

The most common ocular and non-ocular adverse events are as follows:

MedDRA Term	OZURDEX [®] N=347 (%)	Sham N=350 (%)
Ocular		
Cataract ¹	178/262 ² (68%)	51/249 (20%)
Cataract surgery	155/262 (59%)	18/249 (7%)
Intraocular pressure increased ³	125 (36%)	18 (5%)
Conjunctival haemorrhage	76 (22%)	45 (13%)
Macular edema	51 (15%)	36 (10%)
Vitreous haemorrhage	40 (12%)	36 (10%)
Non-ocular		
Hypertension	52 (15%)	27 (8%)
Hypercholesterolemia	16 (5%)	12 (3%)
Nasopharyngitis	18 (5%)	22 (6%)

¹ Includes cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, lenticular opacities.

Includes subjects who were phakic at baseline.

² 262 of the 347 OZURDEX subjects were phakic at baseline; 249 of 350 sham-controlled subjects were phakic at baseline.

³Includes IOP increased, IOP fluctuation, ocular hypertension, angle closure glaucoma, borderline glaucoma, diabetic glaucoma, glaucoma, glaucoma traumatic, glaucomatous optic disc atrophy, open angle glaucoma, pigmentary glaucoma, normal tension glaucoma.

Approximately 40% of the patients who received Ozurdex required IOP lowering medications during the study and 0.6% required surgical procedures for management of elevated IOP. In the sham control group, IOP lowering medications were used in approximately 5% of patients and 0.3% required surgical IOP lowering procedure.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Allergan requested a full waiver in their June 13, 2013, submission:

Allergan is requesting a full waiver of the pediatric assessment requirement of OZURDEX in patients (16 years of age or less) based on the fact that diabetic macular edema (DME) rarely occurs in this population. Because the pediatric patient population is so small, conducting the necessary studies would be impossible or highly impractical. Therefore, based on the rarity of the disease in this population, and in accordance with 21 CFR 314.55(c)(2)(ii), Allergan believes that full waiver of the pediatric assessment requirement is justified.

The application went to PeRC on 10/16/2013, and a full waiver was granted for the diabetic macular edema indication. The PeRC agreed with the Division that studies would be impossible or highly impractical.

Safety and effectiveness of Ozurdex in pediatric patients have not been established.

11. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, and CMC have recommended approval of this supplemental new drug application. Biostatistics defers the assessment of the overall risk-benefit profile of this product to other disciplines.

OSI

An Office of Scientific Investigation consultation request was submitted on July 15, 2013.

Per the OSI Clinical Inspection Summary dated 2/10/14:

Name of CI	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
Glenn L. Wing, MD. National Ophthalmic Research Institute 6901 International Center Blvd. Ft. Myers, FL 33912	Protocol # 206207-010 Site #10024 14 subjects	August 26 – September 12, 2013	NAI
Kenneth Sall, MD. Sall Research Medical Center 11423 187 th Street, Suite 200 Artesia, CA 90701	Protocol #206207-011 Site #10022 68 subjects	September 3 – 11, 2013	VAI
Steven Rose MD Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618	Protocol #206207-011 Site #10021 15 subjects	October 15 – 21, 2013	NAI
Allergan, Inc. 2525 Dupont Drive Irvine, CA 92612-1599	Protocols # 206207-010 and 206207-011	December 12 – 23, 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

Three clinical investigator sites were inspected in support of NDA 22-315 SE1-009, as well as the applicant, Allergan. There were no significant regulatory violations at the sites of Drs. Wing and Rose. At Dr. Sall's site, which was chosen because the most domestic subjects were enrolled in Study 011, evidence of fraud was described. Substitution of OCT scans to ensure that subjects met inclusion criteria was noted, as well as falsification of BCVA values by an employee was observed during a previous inspection, and this employee also participated in Study 011. The employee has since left the firm, and Dr. Sall has taken corrective action to prevent such occurrences in the future. However, OSI cannot endorse data integrity and subject safety at Dr. Sall's site. Inspection of the applicant did not reveal significant regulatory violations. In particular, monitoring appeared to be adequate. The data from the two sites inspected as well as from the applicant may be considered reliable.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 3/10/2014:

The primary efficacy endpoint was the proportion of subjects with a 15 letter or more improvement in BCVA from baseline at 3 years. In both studies, DEX 700 had a significantly higher proportion of

subjects with a 15 letter or more improvement from baseline at 3 years compared to the Sham, whereas a significant difference was observed between DEX 350 and Sham in only one of the two studies (Table 5).

Table 5: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
011	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

The overall study conclusion regarding the primary efficacy endpoint does not seem to have been significantly impacted by the method used to handle missing data.

Table 6: Sensitivity Analysis for the Primary Efficacy Endpoint

Studies	Methods	Treatment: N (%)			%Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
206207-010	Multiple Imputation	34/163 (20.8%)	39/166 (23.4%)	25/165 (15.1%)	5.7% (-5.6%, 16.7%)	8.4% (-5.2%, 22.0%)
	Per-Protocol	31/144 (21.5%)	31/155 (20.0%)	18/143 (12.6%)	8.9% (0.3%, 17.6%)	7.4% (-0.9%, 15.7%)
	Complete Case	25/104 (24.0%)	29/107 (27.1%)	13/63 (20.6%)	3.4% (-9.5%, 16.3%)	6.5% (-6.6%, 19.5%)
206207-011	Multiple Imputation	35/188 (18.6%)	35/181 (19.3%)	19/185 (10.5%)	8.1% (0.8%, 16.4%)	9.0% (-0.01%, 18.1%)
	Per-Protocol	31/170 (18.2%)	27/159 (17.0%)	19 /162 (11.7%)	6.5% (-1.0%, 14.1%)	5.2% (-2.4%, 12.9%)
	Complete Case	27/107 (25.2%)	25/101 (24.7%)	16/68 (23.5%)	1.7% (-11.3%, 14.7%)	1.2% (-11.9%, 14.4%)

Source: Reviewer's Analysis. For per-protocol analysis, LOCF was used to impute missing data for all subjects with missing data except for non-protocol violators. The complete case analysis is based on subjects who had a BCVA measurement at Month 36. For all analyses, subjects who received escape therapy prior to 3 years were set as treatment failures.

Amendment 4 of the study protocol (08 May 2010) allowed a possible re-treatment at Month 36 visit and included an additional visit at a Month 39 to provide assessment of efficacy and safety for subjects who received a re-treatment at Month 36 visit. Consequentially, the applicant re-defined the primary efficacy endpoint as the proportion of subjects who had a 15 letter or more gain in BCVA from baseline at final study visit (Month 39 or earlier) to accommodate efficacy measures from the additional re-treatment. However, only 173 (16.5%) of the 1048 randomized subjects had completed the Month 39 visit, and only 161(15.3%) of the randomized subjects had a BCVA measurement at the Month 39 visit.

OPDP

A review of the substantially complete labeling was completed by the Office of Prescription Drug Promotion (OPDP) on 3/20/14.

The suggested OPDP revisions to the Highlights and Section 5 were made in the body of the package insert only. The revisions are not appropriate for the Highlights because of their concise nature.

The suggested revision to Section 2 was not incorporated; the decision to retreat was potentially based on physician discretion. This cannot be adequately described in the labeling because physician discretion varied substantially between investigators.

The suggested revision to Section 6 regarding discontinued patients is not appropriate; no subject had an explanted dexamethasone implant.

The suggested revision to Section 11 regarding the applicator is not appropriate because it may imply the implant could be administered via other means than the included applicator.

The suggested revision to Section 14 is not appropriate because it would eliminate discussion within the labeling of variation in visual acuity based on dissolution of the implant over time.

12. Labeling

NDA 22-315 SE1 009, Ozurdex (dexamethasone intravitreal implant) is recommended for approval for the treatment of diabetic macular edema. This reviewer does not agree with the Agency's recommended labeling for this drug product. The revised indication, "the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery," is too restrictive based on the data supplied in this application. Per the steroid class labeling found in Section 5.2 of the proposed package insert, (b) (4)

(b) (4)

The original labeling found in the Appendix at the end of this CDTL review was submitted by Allergan, Inc. on 3/11/2014. The track-changes represent Division edits.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 22-315 SE1 009, Ozurdex (dexamethasone intravitreal implant) is recommended for approval for the treatment of diabetic macular edema. This reviewer does not agree with the Agency's recommended labeling for this drug product. The revised indication, "the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery," is too restrictive based on the data supplied in this application. Per the steroid class labeling found in Section 5.2 of the proposed package insert, (b) (4)

(b) (4)

(4)

)

”

RISK BENEFIT ASSESSMENT:

The clinical data from Studies 206207-010 and 206207-011 submitted in support of this efficacy supplement demonstrates the superiority of dexamethasone intravitreal implant 700 µg (p=0.038 and p=0.003, respectively) as compared to Sham in the treatment of diabetic macular edema.

Corticosteroids as a class are known to increase the risk of elevated IOP in those patients who are steroid responders and to increase the rate of cataract development. With respect to IOP, there was a statistically significant difference ($p < 0.001$) in the rate of elevated IOP adverse events for DEX 700 and DEX 350 (36% and 34%, respectively) as compared to Sham (5%). The percentage of patients that required a filtering procedure to control IOP during the study period was 0.6% for DEX 700 and 0.3% for DEX 350 as compared to Sham (0.0%).

With respect to cataract development, there was a statistically significant difference ($p < 0.001$) in the rate of cataract adverse events for DEX 700 and DEX 350 (68% and 64%, respectively) as compared to Sham (20%). The percentage of patients who underwent cataract surgery was 59% for DEX 700 and 52% for DEX 350 as compared to Sham (7%)

The benefits of using this drug product outweigh the risks for the above indication.

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, and CMC have recommended approval of this supplemental new drug application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

NDA 22-315 SE1 009, Ozurdex (dexamethasone intravitreal implant) is recommended for approval for the treatment of diabetic macular edema. This reviewer does not agree with the Agency's recommended labeling for this drug product. The revised indication, "the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery," is too restrictive based on the data supplied in this application. Per the steroid class labeling found in Section 5.2 of the proposed package insert, (b) (4)

The original labeling found in the Appendix at the end of this CDTL review was submitted by Allergan, Inc. on 3/11/2014. The track-changes represent Division edits.

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

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

/s/

WILLIAM M BOYD
03/28/2014

WILEY A CHAMBERS
03/30/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

MEDICAL REVIEW(S)



To: Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products

From: Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology
Division of Transplant and Ophthalmology Products

Date: July 1, 2014

Subject: Dispute Statement
NDA 22-315, Supplement 9, Ozurdex (dexamethasone intravitreal implant)

Summary of Dispute

On June 27, 2014, a supplement approval letter was issued for supplement 9 of NDA 22-315, revising the labeling to add an indication for the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery.

I do not agree with limiting the indication to patients who are pseudophakic or are phakic and scheduled for cataract surgery. I believe that the application should have been approved for use in patients with macular edema regardless of the status of their lens. The decision to limit the indication is not consistent with the population of patients who may benefit from using the product and is not consistent with other approved corticosteroid products. In addition, I do not agree with the Adverse Reaction section, Table 3 of the labeling because the table inaccurately reports patients with glaucoma or who had IOP lowering procedures.

Introduction/Background

The original New Drug Application (NDA) for this product, Ozurdex (dexamethasone intravitreal implant), was approved on June 17, 2009, for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). An efficacy supplement for the additional use of Ozurdex in the treatment of non-infectious uveitis affecting the posterior segment of the eye (intermediate and/or posterior uveitis) was approved on September 24, 2010. The most recent supplement, S-009, was submitted for an additional indication for the treatment of diabetic macular edema. The applicant's proposal did not include restricting the patient population based on lens status. The restriction was proposed by the Division of Transplant and Ophthalmology Products.

Nature of the Disagreement:

The Medical Officer and Clinical Team Leader who reviewed the application recommended that the supplemental application be approved for the treatment of diabetic macular edema without restricting the patient population to patients who are pseudophakic or are phakic and scheduled for cataract surgery. I agree with that recommendation. The Division Director decided to approve the application for the restricted population as a way to mitigate the risk of significant cataract formation. The higher response rate of three line gainers in visual acuity of pseudophakic patients compared to phakic patients is cited as a reason for this limitation as well as consistency with an unapproved application.

There is no disagreement that there were subpopulations of the studies that had higher levels of improvement than other subpopulations. However, I disagree that the Ozurdex product should be limited to one of the subpopulations, when there were other subpopulations which also benefited, although by lesser amounts or for shorter periods of time. The drug product proposed in this application has a six month duration of action. Patients are not committed to receive a second implant just because they received the first implant. The decision to implant a second Ozurdex will be made by a physician and patient based on the clinical condition of the patient prior to the implantation of a second Ozurdex. The benefit to be expected from the first Ozurdex as well as from subsequent implants can be conveyed to patients and physicians by the graphs presented in the package insert. The impact of cataract development in patients with a lens can be assessed by physicians during their clinical exam of the patient and incorporated into the decision of whether to implant one or more Ozurdex products. The expected outcome after cataract surgery can be conveyed to patients and physicians by the graphs presented in the package insert.

I disagree with preventing patients who may benefit from the six month use of the drug product from using the product when adequate information can be conveyed to them to make an informed decision. The delay in receiving treatment may result in subsequent decreased vision. I believe that for a six month period of time, adequate methods are available to handle potential elevations in intraocular pressure and that a re-assessment of the potential benefits and risks should be made at that six month period of time, prior to any re-administration of the product. This is consistent with the principles listed in the other ophthalmic corticosteroid products which call for the re-examination of patients prior to continued courses of therapy.

I disagree that the unapproved application cited in the Division Director's Review should serve as a precedent for this application. The unapproved application in question has not been approved for any indication and the final determination of its indication (if it is ever approved) has yet to be decided. The Ozurdex application does not cross reference this unapproved application. The unapproved application has a significantly longer duration of action making it impossible or impractical to re-evaluate and change therapy based on the condition of the patient at six month intervals. Additionally, there are a large number of approved corticosteroids (systemic, topical and intraocular) which cause or increase the rate of cataract formation. These approved products are labeled as causing or increasing the rate of cataract formation, sometimes in all treated patients, but their indications are not limited to patients who are pseudophakic or scheduled for cataract surgery.

I disagree with Table 3 of the Adverse Reaction section of the labeling. The term “Glaucoma” in this table should be removed because it is inaccurate and misleading. Elevated intraocular pressure is a risk factor for developing glaucoma, but without visual field changes and optic nerve changes, it is not appropriate to make a diagnosis of glaucoma. In the absence of patients in the studies with visual field and optic nerve changes, none of the patients should have been diagnosed as having glaucoma. The line “IOP lowering procedure” should also be removed because it is inaccurate, not an adverse event and poorly defined. The decision to perform an ocular procedure is not an adverse event. The decision to perform an ocular procedure, including those to lower intraocular pressure is dependent on a number of medical, social and financial considerations, not just the severity of the IOP. The table is also incorrect because iridotomies and iridectomies provide an alternative pathway for aqueous humor to flow; they do not lower intraocular pressure except in cases of acute angle closure. Corticosteroids, including Ozurdex have not been demonstrated to cause anatomically narrow angles or angle closure.

Studies support efficacy in unrestricted population

The supplement was based primarily on two studies, 206207-010 (Study 10) and 206207-011 (Study 11) conducted in patients with diabetic macular edema. There was no restriction of patients entered into the study to be pseudophakic or to be scheduled for cataract surgery.

As demonstrated in the graphs on the following pages, administration of the first implant of Ozurdex in a patient with diabetic macular edema is expected to result in a reduction of the macular thickness and a modest improvement in visual acuity over the span of approximately four months. This effect is demonstrated in both phakic and pseudophakic patients in each of the two studies. The mean visual acuity of each of these subpopulations is shown on the following graphs.

Figure 6403-21.1 (page 1 of 1)
BCVA Change from Baseline in the Study Eye
Subgroup: Phakic
Intent-to-Treat Population: 206207-010

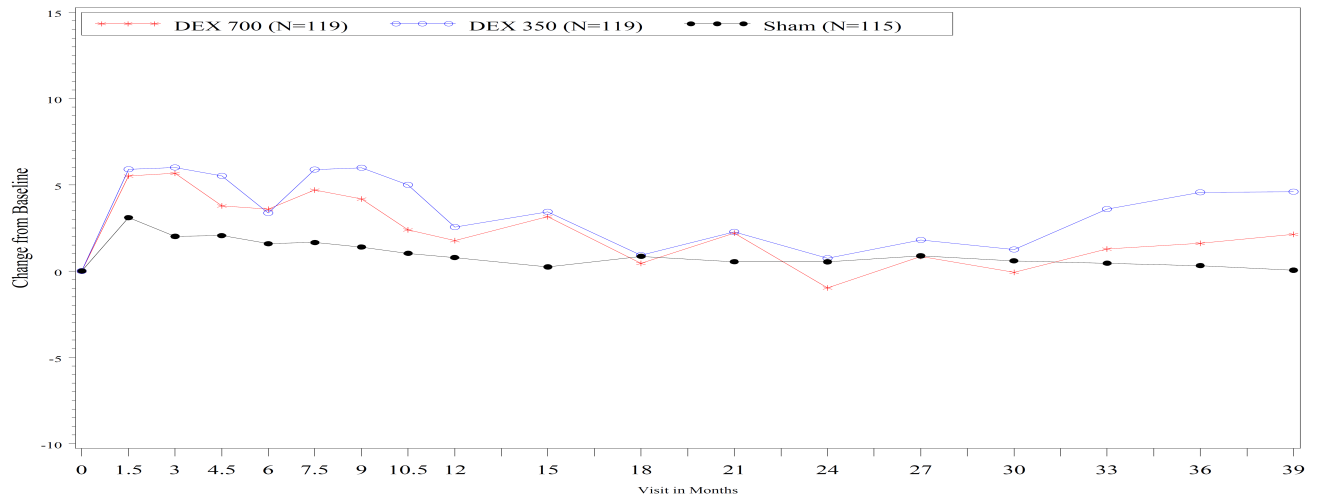
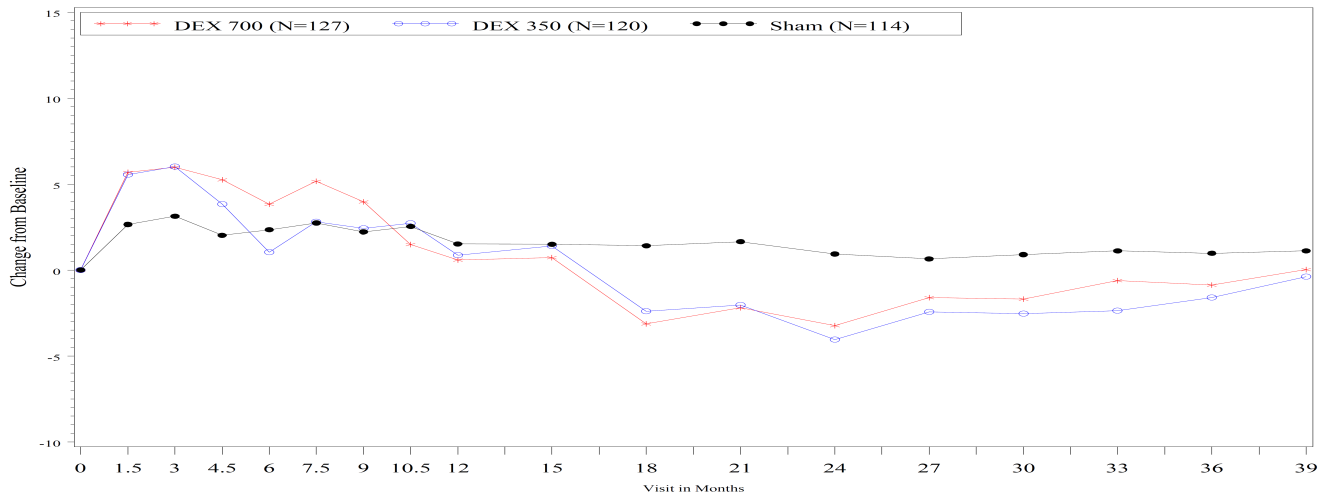
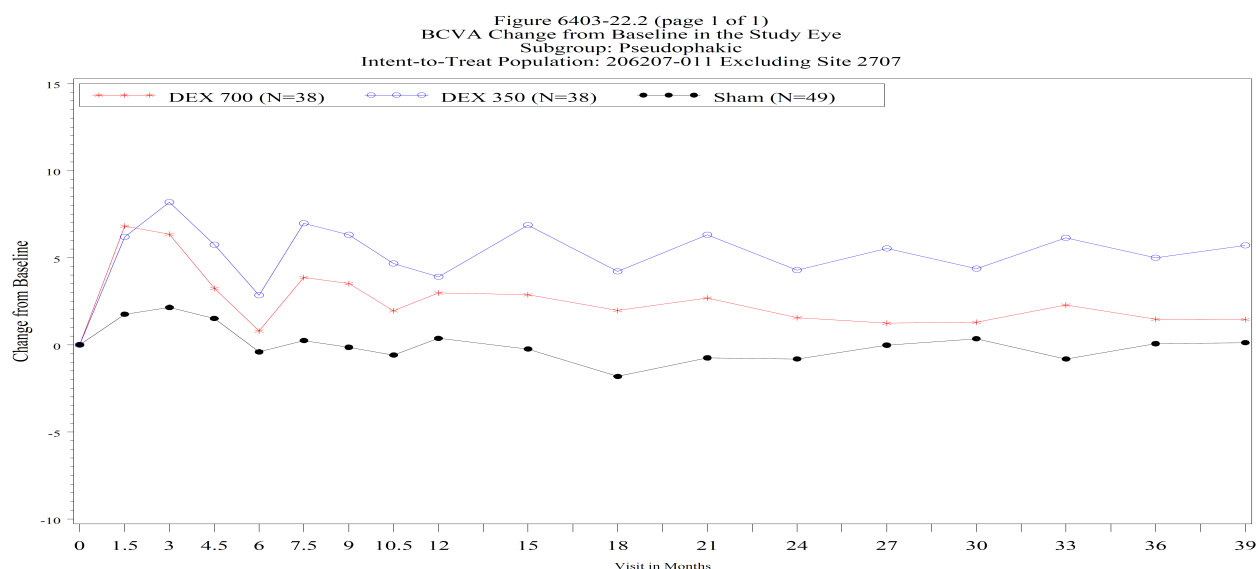
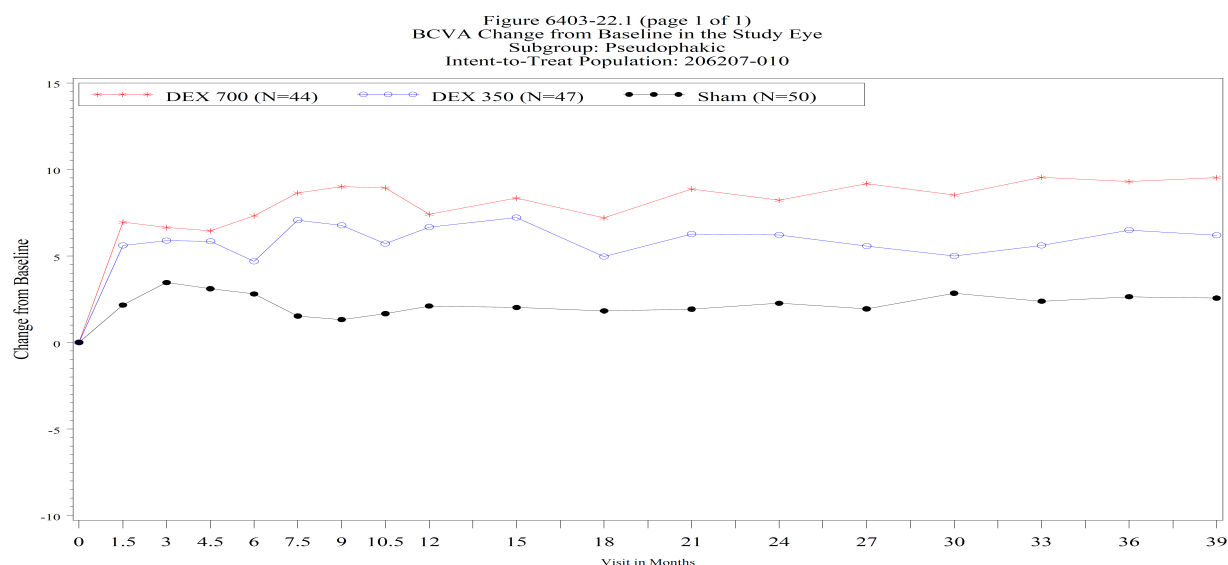


Figure 6403-21.2 (page 1 of 1)
BCVA Change from Baseline in the Study Eye
Subgroup: Phakic
Intent-to-Treat Population: 206207-011 Excluding Site 2707





Administration of a second implant also resulted in an increase in visual acuity, but the effect was not as great as the first implant. Subsequent implants resulted in continually, but less pronounced effects.

Cataract formation follows a known predictable pattern

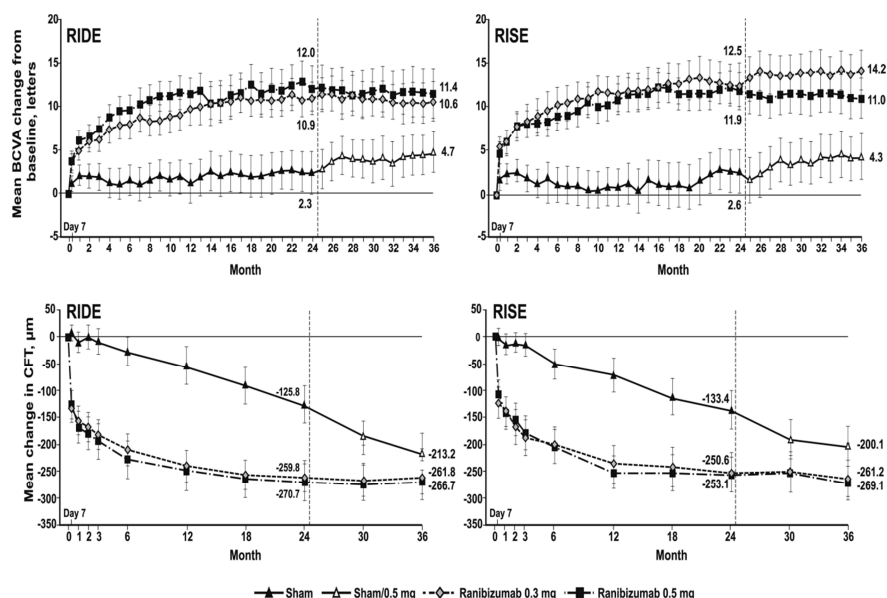
In phakic patients, the time and duration of corticosteroid use such as dexamethasone increases the rate of cataract formation with a consequential decrease in visual acuity until the cataract is removed and replaced with an intraocular lens. Clinically significant cataract development is most commonly noted after 9-24 months of intraocular or periocular corticosteroid exposure. This effect by corticosteroids occurs following administration of corticosteroids by a variety of different routes (topically, systemically, and intraocularly). The 36-39 month time points in these studies provided an opportunity to evaluate effect of initial implants and subsequent implants as

well as to evaluate the potential for visual function improvement during and after cataract development and removal. Visual acuity evaluations in phakic patients treated with one or more Ozurdex implants were generally noted to have improvement in vision from month 24 through month 39, following the removal of cataracts and insertion of intraocular lenses.

Visual acuity evaluations in pseudophakic patients were generally noted to increase during the one to five month period following administration of the first implant. Repeated administrations of Ozurdex improved visual acuity in pseudophakic patients during this four month window following each Ozurdex implantation, but as noted above, the amount of improvement often declined with each subsequent administration.

Negative consequences due to delaying treatment

While pseudophakic patients had a more rapid improvement in visual acuity compared to phakic patients, delaying treatment of diabetic macular edema until patients have had or are scheduled to have cataract surgery is likely to be detrimental to their ultimate vision. As noted in these trials, treatment with Ozurdex is more effective in improving visual acuity when it is administered earlier in the course of the disease. This was also true in studies where VEGF-F inhibitors were administered to patients with diabetic macular edema. As seen in the graphs below from studies of Lucentis, the delay in initiating VEGF therapy appears to have dampened the ultimate response to VEGF treatment.¹ At month 24, patients treated with sham injections were allowed to cross over to Lucentis treatment, but they did not respond as well as patients initially randomized to Lucentis treatment.



¹ Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013 Oct;120(10):2013-22. doi: 10.1016/j.opht. 2013.02.034. Epub 2013 May 22.

For some patients, corticosteroid treatment may be their best option for treating diabetic macular edema. The product demonstrated efficacy in the full study population. The consequences of delaying treatment of diabetic macular edema may be permanent visual loss. While a portion of patients with diabetic macular edema will have spontaneous resolution of their edema, for those patients who do not resolve (either on their own or with alternative treatments), treatment to reduce the edema is important in preserving visual function. A delay, waiting to become aphakic/pseudophakic or a delay until a cataract forms, risks permanent visual loss while waiting for the very adverse event which is trying to be avoided. The consequence of this delay does not avoid cataract formation, it only avoids an association between Ozurdex and cataract formulation. With restrictive labeling, Ozurdex may not be the cause of the cataract, but the treatment will not be available until after an individual has had the very event for which Ozurdex use was prohibited. This restriction is not necessarily in the patient's best interest and may lead to permanent visual loss in an attempt to avoid the temporary visual decrease caused by a cataract.

Indication inconsistent with prior precedent

The decision to restrict the indication for Ozurdex to aphakic/pseudophakic patients (or patients scheduled for surgery) was inconsistent with the Agency's previous decisions regarding the approval of corticosteroids. All topical ophthalmic, systemically administered or intraocularly injected corticosteroids increase the development of cataracts. All are labeled to cause cataracts. None are limited to aphakic/pseudophakic patients.

Retisert (fluocinolone acetonide intravitreal implant) approved for the treatment of chronic non-infectious uveitis is not limited to aphakic/pseudophakic patients (or patients scheduled for surgery) in spite of labeling that states during the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

Systemically administered corticosteroids are not restricted to pseudophakic/aphakic patients for any of their approved indications in spite of the potential risk of cataract development. Oral, intravenous, and intramuscular hydrocortisone, methylprednisolone, prednisone, prednisolone, dexamethasone, triamcinolone, and betamethasone have ophthalmic indications and a warning that the products may produce posterior subcapsular cataracts. Since the 1960s it has been reported² that a fifth of children treated with systemic corticosteroids for more than one year and over half of children treated with systemic corticosteroids for more than two years will develop cataracts.

Topical ophthalmic corticosteroids, dexamethasone, prednisolone, and fluorometholone are all approved for ophthalmic indications and have warnings concerning the development of cataracts. They are known to cause a dose dependent acceleration of the development of cataracts. None of the indications of these products is limited to aphakic/pseudophakic patients (or patients scheduled for surgery). All are labeled for re-evaluation of the patient's clinical condition before renewing courses of therapy.

² Braver DA, Richards RD and Good TA. Posterior Subcapsular Cataracts in Steroid Treated Children. *Arch Ophthalmol*. 1967;77:161-162.

Neither of the previously approved indications for Ozurdex is limited to pseudophakic/aphakic patients (or patients scheduled for surgery). The package insert for Ozurdex has a warning that use of the product may cause cataracts to develop. Previous studies of macular edema due to vein occlusions evaluated the difference between one Ozurdex implant and two Ozurdex implants on the development of cataracts.

<u>Treatment</u>	<u>Cataract Adverse Events at 1 year</u>
Fellow Eye	5%
Single Sham	5%
Single Ozurdex 700	6%
Single Ozurdex 350	7%
Sham followed by Ozurdex 700	9%
Ozurdex 350 followed by Ozurdex 700	17%
Ozurdex 700 followed by Ozurdex 700	26%

Cataract incidence increases with multiple implants. There is no reason to believe that cataract development due to the use of Ozurdex is indication dependent.

Incorrect Use of Terms in Adverse Reaction Table

Table 3: Summary of Elevated IOP Related Adverse Reactions includes two lines which do not properly classify some of the listed events.

The table includes a line titled “Glaucoma,” however, glaucoma is an optic neuropathy. The diagnosis is not based on elevated intraocular pressure. Elevated intraocular pressure is a risk factor for developing glaucoma, but without visual field changes and optic nerve changes, it is not appropriate to make a diagnosis of glaucoma. The table lists five patients as having glaucoma (four in the Ozurdex group and one in the Sham group). There were no patients reported in the studies to have visual field and optic nerve changes, therefore none of the patients should have been diagnosed as having glaucoma. The line should therefore be removed.

The table includes a line titled “IOP lowering procedure*.” The asterisk identifies the cases as: Ozurdex: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridomy, 1 surgical iridectomy. Sham: 1 laser iridotomy. The table is incorrect because iridotomies and iridectomies do not lower intraocular pressure except in cases of acute angle closure. Corticosteroids, including Ozurdex, have not been demonstrated to cause narrow angles or angle closure. Iridotomies and iridectomies provide an alternative pathway for aqueous humor flow and prevent angle closure. Depending on the type of intraocular lens placed in the eye, they may be required as part of the cataract/intraocular lens procedure to prevent pupil block with the intraocular lens. Iris neovascularization is a complication of diabetes. The trabeculectomy would provide an alternative pathway for fluid since the normal pathway is blocked by the neovascularization. It is not clear why this would be listed in a summary of elevated intraocular pressure. The decision to perform an ocular procedure, including those to lower intraocular pressure is dependent on a number of medical, social and

financial considerations, not just the severity of the IOP. Technically, cataract surgery routinely lowers intraocular pressure, yet it was not included in this line. The term “Glaucoma” in this table should be removed because it is inaccurate and misleading. The line “IOP lowering procedure” should also be removed because it is inaccurate, not an adverse event and poorly defined.

Requested Action:

1. It is requested that labeling of NDA 22-315, Ozurdex (dexamethasone intravitreal implant) be amended such that the indication include phakic patients with diabetic macular edema
(b) (4) .
2. It is requested that the Adverse Reaction section of the labeling be revised. It is recommended that the lines “Glaucoma” and “IOP lowering procedures” be removed from Table 3.

cc: Renata Albrecht, MD
David Roeder

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

/s/

WILEY A CHAMBERS
07/01/2014

CLINICAL REVIEW of NDA 22-315/S-009

Application Type	SE1-009
Application Number(s)	22-315
Priority or Standard	Standard
Submit Date(s)	June 13, 2013
Received Date(s)	June 13, 2013
PDUFA Goal Date	April 12, 2014
Division / Office	DTOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	December 1, 2013
Established Name	Dexamethasone intravitreal implant 0.7 mg
(Proposed) Trade Name	Ozurdex
Therapeutic Class	Corticosteroid
Applicant	Allergan, Ltd.
Formulation(s)	Intravitreal implant
Dosing Regimen	Extended release implant
Indication(s)	Treatment of diabetic macular edema
Intended Population(s)	Patients ≥ 18 y.o. with diabetic macular edema

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	5
1.1	Recommendation on Regulatory Action	5
1.2	Risk Benefit Assessment	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	5
1.4	Recommendations for Postmarket Requirements and Commitments	5
2	INTRODUCTION AND REGULATORY BACKGROUND.....	5
2.1	Product Information.....	5
2.2	Tables of Currently Available Treatments for Proposed Indications	6
2.3	Availability of Proposed Active Ingredient in the United States	6
2.4	Important Safety Issues With Consideration to Related Drugs	6
2.5	Summary of Presubmission Regulatory Activity Related to Submission	6
2.6	Other Relevant Background Information	6
3	ETHICS AND GOOD CLINICAL PRACTICES	7
3.1	Submission Quality and Integrity	7
3.2	Compliance with Good Clinical Practices.....	7
3.3	Financial Disclosures.....	7
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	8
4.1	Chemistry Manufacturing and Controls	8
4.2	Clinical Microbiology.....	8
4.3	Preclinical Pharmacology/Toxicology	9
4.4	Clinical Pharmacology	9
5	SOURCES OF CLINICAL DATA.....	9
5.1	Tables of Studies/Clinical Trials	9
5.2	Review Strategy.....	10
5.3	Discussion of Individual Studies/Clinical Trials	11
6	REVIEW OF EFFICACY	30
6.1	Indication	30
6.1.1	Methods.....	30
6.1.2	Demographics.....	30
6.1.3	Subject Disposition.....	32
6.1.4	Analysis of Primary Endpoint(s).....	34
6.1.5	Analysis of Secondary Endpoints(s)	37
6.1.6	Other Endpoints.....	38
6.1.7	Subpopulations	38
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	38
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	39

6.1.10	Additional Efficacy Issues/Analyses	39
7	REVIEW OF SAFETY	39
7.1	Methods	39
	Studies/Clinical Trials Used to Evaluate Safety	39
7.1.2	Categorization of Adverse Events	39
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	39
7.2	Adequacy of Safety Assessments	39
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	39
7.2.2	Explorations for Dose Response	40
7.2.3	Special Animal and/or In Vitro Testing	40
7.2.4	Routine Clinical Testing.....	40
7.2.5	Metabolic, Clearance, and Interaction Workup.....	41
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	41
7.3	Major Safety Results	41
7.3.1	Deaths.....	41
7.3.2	Nonfatal Serious Adverse Events.....	42
7.3.3	Dropouts and/or Discontinuations.....	45
7.3.5	Submission Specific Primary Safety Concerns	57
7.4	Supportive Safety Results.....	57
7.4.1	Common Adverse Events.....	61
7.4.2	Laboratory Findings	66
7.4.3	Vital Signs	66
7.4.4	Electrocardiograms (ECGs)	66
7.4.5	Special Safety Studies/Clinical Trials	66
7.4.6	Immunogenicity.....	66
7.5	Other Safety Explorations	66
7.5.1	Dose Dependency for Adverse Events.....	66
7.5.2	Time Dependency for Adverse Events.....	66
7.5.3	Drug-Demographic Interactions.....	66
7.5.4	Drug-Disease Interactions	66
7.5.5	Drug-Drug Interactions	67
7.6	Additional Safety Evaluations.....	67
7.6.1	Human Carcinogenicity.....	67
7.6.2	Human Reproduction and Pregnancy Data	67
7.6.3	Pediatrics and Assessment of Effects on Growth.....	67
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	67
7.7	Additional Submissions / Safety Issues.....	67
8	POSTMARKET EXPERIENCE.....	67
9	APPENDICES.....	68
9.1	Literature Review/References	68

9.2	Advisory Committee Meeting	68
9.3	Financial Disclosure Form.....	68
9.3	Labeling Recommendations	70

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-315 SE1-009 Ozurdex (dexamethasone intravitreal implant) be approved with the labeling revisions found in this review.

1.2 Risk Benefit Assessment

The clinical data from Studies 206207-010 and 206207-011 submitted in support of this efficacy supplement demonstrates the superiority of dexamethasone intravitreal implant 700 µg ($p=0.038$ and $p=0.003$, respectively) as compared to Sham in the treatment of diabetic macular edema.

Corticosteroids as a class are known to increase the risk of elevated IOP in those patients who are steroid responders and to increase the rate of cataract development. With respect to IOP, there was a statistically significant difference ($p<0.001$) in the rate of elevated IOP adverse events for DEX 700 and DEX 350 (36% and 34%, respectively) as compared to Sham (5%). The percentage of patients that required a filtering procedure to control IOP during the study period was 0.6% for DEX 700 and 0.3% for DEX 350 as compared to Sham (0.0%).

With respect to cataract development, there was a statistically significant difference ($p<0.001$) in the rate of cataract adverse events for DEX 700 and DEX 350 (68% and 64%, respectively) as compared to Sham (20%). The percentage of patients who underwent cataract surgery was 59% for DEX 700 and 52% for DEX 350 as compared to Sham (7%).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluations and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket clinical study requirements and commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name:	dexamethasone intravitreal implant 0.7 mg
Proposed Trade Name:	Ozurdex
Pharmacological Class:	corticosteroid
Indication(s)	treatment of diabetic macular edema

Dosing Regimen: Single intravitreal dose

2.2 Tables of Currently Available Treatments for Proposed Indications

Lucentis (ranibizumab injection)

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is currently available in the following marketed products:

Ozurdex (dexamethasone intravitreal implant)

Maxidex (dexamethasone sodium phosphate 0.1%)

Ocu-Dex (dexamethasone ophthalmic solution or ointment, 0.1%, 0.5%)

2.4 Important Safety Issues with Consideration to Related Drugs

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Prolonged topical use of steroids is also associated with increased risk of posterior subcapsular cataract formation. Prolonged topical use may also suppress the host immune response and increase the hazard of secondary ocular infections.

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to corneal perforation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original New Drug Application (NDA) for this product, Ozurdex (dexamethasone intravitreal implant), was approved on June 17, 2009, for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Subsequently, Ozurdex was approved on September 24, 2010, for the treatment of non-infectious uveitis affecting the posterior segment of the eye (NDA 22-315/S-003).

An end-of-phase 2 was conducted on September 18, 2003, with Oculex, the original IND sponsor (the IND was transferred to Allergan on November 24, 2003) to discuss the development of Ozurdex for the treatment of persistent diabetic macular edema (DME). The Agency made the following key recommendations:

- The Agency prefers the use of the vehicle or an alternate dose in clinical trials. Despite the use of masked and unmasked investigators, the potential exists for the introduction of significant bias with sham injection alone. While not preferred, a sham would not even be considered unless there was more than one dose included.
- The macular edema seen in diabetes mellitus is sufficiently different in nature from acute macular edema so as to require replication of efficacy in 2 adequate and well-controlled trials.

- The primary efficacy endpoint should be the proportion of patients with BCVA improvement of 15 or more letters from baseline in the study eye at 36 months.
- Intent-to-treat (ITT) with last observation carried forward (LOCF) and the per-protocol with observed cases analyses for each protocol should be provided in the final study report.

On December 6, 2004, the initial protocols for the phase 3 studies in DME were submitted to the IND, and then initiated in February 2005.

On September 30, 2011, in a briefing package submitted to the Agency in preparation for a Type-C meeting, Allergan proposed to change the primary efficacy endpoint to “BCVA average change from baseline during the study (AUC approach) in the study eye” for the 2 ongoing phase 3 DME studies. The Agency responded on October 31, 2011 that the primary efficacy endpoint should remain “BCVA improvement of 15 or more letters from baseline at 3 years.”

Allergan submitted a pre-NDA briefing package on July 13, 2013. Responses to the pre-NDA meeting questions were provided to Allergan on August 8, 2013.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of sufficient quality to allow for a substantive review. A routine Division of Scientific Investigations (DSI) audit was requested. Refer to the DSI review for additional information.

3.2 Compliance with Good Clinical Practices

Studies 206207-010 and 206207-011 were conducted in accordance with the principles of Good Clinical Practice (ICH E6).

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There are financial interests or arrangements to disclose from one investigator that participated in the covered clinical trials (206-207-010 and 206207-011). See Appendix 9.3 of this review.

Description of Financial Interests and Arrangements
Study 206207-010

Principal Investigator Name (Site/PI Number), Address	Description
Dirk Sander, M.D. (12509/8092)	(b) (6) (sub-investigator) at this site completed a Financial Disclosure Form on 14-Jun-2007, indicating a financial interest in the form of a grant from Allergan in 2004. However, (b) (6) then completed another form on 17-Jun-2007 indicating no financial interest and also did the same on 2 later forms dated 30-Aug-2007 and 09-Mar-2009. No other record of such a grant being paid to (b) (6) can be located; however (b) (6) has since left the site, so it is impossible to follow-up for clarification.

Reviewer's Comments:

This investigator contributed 2 patients to the study. Removal of the data from this site would have no significant impact on the final conclusions of either this study or the application as a whole.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no proposed changes to the Chemistry and Manufacturing Controls for Ozurdex in this supplemental application.

See CMC review for the original application.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology studies submitted in this supplemental application. No changes were made to the sections of the label relevant to Pharmacology/Toxicology.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were submitted to support the supplement. However, pharmacokinetic plasma samples were collected from selected patients in studies 206207-010 and 206207-011. The pharmacokinetic results show that the majority plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ) of 0.05 ng/mL

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol #	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subject/Patients Enrolled/Treatment
206207-010 Phase 3 Safety/ efficacy study	Prospective, multicenter randomized, masked, sham- controlled	Patients ≥ 18 years of age with DME, BCVA score 34-68 letters	DEX 700 DEX 350 Sham	Initial treatment on day 0 with eligible patients receiving up to 6 additional retreatment s ≥ 6 months apart	36 months	496 randomized DEX 700: 163 DEX 350: 166 Sham: 165
206207-011 Phase 3 Safety/ efficacy study	Prospective, multicenter randomized, masked, sham- controlled	Patients ≥ 18 years of age with DME, BCVA score 34-68 letters	DEX 700 DEX 350 Sham	Initial treatment on day 0 with eligible patients receiving up to 6 additional retreatment s ≥ 6 months apart	36 months	554 randomized DEX 700: 188 DEX 350: 181 Sham: 185

206207-012 Phase 2 Safety/ efficacy study	Prospective, multicenter randomized, masked, sham- controlled	Patients ≥ 18 years of age with diffuse DME	DEX 700 + Laser Sham + Laser	Initial treatment on day 0 with eligible patients receiving up to 3 additional laser treatments (13 weeks apart) and 1 additional DEX 700/Sham treatment ≥ 26 weeks after initial treatment	52 weeks	235 randomized DEX 700 + Laser: 126 Sham + Laser: 127
206207-018 Phase 2 Safety/ efficacy study	Prospective, multicenter open-label, uncontrolled	Patients ≥ 18 years of age with DME who had a pars plana vitrectomy in study eye	DEX 700	Single treatment on day 1	26 weeks	56 randomized DEX 700: 56

5.2 Review Strategy

The sources of clinical data utilized in this review include the clinical trials listed above in Section 5.1.

The applicant conducted four clinical trials in patients with DME. Studies 206207-010 and 206207-011 were phase 3 adequate and well controlled trials that compared two active treatment groups, dexamethasone 700 μg DEX PS DDS Applicator System (DEX 700) and dexamethasone 350 μg DEX PS DDS Applicator System (DEX 350), to the control group that received a sham needleless injection [Sham DEX PS DDS Applicator System (Sham)]. Study 206207-012 was a phase 2 adequate and well-controlled trial that compared the active treatment of DEX 700 in combination with laser photocoagulation to laser photocoagulation alone. Study 206207-018 was a phase 2 open-label, uncontrolled trial that evaluated a single treatment of DEX 700 in patients who had pars plana vitrectomy.

5.3 Discussion of Individual Studies/Clinical Trials

Study 206207-010

Title: A 3-Year, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

Study Design

This study was 3-year, prospective, multi-center, randomized, masked, sham-controlled, parallel-group safety and efficacy study. Patients were randomized in a 1:1:1 ratio to receive DEX 700, DEX 350, or Sham in patients with DME. Approximately 510 patients were planned. After the qualification/baseline visit, the randomization (day 0) visit, at which patients received the first treatment, occurred within 4-14 days. Study visits occurred every 1.5 months during the first year and every 3 months during years 2 and 3. Starting from the month 6 visit, patients were evaluated for re-treatment eligibility every 3 months but the study procedure was not to be performed more often than approximately every 6 months. Post-injection safety visits, required only when patients received a treatment or re-treatment, were scheduled 1, 7, and 21 days after the day of treatment or re-treatment.

Schedule of Visits and Procedures

Table 1 **SCHEDULE OF VISITS AND PROCEDURES**

Abbreviations: TI = Treating Investigator FI = Follow-up Investigator 7F = 7-field fundus photography 3F = 3-field fundus photography	Qual/ base line	Rando mizati on	Post-insertion safety visits (# days after any treatment or retreatment)			Year 1 Outcome Assessment Visits							
	Day -14 to -4	Day 0	Day 1	Day 7	Day 21	M 1.5 (-3wks)	M 3 (-3wks)	M 4.5 (-3wks)	M 6 (-3wks)	M 7.5 (-3wks)	M 9 (-3wks)	M 10.5 (-3wks)	M 12 (-3wks)
Informed Consent /Data Protection Form	X												
VFQ-25	X						X		X		X		X
SF-36 and EQ-5D	X												
VA/ BCVA by ETDRS	BCVA		VA	VA	VA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA
Contrast Sensitivity	X ^a								X ^a				X ^a
Medical and Ophthalmic Histories	X ^b	X											
Vital signs (blood pressure and pulse rate)	X						X		X		X		X
IOP	X		X	X	X	X	X	X	X	X	X	X	X
Endothelial Cell Density (selected sites)	X												X
Biomicroscopic Examination	FI ^c		TI ^a	TI ^a	TI ^a	FI	FI	FI	FI ^c	FI	FI	FI	FI ^c
Indirect Ophthalmoscopy	FI ^d		TI ^a	TI ^a	TI ^a	FI	FI	FI	FI	FI	FI	FI	FI
DDS Assessment with scleral depression							FI ^a		FI ^a		FI ^a		FI ^a
OCT	X						X ^a		X ^a		X ^a		X ^a
Fundus Photograph	7F/3F ^e						3F ^a		7F/3F ^e		3F ^a		7F/3F ^e
Fluorescein Angiography	X								X				X
Blood HbA1c Level	X						X		X				X
Glomerular Filtration Rate (GFR)	X												X
Therapeutic Drug Monitoring (selected sites)	X		X	X	X	X	X						
Urine Pregnancy Test		X ^e							X ^a		X ^a		X ^a
Concomitant Meds & Procedures		X	X	X	X	X	X	X	X	X	X	X	X
DEX PS DDS or sham procedure followed by indirect ophthalmoscopy		TI ^f							TI ^f		TI ^f		TI ^f
Dispense pre/post-operative antibiotics	X							X		X		X	
Serious Medical Events	FI	TI											
Adverse Events		TI	TI	TI	TI	FI	FI	FI	FI/TI	FI	FI/TI	FI	FI/TI

Note: Unless indicated otherwise, examinations are performed in both eyes

SCHEDULE OF VISITS AND PROCEDURES (Cont'd)

Note: Unless indicated otherwise, examinations are performed in both eyes

Abbreviations: TI = Treating Investigator FI = Follow-up Investigator 7F = 7-field fundus photography 3F = 3-field fundus photography	Post-insertion safety visits (# days after any treatment or retreatment)			Year 2 Outcome Assessment Visits				Year 3 Outcome Assessment Visits				
	Day 1	Day 7	Day 21	M 15 (-3wks)	M 18 (-3wks)	M 21 (-3wks)	M 24 (-3wks)	M 27 (-3wks)	M 30 (-3wks)	M 33 (-3wks)	M 36/ Exit/ Early Study Discontinuation (-3wks)	M 39/Exit (-3wks)
VFQ-25				X	X	X	X	X	X	X	X	X
VA/ BCVA by ETDRS	VA	VA	VA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA	BCVA
Contrast Sensitivity					X ^a		X ^a		X ^a		X ^{ah}	X ^a
Vital signs (blood pressure and pulse rate)				X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X	X	X	X
Endothelial Cell Density (selected sites)							X				X	
Biomicroscopic Examination	TI ^a	TI ^a	TI ^a	FI	FI ^c	FI	FI ^c	FI	FI ^c	FI	FI ^c	FI ^c
Indirect Ophthalmoscopy	TI ^a	TI ^a	TI ^a	FI	FI	FI	FI	FI	FI	FI	FI	FI
DDS Assessment with scleral depression				FI ^a	FI ^a	FI ^a	FI ^a	FI ^a	FI ^a	FI ^a	FI ^a	FI ^a
OCT				X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Fundus Photograph					3F ^a		7F/3F ^b		3F ^a		7F/3F ^b	7F/3F ^b
Fluorescein Angiography							X				X	X
Blood HbA1c Level					X		X		X		X ^h	X
Glomerular Filtration Rate (GFR)							X				X ^h	X
Therapeutic Drug Monitoring (selected sites)												
Urine Pregnancy Test				X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e
Concomitant Meds & Procedures				X	X	X	X	X	X	X	X	X
DEX PS DDS placement or sham procedure followed by indirect ophthalmoscopy				TI ^f	TI ^f	TI ^f	TI ^f	TI ^f	TI ^f	TI ^f	TI ^f	
Dispense pre/post-operative antibiotics				X	X	X	X	X	X	X		
Adverse Events	X	X	X	FI/TI	FI/TI	FI/TI	FI/TI	FI/TI	FI/TI	FI/TI	FI/TI	FI

- ^a Study eye only
- ^b Medical history includes pre-study medication and demographic data. Height and weight should be measured at qualification/baseline as part of the demographic data
- ^c Includes cup/disc ratio
- ^d Scleral depression (study eye only)
- ^e Required for females of childbearing potential at baseline, prior to each retreatment, and at study discontinuation or exit
- ^f Includes assessment of treatment eligibility and assessment of insertion site after the study treatment procedure
- ^g 3-field Fundus Photography at selected sites.
- ^h Procedure should not be performed if the patient is determined to be eligible for retreatment at month 36. Only required for patients who are exiting at this visit.

Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, at least 18 years of age
2. Diagnosis of diabetes mellitus (type 1 or type 2). Any of the following will be considered to be sufficient evidence that diabetes is present:
 - Current regular use of insulin for the treatment of diabetes
 - Current regular use of oral hypoglycemic agent(s) for the treatment of diabetes
 - Diabetes defined by American Diabetes Association (ADA) guidelines:
 - Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus plasma glucose concentration at any time of the day regardless of time since last meal ≥ 200 mg/dl (11.1 mmol/l) or
 - 8-hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l) or
 - 2-hour postload (75 g) glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test
3. Diabetic macular edema in the study eye defined as clinically observable macular edema involving the center of the macula (fovea) associated with diabetic retinopathy with any of the following characteristics:
 - a) Prior medical therapy for diabetic macular edema
 - b) Prior macular laser(s) for diabetic macular edema with the most recent laser at least 3 months prior to Baseline/Qualification where, in the opinion of the investigator, the patient will be able to improve 15 or more letters in BCVA from baseline with the resolution of the macular edema despite the presence of macular laser scars
 - c) In the investigator's opinion the patient would not benefit from macular laser treatment
 - d) The patient refuses laser treatment
4. BCVA score between 34 letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye measured by the ETDRS method at qualification/baseline
5. Retinal thickness of ≥ 300 μ m by OCT in the 1 mm central macular subfield of the study eye at qualification/baseline as determined by the investigator
6. Patients who have received intravitreal triamcinolone acetonide must satisfy the following:
 - The intended dose for each injection was 4 mg or less
 - The most recent dose was at least 6 months prior to qualification/baseline visit
 - No treatment-related adverse event was seen that, in the opinion of the investigator, has the potential to worsen or reoccur with study treatment
7. Female patients of childbearing potential must have a negative urine pregnancy test at the randomization (day 0) visit
8. Written informed consent has been obtained
9. Written Authorization for Use and Release of Health and Research Study Information (US sites only) has been obtained
10. Written Data Protection Consent (European sites only) has been obtained
11. Written documentation has been obtained, in accordance with state and country privacy requirements, where applicable

Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Uncontrolled systemic disease or current immunosuppressive diseases (e.g., HIV+ or AIDS)
2. Initiation of medical therapy for diabetes or a change from oral hypoglycemic agents to insulin therapy within 4 months prior to the qualification/baseline visit
3. Blood HbA1c level greater than 10% at the qualification/baseline visit
4. Renal failure requiring hemodialysis or peritoneal dialysis within 6 months prior to the qualification/baseline visit
5. Adjusted glomerular filtration rate (GFR) less than 50 mL/min based on the Modified Diet in Renal Disease (MDRD) formula adjusted for body surface area, at the qualification/baseline visit
6. Any ocular condition in the study eye that in the opinion of the investigator would prevent a 15-letter improvement in visual acuity (e.g., severe macular ischemia, extensive macular laser scarring or atrophy)
7. Presence of branch retinal vein occlusion, central retinal vein occlusion, uveitis, pseudophakic cystoid macular edema or any other condition in the study eye which could be contributing to macular edema
8. Presence of an epiretinal membrane or vitreo-retinal interface changes in the study eye which, in the opinion of the investigator, is the primary cause of macular edema, or is severe enough to prevent improvement in visual acuity despite reduction in macular edema
9. History of IOP elevation in response to steroid treatment in either eye that resulted in any of the following:
 - A ≥ 10 mmHg increase in IOP from baseline with an absolute IOP ≥ 25 mmHg
 - Required therapy with 3 or more anti-glaucoma medications
10. History of glaucoma or optic nerve head change consistent with glaucoma damage and/or glaucomatous visual field loss in the study eye. Patients with a history of previous angle-closure or similar conditions that have been successfully treated with either a laser or surgical peripheral iridotomy are allowed as long as the visual fields and optic nerves have been stable for > 1 year prior to study entry and the patient has been and can be safely dilated
11. Ocular hypertension in the study eye at qualification/baseline with any of the following:
 - IOP > 23 mmHg if taking no anti-glaucoma medications
 - IOP > 21 mm Hg if taking 1 anti-glaucoma medication
 - Use of 2 or more anti-glaucoma medications (combination products should be considered 2 medications)

Note: Anti-glaucoma medications or lack thereof must be stable for at least 4 weeks prior to qualification/baseline
12. Aphakia or presence of anterior chamber intraocular lens in the study eye
13. Active optic disc or retinal neovascularization in the study eye at qualification/baseline
14. Active or history of choroidal neovascularization in the study eye
15. Presence of rubeosis iridis in the study eye at qualification/baseline
16. Any active ocular infection (i.e., bacterial, viral, parasitic, or fungal) in either eye at qualification/baseline
17. History of herpetic infection in the study eye or adnexa
18. Presence of active or inactive toxoplasmosis in either eye at qualification/baseline
19. Presence of visible scleral thinning or ectasia in the study eye

20. Media opacity in the study eye at qualification/baseline that precludes clinical and photographic evaluation (including but not limited to preretinal or vitreous hemorrhage, lens opacity)
21. Intraocular surgery, including cataract surgery, and/or laser of any type in the study eye within 90 days prior to qualification/baseline
22. History of central serous chorioretinopathy in either eye
23. History of pars plana vitrectomy in the study eye
24. Anticipated need for ocular surgery or laser in the study eye within 1 year following the qualification/baseline visit [e.g., panretinal photocoagulation (PRP), cataract surgery]
25. History of use of intravitreal steroids in the study eye other than triamcinolone acetonide
26. History of use of intravitreal bevacizumab, ranibizumab, or pegaptanib in the study eye within 3 months prior to qualification/baseline visit
27. History of use of any intravitreal agent in the study eye other than triamcinolone acetonide, bevacizumab, ranibizumab, or pegaptanib, or intravitreal doses of triamcinolone acetonide > 4 mg, bevacizumab > 1.25 mg, ranibizumab > 0.5 mg, or pegaptanib > 0.3 mg
28. Periocular depot of steroids to the study eye within 6 months prior to qualification/baseline
29. Use of systemic steroids (e.g., oral, intravenous, intra-articular, epidural, intra-bursal) within 1 month prior to the qualification/baseline visit or anticipated use at any time during the study. Inhaled and intranasal steroids are allowed
30. For patients who participated in therapeutic drug monitoring evaluation only: use of dexamethasone within 1 month prior to qualification/baseline or anticipated use during the first 90 days in any form/route of administration
31. Use of immunosuppressants, immunomodulators, antimetabolites and/or alkylating agents within 6 months prior to qualification/baseline or anticipated use at any time during the study
32. Use of warfarin enoxaparin, or heparin within 2 weeks prior to qualification/baseline or anticipated use within the 3-year study period
33. BCVA score < 34 letters (approximately 20/200 Snellen equivalent) in the nonstudy eye using the ETDRS method at qualification/baseline
34. Known allergy or hypersensitivity to the study medication or its components
35. Known allergy or contraindication to the use of fluorescein or povidone iodine
36. Contraindication to pupil dilation in either eye
37. Previous enrollment in a POSURDEX (DEX PS DDS Applicator System) clinical trial
38. Patients who plan for an extended absence away from the immediate area of the study center that would preclude them from returning for all protocol specified study visits
39. Any condition (including inability to read visual acuity charts or language barrier) which precludes patient's ability to comply with study requirements including completion of the study
40. Female patients who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not using a reliable means of contraception
41. Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to qualification/baseline

Patient has a condition or is in a situation which, in the Investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study.

Primary Efficacy Variable

The primary efficacy variable was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at the year 3/final visit.

Secondary Efficacy Variables

The secondary efficacy variables were contrast sensitivity, optical coherence tomography (OCT), fundus photography and fluorescein angiography (FA).

Table of Investigators

Investigator (Investigator #)	Number of Subjects Enrolled N=496			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Juan Orellana, M.D. (0448) Richmond, VA 23219 USA	2 (0.4)	1		1
Itamar Klemperer, MD (2341) POB 151 Beer Sheva 84101 Israel	9 (1.8)	3	3	3
Petrus Gous, MD (3084) Arcadia Pretoria 0007 South Africa	12 (2.4)	4	4	4
Stefanie Schmickler, MD (3193) D-48683 Ahaus Germany	7 (1.4)	2		2
Stewart Lake, MD (6354) Bedford Park, SA 5042 Australia <i>Replaced Russell Phillips, MD (3395) at the same address</i>	0 (0.0)			
Gil Sartani, MD (3983) Afula 18101 Israel	10 (2.0)	3	4	3
Joel Corwin, MD (4082) Ventura, CA 93003 USA	2 (0.4)	1		1
Andrew Antoszyk, MD (4221) Charlotte, NC 10023 USA	7 (1.4)	2	2	3
David M. Brown, MD (4231) Houston, TX 77030 USA	2 (0.4)	1	1	
Robert G. Devenyi, MD (4241) Toronto, ONT M5T 2S8 Canada	1 (0.2)			1
Richard Dreyer, MD (4243)	1 (0.2)			1

Investigator (Investigator #)	Number of Subjects Enrolled N=496			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Portland, OR 97210 USA				
Gregory M. Fox, MD (4250) Shawnee Mission, KS 66204 USA	7 (1.4)	2	2	3
David Glaser, MD (4252) Florissant, MO 63031 USA	4 (0.8)	1	2	1
Lawrence Halperin, MD (4256) Ft. Lauderdale, FL 33334 USA	5 (1.0)	2	1	2
Dennis Han, MD (4258) Milwaukee, WI 53226 USA	4 (0.8)	1	2	1
Raj K. Maturi, MD (4277) Indianapolis, IN 46290 USA	11 (2.2)	4	4	3
James Miller, Jr., MD (4280) Knoxville, TN 37920 USA	3 (0.6)	1	1	1
James Peace, MD (4288) Inglewood, CA 90301 USA	7 (1.4)	2	3	2
Glenn L. Wing, MD (4311) Fort Myers, FL 33912 USA	14 (2.8)	5	4	5
Ingrid E. Zimmer-Galler, MD. (4314) Baltimore, MD 21287 USA	1 (0.2)		1	
Patrick L. Tsai, MD (4316) Tucson, AZ 85711 USA <i>Replaced John Nichols, MD (4316) at the same address</i> <i>J. Nichols, MD replaced Robert Park, MD (4316) at the same address</i>	2 (0.4)	1		1
Alan Cruess, MD (4341) Halifax, NS B3H 2Y9 Canada	9 (1.8)	3	3	3
Albert J. Augustin, MD (4353) D-76133 Karlsruhe Germany	11 (2.2)	4	4	3

Investigator (Investigator #)	Number of Subjects Enrolled N=496			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Mark Daniell, MD (4368) Parkville, VIC 3052 Australia	7 (1.4)	3	2	2
Prof. Mark Gillies (4374) Sydney, NSW 2000 Australia	2 (0.4)	1		1
Prof. Tien Wong (4375) East Melbourne, VIC 3002 Australia	3 (0.6)	1	1	1
Prof. Paul Mitchell (4377) Westmead, NSW 2145 Australia	11 (2.2)	3	4	4
Prof. Karl Ulrich Bartz-Schmidt (4391) 72076 Tuebingen Germany	3 (0.6)	1	1	1
Jose Maria Ruiz Moreno, MD (4396) 03016 Alicante Spain	10 (2.0)	3	4	3
Alvaro Fernandez-Vega Sanz, MD (4397) 33012 Oviedo Spain	17 (3.4)	5	6	6
Ramakrishna Ratnakaram, MD (4411) Gainesville, FL 32610 USA	1 (0.2)			1
Marta Suarez-Figueroa, MD (4416) 28002 Madrid Spain	2 (0.4)	1	1	
Barrett Katz, MD, MBA (4417) Bronx, NY 10467 USA <i>Replaced Daniel Chechik, MD (4417) at the same address</i> <i>D. Chechik, MD replaced Harry M. Engel, MD at the same address</i>	2 (0.4)	1		1
Prof. Frank G. Holz (4421) 53105 Bonn Germany	8 (1.6)	2	3	3
Judianne Kellaway, MD (4431) Houston, TX 77030 USA	2 (0.4)		1	1
Adiel Barak, MD (4447)	31 (6.3)	10	10	11

Investigator (Investigator #)	Number of Subjects Enrolled N=496			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Tel Aviv 64239 Israel				
Joseph R. Ferenez, MD (4449) Kfar-Saba 44281 Israel	42 (8.5)	14	14	14
Joseph Moisseiev, MD (4450) Tel-Hashomer 52621 Israel	4 (0.8)	1	1	2
Prof. Ayala Pollack (4451) Rehovot 76100 Israel	31 (6.3)	11	10	10
Dov Weinberger, MD (4452) Petach – Tikva 49100 Israel	20 (4.0)	6	7	7
Jiong Yan, MD (4458) Atlanta, GA 30322 USA	2 (0.4)	1	1	
John R. Gonder, MD (4474) London, ONT N6A 4V2 Canada	12 (2.4)	4	4	4
Paul McCartney, MD (4496) Hobart, TAS Australia	1 (0.2)	1		
Susanna Park, MD, PhD (4513) Sacramento, CA 95817 USA <i>Replaced Lawrence Morse, MD, PhD (4514) at the same address</i>	6 (1.2)	2	2	2
Henry Newland, MD (4520) Adelaide, SA Australia	2 (0.4)		1	1
Richard B. Rosen, MD (4539) New York, NY USA	3 (0.6)	1	1	1
Oliver Zeitz, MD (5295) 20246 Hamburg Germany	0 (0.0)			
Ivan Fiser, MD (6413) 140 00 Prague 4 Czech Republic	3 (0.6)	1	1	1
Jiri Rehak, MD, CSc (6415) 775 20 Olomouc	12 (2.4)	4	4	4

Investigator (Investigator #)	Number of Subjects Enrolled N=496			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Czech Republic				
Jan Studnicks, MD, PhD (6417) 500 05 Hradee Kralove Czech Republic	8 (1.6)	3	2	3
Igor Vicha, MD (6418) 625 00 Brno Czech Republic	25 (5.0)	8	9	8
Bohdana Kalvodova, MD, PhD (6652) 128 08 Prague 2 Czech Republic	4 (0.8)	2	1	1
James Acton, MD (6653) Cape Town, 7530 South Africa	7 (1.4)	2	3	2
Linda Visser, MD (6654) Durban, 4001 South Africa	3 (0.6)	1	1	1
Trevor Carmichael, MD (6655) Johannesburg, 2157 South Africa	12 (2.4)	4	4	4
Joao Figueira, MD (6685) 3000-548 Coimbra Portugal	18 (3.6)	6	6	6
Rafael Navarro, MD (7605) 08035 Barcelona Spain	2 (0.4)	1	1	
Harvey Uy, MD (7871) Makati, 1200 Philippines	28 (5.6)	9	10	9
Dirk Sandner, MD (8092) 01307 Dresden Germany	2 (0.4)	1	1	
Miroslav Veith, MD (31120) 100 34 Prague 10 Czech Republic <i>Replaced Peter Soucek, MD, PhD (8093) at the same address</i>	10 (2.0)	4	3	3
Jan Ernest, MD, PhD (8907) 169 02 Praha Czech Republic	7 (1.4)	2	2	3

Study 206207-011

Title: A 3-Year, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

Study Design

The study design was identical to Study 206207-010.

Table of Investigators

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Rubens Belfort, Jr., M.D. (0469) Sao Paulo – SP 04023-062 Brazil	32 (5.8)	10	11	11
Prof. Luca Rossetti (0914) 20142 Milano Italy <i>Replaced Prof. Nicola Orzalesi (0914) at the same address</i>	3 (0.5)	1	1	1
Srinivas Sadda, MD (6236) Los Angeles, CA 90033 USA <i>Replaced Dean Elliott, MD (2680) at the same address</i> <i>D. Elliott, MD (2680) replaced Lawrence P. Chang, MD (1671) at the same address</i> <i>L. P. Chang, MD (1671) replaced Tom Chang, MD at the same address</i>	13 (2.3)	4	4	5
Kenneth Sall, MD (2707) Artesia, CA 90701 USA	68 (12.3)	23	23	22
Prof. Jean-Paul Romanet (2793) 38043 Grenoble Cedex 09 France	4 (0.7)	1	1	2
Prof. Eric Souied (28409) Creteil 94010 France	6 (1.0)	2	2	2

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
<i>Replaced Prof. Gisele Soubrane (3059) at the same address</i>				
Prof. Catherine Creuzot-Garcher (3361) 21033 Dijon France	3 (0.5)	1	1	1
Kim Ramaswamy, MD (4019) Madurai-625020, Tamilnadu India	3 (0.5)	1	1	1
Prof. Ugo Menchini (4044) 50134 Firenze Italy	12 (2.2)	4	4	4
David S. Boyer, MD (4207) Beverly Hills, CA 90211 USA	3 (0.5)	1	1	1
Baruch Kuppermann, MD, PhD (4209) Orange, CA 92868 USA	2 (0.4)	1		1
Prof. Paolo Lanzetta (4217) 33100 Udine Italy	12 (2.2)	4	4	4
Andre M. V. Gomes, MD (5603) Sao Paulo/SP-01525-001 Brazil	16 (2.9)	6	5	5
<i>Replaced Suel Abujamra (4220) at the same address</i>				
Marcos P. de Avila, MD (4223) Goiania—GO 74210-010 Brazil	1 (0.2)		1	
Caroline Bauman, MD (4224) Boston, MA 02111 USA	5 (0.9)	2	1	2
Isaac Loose, MD (4227) Austin, TX 78705 USA	7 (1.3)	3	2	2
William Z. Bridges, Jr., MD (4230) Asheville, NC 28803 USA	4 (0.7)	2	1	1
Ken Carnevale, MD (4234) Lynbrook, NY 11563 USA	3 (0.5)	1	1	1
Bernard H. Doft, MD (4242)	18 (3.2)	6	6	6

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Pittsburgh, PA 15213 USA				
Sharon Fekrat, MD (4247) Durham, NC 27710 USA	3 (0.5)	1	1	1
Steven D. Schwartz, MD (4255) Los Angeles, CA 90095 <i>Replaced Anurag Gupta, MD (4355) at the same address</i>	2 (0.4)		1	1
Peter Kaiser, MD (4265) Cleveland, OH 44195 USA	2 (0.4)		1	1
Jose A. Martinez, MD (4276) Austin, TX 78705 USA	6 (1.0)	2	2	2
Peter R. Pavan, MD (4287) Tampa, FL 33612 USA <i>Replaced Burton G. Goldstein, MD (4409) at the same address</i>	6 (1.0)	2	2	2
Don J. Perez-Ortiz, MD (4289) Tampa, FL 33603 USA	1 (0.2)	1		
Seenu M. Hariprasad, MD (5099) Chicago, IL 60637 USA <i>Replaced Kourous Rezaei, MD (4292) at the same address</i>	9 (1.6)	3	3	3
Daniel Rosberger, MD, PhD (4294) New York, NY 10021 USA	0 (0.0)			
Michael Singer, MD (4298) San Antonio, TX 78240 USA	6 (1.0)	3	3	3
Walter Y. Takahashi, MD (4303) Sao Paulo – SP – 05403-010 Brazil	8 (1.4)	3	2	3
Lucy H. Young, MD, PhD (4313) Boston, MA 02114 USA	4 (0.7)	2	1	1

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Steven Rose, MD (4338) Rochester, NY 14618 USA	15 (2.7)	5	5	5
Prof. Pascale Massin (4348) 75571 Paris Cedex 12 France	4 (0.7)	1	1	2
Prof. Edoardo Midena (4355) 35128 Padova Italy <i>Engel, MD at the same address</i>	11 (2.0)	3	4	4
William R. Freeman, MD (4361) La Jolla, CA 92093 USA	1 (0.2)	1		
Carl Awh, MD (4364) Nashville, TN 37203 USA	4 (0.7)	1	1	2
Mark Donaldson, MD (4379) Epsom, Auckland New Zealand	7 (1.3)	2	3	2
Monique Leys, MD (4380) Morgantown, WV 26506 USA	7 (1.3)	2	2	3
Prof. Andrew Lotery (5271) Southampton, S016 6YD United Kingdom <i>Replaced Richard Newsom, MD (4394) at the same address</i>	2 (0.4)	1		1
Rosangela Lattanzio, MD (4401) 20132 Milano Italy	11 (2.0)	4	3	4
Mark Michels, MD (4406) Palm Beach Gardens, FL 33410 USA	6 (1.0)	2	2	2
Prof. Giovanni Staurenghi (4408) 20157 Milano Italy	7 (1.3)	3	2	2
Antonio M. Casella, MD (4453) Londrina – PR – 86051-990 Brazil	3 (0.5)	1	1	1
Joao L. Ferreira, MD (4454) Florianopolis – SC – 88015-080 Brazil	2 (0.4)	1	1	
Randy S. Katz, MD (4456)	1 (0.2)	1		

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Boynton Beach, FL 33426 USA				
Fareed Ali, MD, FRCSC (4473) Mississauga, ON L4W 1W9 Canada	1 (0.2)			1
Prof. Daniele Tognetto (32070) 34129 Trieste Italy <i>Replaced Prof. Giuseppe Ravalico (0471) at the same address</i> <i>Prof. G. Ravalico replaced Maurizio Battaglia Parodi, MD (4498) at the same address</i>	11 (2.0)	4	4	3
Lawrence J. Ulanski, II, MD (4523) Chicago, IL 60612 USA	3 (0.5)	1	1	1
Thomas F. Essman, MD (4529) Springfield, MO 65804 USA	1 (0.2)	1		
Edmund Wong, MD (4531) Singapore 168751 Singapore	5 (0.9)	2	1	2
Muna Bhende, MD (4614) Chennai-600 006, Tamil Nadu India <i>Replaced Lingam Gopal, MD (4533) at the same address</i>	19 (3.4)	7	6	6
John Lehr, MD (4569) Orlando, FL 32803 USA	1 (0.2)		1	
Ajit B. Majji, MD (4571) Hyderabad, Andhra Pradesh 500 034 India	4 (0.7)	2	1	1
Francisco J. Rodriguez Alvira, MD (4580) Bogota Colombia	9 (1.6)	3	3	3
Augusto Paranhos, Jr., MD (4582) Sao Paulo – SP – 05651-901 Brazil	5 (0.9)	2	1	2
Philip M. Falcone, MD (4583)	1 (0.2)	1		

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Bridgeport, CT 06606 USA				
Prof. Young Hee Yoon (4618) Seoul 138-736 South Korea	39 (7.0)	13	13	13
Bradley Foster, MD (5020) Springfield, MO 01107 USA	5 (0.9)	1	2	2
Dr. Sobha Sivaprasad (5255) London, SE5 9RS United Kingdom <i>Replaced Victor Chong, MD (4360) at the same address</i>	3 (0.5)	1	1	1
Y.R. Sharma, MD (36430) New Delhi, 110029 India <i>Replaced S.P. Garg, MD (5941) at the same address</i>	9 (1.6)	3	3	3
Amod Gupta, MD (5942) Sector 12, Chandigarh PIN 160012 India	8 (1.4)	3	3	2
Prof. Dariusz Kecik (6425) 02-005 Warszawa Poland	2 (0.4)	1		1
Ass. Prof. Edward Wylegala (6682) 40-760 Katowice Poland	10 (1.8)	3	4	3
Francesco Viola, MD (6683) 20122 Milano Italy	12 (2.2)	4	4	4
Janos Nemeth, MD (6684) Budapest 1083 Hungary	7 (1.3)	2	3	2
Da-Wen Lu, MD (6687) Taipei 114 Taiwan	1 (0.2)		1	
San-Ni Chen, MD (6689) Changhua 500 Taiwan	1 (0.2)		1	
Shwu-Jiuan Sheu, MD (6690) Kaohsiung 813	10 (1.8)	3	3	4

Investigator (Investigator #)	Number of Subjects Enrolled N=554			
	Total n (%)	DEX 700 n	DEX 350 n	Sham n
Taiwan				
Stanislao Rizzo, MD (7412) 56124 Pisa Italy	1 (0.2)			1
Prof. Won-Ki Lee (7873) Seoul 137-040 South Korea	5 (0.9)	2	2	1
Prof. Hyeong G. Yu (8271) Seoul 110-744 South Korea	12 (2.2)	4	4	4
Haroldo Vieira de Moraes, Jr., MD (8295) Rio de Janeiro – RJ -21941-913 Brazil	6 (1.0)	2	2	2
Monica Varano, MD (9095) 00191 Rome Italy	19 (3.4)	6	6	7
Geeta Menon, MD, MBBS, MS (9132) Surrey, GU16 7UJ United Kingdom	1 (0.2)	1		

Study 206207-012

Title: A 52-Week, Masked, Multicenter, Randomized, Controlled Trial (Up to 13 Weeks Additional Follow-up) to Assess the Safety and Efficacy of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in Combination with Laser Photocoagulation Compared with Laser Photocoagulation Alone in the Treatment of Subjects With Diffuse Diabetic Macular Edema (DME)

Study Design

This study was a 52 to 53-weeks, prospective, multicenter, randomized, masked, parallel group, safety and efficacy study with up to 13 weeks additional follow-up. Prior to randomization, patients were stratified into 1 of 2 groups based on baseline BCVA score using the modified ETDRS method (≥ 34 to ≤ 49 letters or ≥ 50 to ≤ 70 letters). Within each stratum, patients were randomly assigned in a 1:1 ratio to Combination Therapy or Laser Alone. Approximately 248 patients were planned.

At the initial treatment (Day 0), the study eye of each patient will receive either DEX or Sham DEX, followed 3 to 4 weeks later by laser photocoagulation. After initial treatment, a maximum of 3 additional laser treatments could be administered at intervals no less than 13 weeks and a maximum of 1 additional treatment of DEX/Sham DEX may be administered with a minimum interval of 26 weeks.

The primary efficacy variable was the proportion of patients with a BCVA improvement of ≥ 10 letters in the study eye from baseline at month 12. Safety variables include adverse events, BCVA, IOP, biomicroscopy, indirect ophthalmoscopy, DEX PS DDS residual assessment, blood pressure, pulse rate, urine pregnancy test, HbA1c level, GFR.

Study 206207-018

Title: A 26-Week, Open-Label Study to Assess the Safety and Efficacy of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the treatment of Vitrectomized Subjects with Diabetic Macular Edema

Study Design

This study was an exploratory, multicenter, open-label, study of DEX PS DDS Applicator System in approximately 40 DME patients with a history pars plana vitrectomy. Approximately 40 patients were planned. Patients received a single intravitreal injection of 700 µg DEX PS DDS. Patients were evaluated at 9 scheduled visits. The duration of evaluation of each patient was up to 28 weeks. The primary efficacy was the change from baseline central retinal thickness as measured by OCT. Safety was monitored using BCVA, IOP, biomicroscopy, ophthalmoscopy, as well as other standard safety variables.

6 Review of Efficacy

6.1 Indication

The proposed indication is treatment of diabetic macular edema.

6.1.1 Methods

The primary support for efficacy for DEX 700 comes from Studies 206207-0110 and 206207-011. The two phase 2 studies, Study 206207-012 and Study 206207-018, are supportive. Both phase 2 studies specified primary efficacy endpoints that are not considered acceptable primary endpoints. Hence, the efficacy results from these two studies will not be presented in this review.

6.1.2 Demographics

Study 206207-010: Demographic Statistics by Treatment (ITT Population)

Characteristic	DEX 700 N=163 n (%)	DEX 350 N=166 n (%)	Sham N=165 n (%)	Total N=494 n (%)
Age (years)				p=0.696 ^a
Mean (SD)	63.1 (8.01)	63.3 (9.01)	62.6 (9.10)	63.0 (8.71)
Range	33 to 84	27 to 82	26 to 83	26 to 84
< 45	4 (2.5)	5 (3.0)	7 (4.2)	16 (3.2)
45 to 65	89 (54.6)	97 (58.4)	95 (57.6)	281 (56.9)

> 65	70 (42.9)	64 (38.6)	63 (38.2)	197 (39.9)
Sex				p=0.906 ^a
Male	102 (62.6)	100 (60.2)	102 (61.8)	304 (61.5)
Female	61 (37.4)	66 (39.8)	63 (38.2)	190 (38.5)
Race				p=0.649 ^a
Caucasian	138 (84.7)	140 (84.3)	134 (81.2)	412 (83.4)
Non-Caucasian	25 (15.3)	26 (15.7)	31 (18.8)	82 (16.6)
Black	7 (4.3)	7 (4.2)	13 (7.9)	27 (5.5)
Asian ^b	12 (7.4)	14 (8.4)	13 (7.9)	39 (7.9)
Hispanic	1 (0.6)	2 (1.2)	2 (1.2)	5 (1.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other ^c	5 (3.1)	3 (1.8)	3 (1.8)	11 (2.2)
Iris Color				p=0.907 ^a
Light	69 (42.3)	74 (44.6)	73 (44.2)	216 (43.7)
Dark	94 (57.7)	92 (55.4)	92 (55.8)	278 (56.3)
Weight (kg)				p=0.337 ^a
Mean (SD)	84.3 (17.79)	85.1 (20.43)	82.2 (16.95)	83.8 (18.46)
Range	48 to 144	43 to 155	50 to 150	43 to 155
Height				p=0.957 ^a
Mean (SD)	167.2 (9.30)	167.3 (10.12)	167.0 (8.84)	167.1 (9.42)
Range	146 to 188	139 to 191	142 to 188	139 to 191

ITT=intent-to-treat, SD=standard deviation

^a P-value for continuous variables of age, height, and weight are from a 1-way analysis of variance (ANOVA). P-values for categorical values of sex, race (Caucasian versus non-Caucasian), and iris color (light versus dark) are from Pearson's chi-square test.

^b Asian race excludes Japanese.

^c Other included Gypsy, Mixed origins/mixed ethnicity, and Cypriot.

Study 206207-011: Demographic Statistics by Treatment (ITT Population)

Characteristic	DEX 700 N=188 n (%)	DEX 350 N=181 n (%)	Sham N=185 n (%)	Total N=554 n (%)
Age (years)				p=0.558 ^a
Mean (SD)	61.9 (8.57)	61.3 (9.34)	62.4 (9.85)	61.9 (9.26)
Range	40 to 85	25 to 84	29 to 88	25 to 88
< 45	2 (1.1)	8 (4.4)	6 (3.2)	16 (2.9)
45 to 65	116 (61.7)	109 (60.2)	108 (58.4)	333 (60.1)
> 65	70 (37.2)	64 (35.4)	71 (38.4)	205 (37.0)
Sex				p=0.746 ^a
Male	111 (59.0)	106 (58.6)	115 (62.2)	332 (59.9)
Female	77 (41.0)	75 (41.4)	70 (37.8)	222 (40.1)
Race				p=0.891 ^a

Caucasian	96 (51.1)	94 (51.9)	99 (53.5)	289 (52.2)
Non-Caucasian	92 (48.9)	87 (48.1)	86 (46.5)	265(47.8)
Black	9 (4.8)	9 (5.0)	7 (3.8)	25 (4.5)
Asian ^b	42 (22.3)	42 (23.2)	40 (21.6)	124 (22.4)
Hispanic	34 (18.1)	32 (17.7)	31 (16.8)	97 (17.5)
Japanese	1 (0.5)	2 (1.1)	1 (0.5)	4 (0.7)
Other ^c	6 (3.2)	2 (1.1)	7 (3.8)	15 (2.7)
Iris Color				p=0.582 ^a
Light	58 (30.9)	47 (26.0)	53 (28.6)	158 (28.5)
Dark	130 (69.1)	134 (74.0)	132 (71.4)	396 (71.5)
Weight (kg)				p=0.483 ^a
Mean (SD)	81.2 (22.60)	79.0 (20.11)	78.9 (18.10)	83.8 (18.46)
Range	41 to 204	43 to 160	45 to 135	41 to 204
Height				p=0.502 ^a
Mean (SD)	163.8 (9.39)	164.5 (9.74)	165.0 (9.51)	164.4 (9.54)
Range	137 to 196	135 to 186	133 to 190	133 to 196

ITT=intent-to-treat, SD=standard deviation

^a P-value for continuous variables of age, height, and weight are from a 1-way analysis of variance (ANOVA). P-values for categorical values of sex, race (Caucasian versus non-Caucasian), and iris color (light versus dark) are from Pearson's chi-square test.

^b Asian race excludes Japanese.

^c Other included Mixed origins/mixed ethnicity, Pakistan, Moari, Arab, Armenian, North African, and Fijian.

Reviewer's Comments:

There were no remarkable differences between treatment groups regarding age, gender, race, eye color, weight or height in studies 206207-010 and 206207-011.

6.1.3 Subject Disposition

Study 206207-010: Subject Disposition and Primary Reason for Discontinuation (ITT Population)

Disposition and Discontinuation	DEX 700 n (%)	DEX 350 n (%)	Sham n (%)	Total n (%)
Total Randomized	163 ^a	166 ^b	165 ^c	494
Treated	160	165	164	489
As randomized	160 (98.2)	165 (99.4)	164 (99.4)	489 (99.0)
Never received treatment	3 (1.8)	1 (0.6)	1 (0.6)	5 (1.0)
ITT Population	163	166	165	494
Completed	107 (65.6)	118 (71.1)	70 (42.4)	295 (59.7)
Discontinued	56 (34.4)	48 (28.9)	95 (57.6)	199 (40.3)
Primary reason for Discontinuation (ITT Population)				

Adverse event	20 (12.3)	18 (10.8)	16 (9.7)	54 (10.9)
Ocular	10 (6.1)	10 (6.0)	13 (7.9)	33 (6.7)
Non-ocular	10 (6.1)	8 (4.8)	3 (1.8)	21 (4.3)
Lack of efficacy	9 (5.5)	14 (8.4)	37 (22.4)	60 (12.1)
Lost to follow-up	5 (3.1)	5 (3.0)	10 (6.1)	20 (4.0)
Personal reasons	7 (4.3)	4 (2.4)	16 (9.7)	27 (5.5)
Protocol violation	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.4)
Other ^d	13 (8.0)	7 (4.2)	16 (9.7)	36 (7.3)
Per Protocol (PP) Population	144	155	143	442
Completed	98 (68.1)	112 (72.3)	61 (42.7)	271 (61.3)
Discontinued	46 (31.9)	43 (27.7)	82 (57.3)	171 (38.7)
Safety Population	160	165	164	489
Completed	107 (66.9)	118 (71.5)	70 (42.7)	295 (60.3)
Discontinued	53 (33.1)	47 (28.5)	94 (57.3)	194 (39.7)

ITT=intent-to-treat

^a Three patients were randomized to DEX 700 but never received treatment.

^b One patient was randomized to DEX 350 but never received treatment.

^c One patient was randomized to Sham but never received treatment.

^d "Other" reasons for discontinuation included site closure, patient withdrawal of consent, poor compliance from patient, sponsor request, patient participation in other trial, etc.

Study 206207-011: Subject Disposition and Primary Reason for Discontinuation (ITT Population)

Disposition and Discontinuation	DEX 700 n (%)	DEX 350 n (%)	Sham n (%)	Total n (%)
Total Randomized	188 ^a	181 ^{b,c}	185 ^c	554
Treated	187	178	186	551
As randomized	187 (99.5)	178 (99.4)	185 (100.0)	550 (99.3)
Never received treatment	1 (0.5)	3 (1.6)	0 (0.0)	4 (0.7)
ITT Population	188	181	185	554
Completed	118 (62.8)	112 (61.9)	82 (44.3)	312 (56.3)
Discontinued	70 (37.2)	69 (38.1)	103 (55.7)	242 (43.7)
Primary reason for Discontinuation (ITT Population)				
Adverse event	25 (13.3)	30 (16.6)	23 (12.4)	78 (14.1)
Ocular	18 (9.6)	18 (9.9)	14 (7.6)	50 (9.0)
Non-ocular	7 (3.7)	12 (6.6)	9 (4.9)	28 (5.1)
Lack of efficacy	14 (7.4)	11 (6.1)	47 (25.4)	72 (13.0)
Lost to follow-up	6 (3.2)	7 (3.9)	8 (4.3)	21 (3.8)
Personal reasons	7 (3.7)	6 (3.3)	10 (5.4)	23 (4.2)
Protocol violation	1 (0.5)	3 (1.7)	1 (0.5)	5 (0.9)
Other ^d	17 (9.0)	12 (6.6)	14 (7.6)	43 (7.8)
Per Protocol (PP) Population	170	159	162	491

Completed	114 (67.1)	106 (66.7)	76 (46.9)	296 (60.3)
Discontinued	56 (32.9)	53 (33.3)	86 (53.1)	195 (39.7)
Safety Population	187	178	186	551
Completed	118 (63.1)	112 (62.9)	82 (44.1)	312 (56.6)
Discontinued	69 (36.9)	66 (37.1)	104 (55.9)	239 (43.4)

ITT=intent-to-treat

^a One patient was randomized to DEX 700 but never received treatment.

^b Two patient were randomized to DEX 350 but never received treatment.

^c One patient was randomized to DEX 350 but actually received Sham. This patient discontinued the study due to a serious AE of macular fibrosis after Sham treatment. The patient is counted in the DEX 350 group for analyses based on the ITT population and in the Sham group for analyses based on the safety population.

^d "Other" reasons for discontinuation included site closure, patient withdrawal of consent, patient relocation, etc.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at the year 3 final assessment with missing values imputed by LOCF.

Primary Efficacy Analysis

The primary analysis of BCVA of 15 or more letters improvement from baseline at year 3 was performed using Pearson's chi-square test. A gate-keeping procedure was used to control the overall type I error at 5% for the 2 between-group comparisons. The comparison of DEX 700 versus Sham was considered significant if the p-value was ≤ 0.05 . Only if the comparison of DEX 700 versus Sham was significant at the 0.05 level was the comparison of DEX 350 versus Sham to be performed at the significance level of 0.05.

Analysis Population

Intent -to-treat (ITT): All randomized patients.

Per Protocol (PP): All randomized patients with no major protocol violations.

Safety: All patients who were treated.

Study 206207-010: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	163	36 (22.1)	166	31 (18.7)	165	22 (13.3)
% Difference (95% CI)	8.8 (0.5, 17.0)		5.3 (-2.5, 13.2)			
p-value	0.038 ^a		0.185 ^a			
PP with observed data only						
Final (36/39 months)	29	6 (20.7)	34	8 (23.5)	15	3 (20.0)
% Difference (95% CI)	0.7 (-24.4, 25.7)		3.5 (-21.2, 28.3)			
p-value	> 0.999 ^b		> 0.999 ^b			

PP with LOCF						
Final (36/39 months)	144	35 (24.3)	155	30 (19.4)	143	21 (14.7)
% Difference (95% CI)	9.6 (0.5, 18.7)		4.7 (-3.8, 13.2)			
p-value	0.040^a		0.285^a			

^a P-value was from Chi-square test.

^b Fisher's Exact test is used.

Reviewer's Comments:

There was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 700 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.038$) and PP with LOCF population ($p=0.040$). Statistical difference was not seen in the PP with observed data only population due to the small sample size.

A statistically significant difference was not seen in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 350 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.185$) and PP with LOCF population ($p=0.285$).

Study 206207-011: Proportion of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye at Final Visit (36/39 months)

Visit	Treatment Group					
	DEX 700		DEX 350		Sham	
	N	n (%)	N	n (%)	N	n (%)
ITT with LOCF						
Final (36/39 months)	188	42 (22.3)	188	42 (22.3)	185	20 (10.8)
% Difference (95% CI)	11.5 (4.1, 19.0)		181			
p-value	0.003 ^a		0.044 ^a			
PP with observed data only						
Final (36/39 months)	22	10 (45.5)	25	6 (24.0)	22	7 (31.8)
% Difference (95% CI)	13.6 (-14.9, 42.1)		-7.8 (-33.5, 17.9)			
p-value	0.353 ^a		0.550 ^a			
PP with LOCF						
Final (36/39 months)	170	41 (24.1)	159	31 (19.5)	162	20 (12.3)
% Difference (95% CI)	11.8 (3.6, 20.0)		7.2 (-0.8, 15.1)			
p-value	0.006 ^a		0.080 ^a			

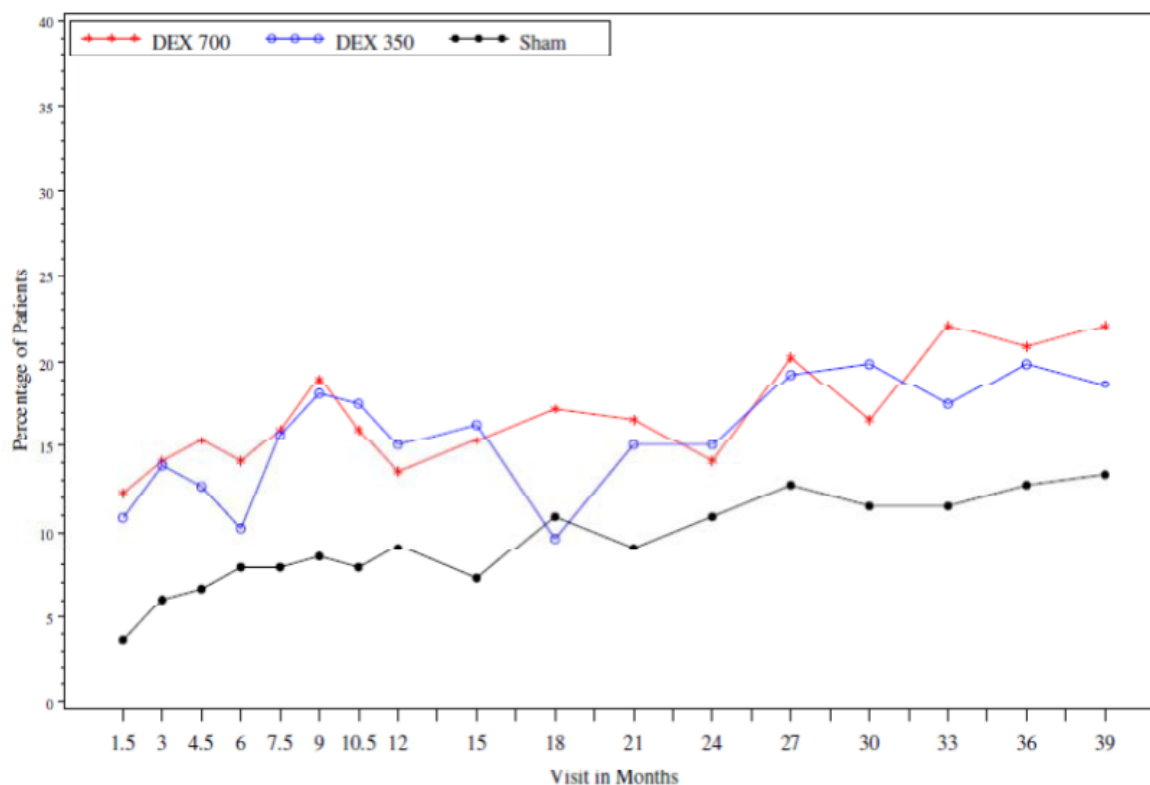
^a P-value was from Chi-square test.

Reviewer's Comments:

There was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 700 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.003$) and PP with LOCF population ($p=0.006$). Statistical difference was not seen in the PP with observed data only population due to the small sample size.

There was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in patients treated with DEX 350 as compared to patients treated with Sham in the ITT with LOCF population ($p=0.044$) but not in the PP with LOCF population ($p=0.080$).

Study 206207010: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye (ITT Population)



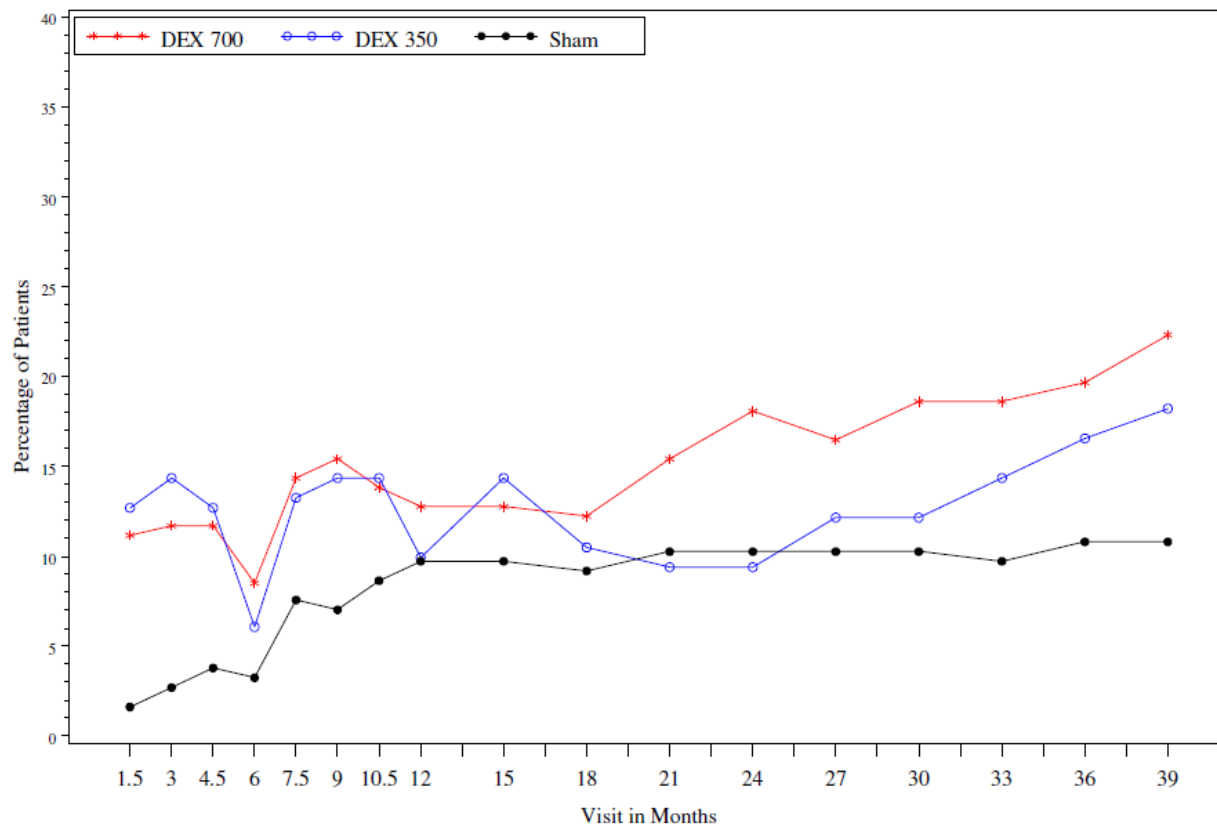
BCVA = best-corrected visual acuity; ITT = intent-to-treat

Note: Missing values are imputed by last observation carried forward at the follow-up visits

Reviewer's Comments:

For Study 206207-010, the percentage of patients with ≥ 15 letters improvement from baseline generally increases at the beginning of each treatment cycle, peaks at 3 months post-treatment, and returns to baseline by month 6. The peak percentage of patients with ≥ 15 letters improvement from baseline appears to increase with each additional treatment cycle.

Study 206207011: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye (ITT Population)



BCVA = best-corrected visual acuity; ITT = intent-to-treat

Note: Missing values are imputed by last observation carried forward at the follow-up visits

Reviewer's Comments:

The results for Study 206207-011 are similar to that of Study 206207-010.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints were contrast sensitivity, OCT (central subfield retinal thickness, macular volume), fundus photography (diabetic retinopathy severity, central retinal thickness, clinically significant macular edema), and FA (fluorescein leakage, capillary loss, ischemic and non-ischemic status).

Reviewer's Comments:

Contrast sensitivity, OCT, fundus photography, and FA results are supportive data. These variables are not acceptable primary endpoints. Hence, contrast sensitivity, OCT, fundus photography, and FA results are not presented in this review.

6.1.6 Other Endpoints

There were numerous exploratory endpoints related to BCVA (BCVA average change from baseline, BCVA change from baseline, BCVA improvement of ≥ 10 letters from baseline, BCVA categorical change from baseline, BCVA worsening of ≥ 15 letters from baseline, BCVA 20/40 or better, percent of visits with BCVA ≥ 15 letters improvement, time to ≥ 15 letters improvement) and Visual Functioning Questionnaire (VFQ)-25 (VFQ-25 average change from baseline, 10-point improvement in VFQ-25).

Reviewer's comments:

These endpoints are exploratory and are not acceptable as primary efficacy endpoints. Therefore, the results are not presented in this review.

6.1.7 Subpopulations

Analyses of the pooled subgroup of subjects with a pseudophakic study eye at baseline were performed for the primary efficacy endpoint, secondary and other endpoints.

Efficacy Results in the Study Eye of Pseudophakic Patients (Studies 206207-010 and 206207-011 Pooled, ITT Population)

Variable/timepoint	DEX 700 (N = 86)	DEX 350 (N = 88)	Sham (N = 101)	P-value ^a	
				DEX 700 vs Sham	DEX 350 vs Sham
Mean BCVA average change from baseline (AUC) during the study (letters)	6.5	5.9	1.7	< 0.001	< 0.001
BCVA ≥ 15 letters improvement from baseline at year 3/final visit(%)	23.3	15.9	10.9	0.024	0.329
Mean percent of visits with BCVA ≥ 15 letters improvement during the study (%)	21.2	17.1	7.6	< 0.001	< 0.001
Time to BCVA ≥ 15 letters improvement (cumulative rate at year 3/final visit [%])	57.4	43.7	26.3	< 0.001	< 0.001
Mean OCT retinal thickness at center subfield average change from baseline (AUC) during the study (μm)	-131.8	-117.1	-50.8		

μm = microns; AUC = area under the curve; BCVA = best-corrected visual acuity; OCT = optical coherence tomography

^a P-value is based on ANCOVA with treatment and study as factors and baseline as covariate for the analyses of mean average change; CMH general association test stratified by study for mean percent of patients with BCVA ≥ 15 letters improvement; Wilcoxon rank-sum test for analyses of mean percent of visits; and log-rank test for time to event analysis.

Reviewer's Comments:

For the pooled pseudophakic subpopulation (N=275) from Studies 206207-010 and 206207-011, there was a statistically significant difference in the proportion of patients with ≥ 15 letters improvement from Baseline in BCVA at the Final Study Visit (36/39 months) in the patients treated with DEX 700 ($p=0.024$), but not in the patients treated with DEX 350 ($p=0.329$) as compared to patients treated with Sham in the ITT population.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There are no additional dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Safety and efficacy data are presented out to 39 months.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7 Review of Safety

7.1 Methods

The safety data from the two phase 3 studies (Studies 206207-010 and 206207-011) and the two phase 2 studies (Studies 206207-012 and 206207-018) were evaluated to assess safety. See section 5.1 Tables of Studies/Clinical Trials for study design details.

7.1.2 Categorization of Adverse Events

All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 13.0) and are presented within the Tables as Preferred Terms organized by System Organ Classification.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from studies 206207-010 and 206207-011 was pooled into the Integrated Safety Analysis Population to provide overall incidence of adverse events for each treatment group.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 527 patients were exposed to DEX 700 during the conduct of studies 206207-010 (160 patients), 206207-011 (187 patients), 206207-012 (125 patients), and 206207-018 (55).

Exposure in Study Treatment
(Studies 206207-010 and 206207-011, Safety Population)

Study Treatment	DEX 700 (N=347)	DEX 350 (N=343)	Sham (N=350)
Cumulative Number (%) of Patients Receiving Study Treatment(s)			
≥ 1 Treatment	347 (100.0)	343 (100.0)	350 (100.0)
≥ 2 Treatments	303 (87.3)	309 (90.1)	244 (69.7)

≥ 3 Treatments	249 (71.8)	264 (77.0)	181 (51.7)
≥ 4 Treatments	210 (60.5)	223 (65.0)	140 (40.0)
≥ 5 Treatments	168 (48.4)	183 (53.4)	114 (32.6)
≥ 6 Treatments	119 (34.3)	142 (41.4)	85 (24.3)
7 Treatments	31 (8.9)	37 (10.8)	35 (10.0)
Number (%) of Patients Who Received 1-7 Treatments			
1 Treatment	44 (12.7)	34 (9.9)	106 (40.3)
2 Treatment	54 (15.6)	45 (13.1)	63 (18.0)
3 Treatment	39 (11.2)	41 (12.0)	41 (11.7)
4 Treatment	42 (12.1)	40 (11.7)	26 (7.4)
5 Treatment	49 (14.1)	41 (12.0)	29 (8.3)
6 Treatment	88 (25.4)	105 (30.6)	50 (14.3)
7 Treatment	31 (8.9)	37 (10.8)	35 (10.0)
Cumulative (Number of Patients [%]) and Average Study Duration of Exposure			
≥ 6 months	339 (97.7)	335 (97.7)	304 (86.9)
≥ 12 months	304 (87.6)	314 (91.5)	242 (69.1)
≥ 18 months	278 (80.1)	295 (86.0)	199 (56.9)
≥ 24 months	261 (75.2)	269 (78.4)	176 (50.3)
≥ 30 months	252 (69.7)	253 (73.8)	164 (46.9)
≥ 36 months	139 (40.1)	145 (42.3)	93 (26.6)
≥ 39 months	18 (5.2)	16 (4.7)	11 (3.1)
Mean Number of Treatments/Patient	4.1	4.4	3.3

Reviewer's Comments:

There was adequate study drug exposure to assess the safety of this drug.

7.2.2 Explorations for Dose Response

Two dose levels of the DEX implant were evaluated, 700µg and 350µg. See section 7.2.1 for dose/duration data.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed for this efficacy supplement.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety of the drug product for this study, population, including biomicroscopy, visual acuity, IOP, HbA1c, and adjusted GFR, were adequately addressed in the design and conduct of the clinical studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

The overview of clinical pharmacology has been previously submitted in original NDA 22-315 dexamethasone intravitreal implant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drugs (ophthalmic steroids) are well known. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

7.3 Major Safety Results

7.3.1 Deaths

There were six deaths during the conduct of study 206207-012, one death in study 206207-018, twelve deaths in study 206207-010, and seventeen deaths in study 206207-011.

In study 206207-012, two subjects treated with DEX 700 died due to 1.) respiratory failure and 2.) malignant lung neoplasm. Four subjects treated with Sham DEX died due to 1.) cardio-respiratory arrest, 2.) myocardial infarction, 3.) malignant lung neoplasm, and 4.) Alzheimer's type dementia with failure to thrive.

In study 206207-018, one subject treated with DEX 700 died due to anoxic encephalopathy after experiencing a thrombosis in an arteriovenous fistula.

In study 206207-010, four of the deaths were in the DEX 700 group, five of the deaths were in the DEX 350 group, and three of the deaths were in the Sham group.

In study 206207-011, five of the deaths were in the DEX 700 group, ten of the deaths were in the DEX 350 group, and two were in the Sham group.

Summary of Death (Studies 206207-010 and 206207-011 Pooled)

Coded Adverse Event ^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	9 (2.6)	15 (4.4)	5 (1.4)
Multi-organ failure	2 (0.6)		
Acute respiratory failure	1 (0.3)	1 (0.3)	
Renal failure acute	1 (0.3)	1 (0.3)	

Coded Adverse Event ^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Adenocarcinoma pancreas	1 (0.3)		
Coma	1 (0.3)		
Hemorrhage intracranial	1 (0.3)		
Hemorrhagic stroke	1 (0.3)		
Hepatic failure	1 (0.3)		
Pancreatic carcinoma metastatic	1 (0.3)		
Pneumonia	1 (0.3)		
Road traffic accident	1 (0.3)		
Sepsis	1 (0.3)		
Victim of homicide	1 (0.3)		
Myocardial infarction		4 (1.2)	1 (0.3)
Cardiac arrest		3 (0.9)	1 (0.3)
Diabetic nephropathy		2 (0.6)	
Acute respiratory distress syndrome		1 (0.3)	
Arrhythmia		1 (0.3)	
Azotemia		1 (0.3)	
Cardiac failure congestive		1 (0.3)	
Gastric cancer		1 (0.3)	
H1N1 influenza		1 (0.3)	
Hyperkalemia		1 (0.3)	
Hypotension		1 (0.3)	
Hypovolemic shock		1 (0.3)	
Pleural effusion		1 (0.3)	
Pneumonia pneumococcal		1 (0.3)	
Pneumonia streptococcal		1 (0.3)	
Pulseless electrical activity		1 (0.3)	
Respiratory distress		1 (0.3)	
Sudden death		1 (0.3)	
Tuberculosis		1 (0.3)	
Ventricular fibrillation		1 (0.3)	
Cardiomyopathy			1 (0.3)
Myocardial ischemia			1 (0.3)
Subdural hematoma			1 (0.3)

^aBased on MEDRA, version 15.0

Reviewer's Comments:

The reported deaths are not unexpected for an elderly diabetic population followed over a study period of more than 3 years.

7.3.2 Nonfatal Serious Adverse Events

A total of 368 subjects experienced a serious adverse event; 138 treated with DEX 700/DEX 700 with Laser, 120 treated with DEX 350, and 110 treated with Sham/Laser alone.

Study 206207-012: Serious Adverse Events

Coded Adverse Event^a	Combination Therapy (N=125) n (%)	Laser Alone (N=127) n (%)
Overall	23 (18.4)	27 (21.3)
Pneumonia	2 (1.6)	1 (0.8)
Coronary artery disease	2 (1.6)	
Neuropathic arthropathy	2 (1.6)	
Osteoarthritis	2 (1.6)	
Cardiac failure congestive	1 (0.8)	2 (1.6)
Respiratory failure	1 (0.8)	2 (1.6)
Cerebrovascular accident	1 (0.8)	1 (0.8)
Intervertebral disc degeneration	1 (0.8)	1 (0.8)
Lung neoplasm maglinant	1 (0.8)	1 (0.8)
Renal failure	1 (0.8)	1 (0.8)
Gangrene		3 (2.4)
Anemia		2 (1.6)
Myocardial infarction		2 (1.6)
Transient ischemic attack		2 (1.6)

^aBased on MEDRA, version 15.0

Study 206207-018: Serious Adverse Events

Coded Adverse Event^a	DEX 700 (N=55) n (%)
Overall	14 (25.5)
Cardiac failure congestive	2 (3.6)
Anoxic encephalopathy	1 (1.8)
Atrioventricular block second degree	1 (1.8)
Carotid artery stenosis	1 (1.8)
Cholecystitis acute	1 (1.8)
Diabetic foot infection	1 (1.8)
Hyperglycemia	1 (1.8)
Ketoacidosis	1 (1.8)
Osteomyelitis	1 (1.8)
Pancreatitis	1 (1.8)
Pneumonia	1 (1.8)
Presyncope	1 (1.8)
Renal failure	1 (1.8)
Soft tissue infection	1 (1.8)
Transient Ischemic attack	1 (1.8)

^aBased on MEDRA, version 15.0

Study 206207-010: Serious Adverse Events

Coded Adverse Event ^a	DEX 700 (N=160) n (%)	DEX 350 (N=165) n (%)	Sham (N=164) n (%)
Overall	52 (32.5)	52 (31.5)	34 (20.7)
Cerebrovascular accident	3 (1.9)	1 (0.6)	1 (0.6)
Cardiac failure congestive	2 (1.3)	3 (1.8)	1 (0.6)
Vitreous hemorrhage	2 (1.3)	3 (1.8)	1 (0.6)
Cataract	2 (1.3)	2 (1.2)	1 (0.6)
Cellulitis	2 (1.3)	2 (1.2)	
Pneumonia	2 (1.3)	2 (1.2)	
Renal failure acute	2 (1.3)	2 (1.2)	
Transient ischemic attack	2 (1.3)	2 (1.2)	
Atrioventricular block complete	2 (1.3)	1 (0.6)	2 (1.2)
Non-cardiac chest pain	2 (1.3)		2 (1.2)
Coronary artery occlusion	2 (1.3)		
Gastroenteritis	2 (1.3)		
Hypertension	2 (1.3)		
Multi-organ failure	2 (1.3)		
Cataract subcapsular	1 (0.6)	2 (1.2)	
Acute myocardial infarction	1 (0.6)	1 (0.6)	2 (1.2)
Myocardial infarction		5 (3.0)	2 (1.2)
Myocardial ischemia		2 (1.2)	2 (1.2)
Prostate cancer ^b		2 (1.2)	2 (1.2)
Diabetic foot		2 (1.2)	1 (0.6)
Acute coronary syndrome		2 (1.2)	
Carotid artery stenosis		2 (1.2)	
Diabetic gangrene		2 (1.2)	
Foot fracture		2 (1.2)	
Urinary tract infection		2 (1.2)	
Coronary artery disease		1 (0.6)	2 (1.2)

^aBased on MEDRA, version 15.0

^bPercentages based on the male population

Study 206207-011: Serious Adverse Events

Coded Adverse Event ^a	DEX 700 (N=187) n (%)	DEX 350 (N=178) n (%)	Sham (N=186) n (%)
Overall	63 (33.7)	68 (38.2)	49 (26.3)
Cataract	8 (4.3)	7 (3.9)	2 (1.1)
Vitreous hemorrhage	8 (4.3)	2 (1.1)	4 (2.2)
Cellulitis	3 (1.6)	3 (1.7)	1 (0.5)
Coronary artery disease	3 (1.6)	3 (1.7)	1 (0.5)
Macular edema	2 (1.1)	3 (1.7)	

Coded Adverse Event^a	DEX 700 (N=187) n (%)	DEX 350 (N=178) n (%)	Sham (N=186) n (%)
Renal failure acute	2 (1.1)	2 (1.1)	2 (1.1)
Syncope	2 (1.1)	2 (1.1)	1 (0.5)
Pneumonia	2 (1.1)	2 (1.1)	
Urinary tract infection	2 (1.1)	2 (1.1)	
Macular fibrosis	2 (1.1)	1 (0.6)	2 (1.1)
Osteoarthritis	2 (1.1)	1 (0.6)	1 (0.5)
Endophthalmitis	2 (1.1)	1 (0.6)	
Acute coronary syndrome	2 (1.1)		
Hypertension	2 (1.1)		
Retinal detachment	2 (1.1)		
Cardiac failure congestive	1 (0.5)	6 (3.4)	1 (0.5)
Myocardial infarction	1 (0.5)	4 (2.2)	2 (1.1)
Prostate cancer ^b	1 (0.5)	3 (2.9)	1 (0.5)
Cerebrovascular accident	1 (0.5)	2 (1.1)	3 (1.6)
Diabetes mellitus inadequate control	1 (0.5)	2 (1.1)	1 (0.5)
Osteomyelitis	1 (0.5)	2 (1.1)	1 (0.5)
Cholelithiasis	1 (0.5)		2 (1.1)
Cardiac arrest	1 (0.5)	3 (1.7)	1 (0.5)
Spinal column stenosis	1 (0.5)	2 (1.1)	1 (0.5)
Diabetic nephropathy	1 (0.5)	2 (1.1)	
Pleural effusion	1 (0.5)	2 (1.1)	
Renal failure chronic	1 (0.5)	1 (0.6)	3 (1.6)
Gangrene	1 (0.5)		2 (1.1)
Hepatic neoplasm malignant			2 (1.1)
Tendon rupture			2 (1.1)

^aBased on MEDRA, version 15.0

^bPercentages based on the male population

Reviewer's Comments:

These adverse events are consistent with the age and general findings in the population of diabetic subjects treated with corticosteroid over a 3 year period and were seen in all treatment groups. The overall incidence of serious adverse events was higher in the DEX treatment groups than Sham.

7.3.3 Dropouts and/or Discontinuations

Study 206207-010: Patient Discontinuations (ITT Population)

Subject	Treatment	Study Day on Exit^a	Reason for Discontinuation
0448-4086	DEX 700	525	Lost to follow-up
3084-5020	DEX 700	519	Adverse event – vitreous adhesions
3084-5047	DEX 700	183	Protocol violation – focal OCT too low
4082-4026	DEX 700	401	Personal reasons

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4252-4114	DEX 700	771	Lost to follow-up
4256-4007	DEX 700	190	Adverse event - fall
4288-4107	DEX 700	351	Lost to follow-up
4311-4556	DEX 700	82	Adverse event – diabetic retinopathy
4311-4628	DEX 700	708	Lack of efficacy
4316-4164	DEX 700	208	Other – study site closed
4353-5037	DEX 700	701	Other – Escape therapy needed for study eye
4368-4784	DEX 700	1	Lost to follow-up
4368-4796	DEX 700	981	Adverse event – hepatic failure, pancreatic carcinoma, renal failure acute
4396-4581	DEX 700	421	Adverse event – IOP increased, iris neovascularization
4396-4765	DEX 700	407	Adverse event – vitreous hemorrhage
4397-5022	DEX 700	210	Other – patient doesn't to continue
4416-4588	DEX 700	190	Lack of efficacy
4417-4212	DEX 700	420	Other – study site closing
4447-4307	DEX 700	810	Other – poor compliance from patient
4447-4316	DEX 700	455	Lack of efficacy
4447-4322	DEX 700	737	Lost to follow-up
4447-4958	DEX 700	585	Other – sponsor request
4449-4254	DEX 700	555	Adverse event – lung abscess, pneumonia, small cell lung cancer metastatic
4449-4256	DEX 700	402	Adverse event – cognitive disorder
4449-4264	DEX 700	443	Lack of efficacy
4449-4267	DEX 700	93	Adverse event – macular edema
4449-4268	DEX 700	1	Other – patient was not enrolled
4449-4375	DEX 700	549	Adverse event – macular edema
4449-4405	DEX 700	365	Lack of efficacy
4449-4659	DEX 700	373	Adverse event – macular edema
4449-4687	DEX 700	429	Other – participate in another trial
4449-4759	DEX 700	766	Adverse event – anterior chamber fibrin, IOP increased
4449-4770	DEX 700	359	Lack of efficacy
4449-4840	DEX 700	366	Lack of efficacy
4451-4271	DEX 700	190	Adverse event – arthritis
4451-4274	DEX 700	287	Other – emergency PRP due to PDR
4451-4280	DEX 700	355	Other – decrease of >15 letters in VA from baseline
4452-4328	DEX 700	306	Adverse event – adenocarcinoma pancreas, multi-organ failure, sepsis
4474-4120	DEX 700	304	Adverse event – VA reduced
4496-4463	DEX 700	366	Adverse event – lens dislocation
4514-4380	DEX 700	132	Lack of efficacy
4514-4384	DEX 700	189	Lack of efficacy
6415-4485	DEX 700	1109	Other – patient did not come for visit month 39
6415-4688	DEX 700	386	Personal reasons

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
6417-4495	DEX 700	806	Personal reasons
6417-4498	DEX 700	848	Personal reasons
6418-4504	DEX 700	1120	Other – month 36 visit out of scheduled window and retreatment no. 6 is not possible. Patient did not want to continue until visit month 39.
6416-4885	DEX 700	1097	Personal reasons
6652-4508	DEX 700	896	Adverse event – renal failure
6653-4667	DEX 700	765	Adverse event – renal failure acute
6655-4750	DEX 700	967	Personal reasons
7871-4804	DEX 700	1068	Adverse event –multi-organ failure
7871-4850	DEX 700	536	Personal reasons
8093-4715	DEX 700	181	Adverse event – cerebrovascular accident
8093-4766	DEX 700	1	Protocol violation – inclusion/exclusion criteria not met
8907-4731	DEX 700	821	Other – early site closure
3983-4289	DEX 350	342	Other – switched to alternative treatment
4221-4021	DEX 350	879	Adverse event - azotemia
4252-4115	DEX 350	905	Other – PI feels subject needed treatments not permitted by study protocol.
4356-4071	DEX 350	213	Other – patient withdrew consent
4277-4132	DEX 350	918	Adverse event –cystoid macular edema
4277-4169	DEX 350	553	Adverse event – diabetic retinal edema
4280-4038	DEX 350	568	Lack of efficacy
4288-4108	DEX 350	457	Adverse event – myocardial infarction
4288-4109	DEX 350	10	Lost to follow-up
4288-4157	DEX 350	874	Other – patient withdrew consent
4314-4421	DEX 350	597	Lack of efficacy
4341-4047	DEX 350	704	Adverse event – macular fibrosis
4353-5192	DEX 350	799	Adverse event – renal failure acute
4368-4781	DEX 350	898	Adverse event - diabetic retinopathy
4368-4786	DEX 350	359	Adverse event - diabetic retinopathy
4391-4724	DEX 350	231	Adverse event – diabetic foot
4396-4583	DEX 350	596	Lost to follow-up
4397-5021	DEX 350	567	Adverse event – retinal exudates
4447-4320	DEX 350	1038	Adverse event – vitreous hemorrhage
4447-4323	DEX 350	639	Personal reasons
4447-4957	DEX 350	969	Lost to follow-up
4449-4255	DEX 350	990	Lack of efficacy
4449-4258	DEX 350	365	Adverse event – macular edema
4449-4261		638	Lack of efficacy
4449-4263	DEX 350	268	Lack of efficacy
4449-4266	DEX 350	351	Lack of efficacy
4449-4373	DEX 350	192	Adverse event – VA reduced
4449-4404	DEX 350	92	Lack of efficacy
4449-4631	DEX 350	729	Lack of efficacy

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4449-4660	DEX 350	989	Lack of efficacy
4449-4685	DEX 350	644	Lack of efficacy
4451-4272	DEX 350	356	Other – patient refused FA and Posurdex injection
4451-4278	DEX 350	1	Other – exclusion criteria not met
4451-4626	DEX 350	358	Adverse event – dementia Alzheimer’s type
4452-4330	DEX 350	449	Lack of efficacy
4458-4368	DEX 350	356	Lack of efficacy
4474-4182	DEX 350	493	Personal reasons
4514-4379	DEX 350	182	Lack of efficacy
6415-4484	DEX 350	561	Personal reasons
6417-4493	DEX 350	166	Adverse event – acute respiratory failure
6418-4670	DEX 350	974	Personal reasons
6418-4889	DEX 350	1114	Lost to follow-up
6654-4982	DEX 700	786	Lack of efficacy
6655-4668	DEX 350	792	Adverse event – acute respiratory distress syndrome, H1N1 influenza, pneumonia pneumococcal
6655-4680	DEX 350	1005	Lost to follow-up
7871-4852	DEX 350	1098	Adverse event – myocardial infarction
8093-4717	DEX 350	730	Adverse event – vitreous hemorrhage
8097-4732	DEX 350	836	Other – early site closure
0448-4085	Sham	668	Other – study terminated at site
2341-4344	Sham	372	Lack of efficacy
2341-4346	Sham	154	Lack of efficacy
2341-4350	Sham	183	Lack of efficacy
3084-5045	Sham	145	Lack of efficacy
3983-4291	Sham	291	Lack of efficacy
3983-4294	Sham	181	Personal reasons
3983-4296	Sham	185	Lack of efficacy
4221-4023	Sham	243	Adverse event – myocardial infarction
4243-4124	Sham	717	Adverse event – retinal neovascularization
4250-4063	Sham	840	Lack of efficacy
4250-4066	Sham	287	Lost to follow-up
4250-4193	Sham	172	Lack of efficacy
4252-4112	Sham	283	Lost to follow-up
4256-4068	Sham	459	Lost to follow-up
4277-4130	Sham	161	Personal reasons
4277-4170	Sham	706	Adverse event – diabetic retinal edema
4280-4037	Sham	190	Other – subject withdrew consent
4288-4106	Sham	464	Other – subject withdrew consent
4288-4111	Sham	927	Lack of efficacy
4311-4074	Sham	415	Other – subject withdrew consent
4311-4557	Sham	16	Personal reasons
4311-4629	Sham	634	Other – early exit due to pregnancy

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4316-4163	Sham	386	Other – PI relocated and closed clinical studies program
4341-4471	Sham	442	Adverse event – VA reduced
4368-4783	Sham	275	Lack of efficacy
4368-4785	Sham	590	Lack of efficacy
4374-5267	Sham	208	Lack of efficacy
4375-4430	Sham	1024	Personal reasons
4377-4578	Sham	470	Adverse event – cardiac arrest
4397-4829	Sham	364	Adverse event – retinal exudates
4397-4995	Sham	721	Personal reasons
4397-5023	Sham	140	Adverse event – retinal exudates
4397-5027	Sham	787	Lost to follow-up
4411-4049	Sham	372	Lack of efficacy
4417-4211	Sham	509	Other – study sit closed by sponsor and PI
4421-4820	Sham	284	Other – subject withdrew from study
4421-4825	Sham	1068	Lost to follow-up
4431-4098	Sham	1	Other - misrandomization
4447-4309	Sham	482	Personal reasons
4447-4312	Sham	1036	Lack of efficacy
4447-4317	Sham	97	Personal reasons
4447-4319	Sham	32	Personal reasons
4447-4324	Sham	317	Lack of efficacy
4447-4960	Sham	206	Other – PI's opinion that laser treatment will be more effective
4447-4961	Sham	576	Lack of efficacy
4447-4973	Sham	199	Other – PI's opinion that Avastin treatment will be more effective for this patient
4449-4253	Sham	184	Lack of efficacy
4449-4257	Sham	51	Adverse event – retinal exudates
4449-4259	Sham	375	Lack of efficacy
4449-4262	Sham	125	Lack of efficacy
4449-4265	Sham	79	Lack of efficacy
4449-4270	Sham	150	Lack of efficacy
4449-4374	Sham	185	Lack of efficacy
4449-4403	Sham	385	Lack of efficacy
4449-4633	Sham	51	Adverse event – macular edema
4449-4658	Sham	51	Adverse event – macular edema
4449-4758	Sham	83	Adverse event – macular edema
4449-4769	Sham	185	Lack of efficacy
4449-4838	Sham	352	Lack of efficacy
4450-4237	Sham	183	Lack of efficacy
4450-4238	Sham	211	Lack of efficacy
4451-4273	Sham	362	Other – patient requested to withdraw
4451-4276	Sham	503	Personal reasons
4451-4277	Sham	364	Lack of efficacy
4451-4284	Sham	183	Lack of efficacy

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4451-4287	Sham	187	Lack of efficacy
4451-4443	Sham	44	Adverse event – macular edema
4451-4573	Sham	23	Other – Patient refused to sign new consent form
4451-4616	Sham	86	Lack of efficacy
4451-4625	Sham	126	Lack of efficacy
4452-4327	Sham	477	Lack of efficacy
4474-4118	Sham	453	Adverse event – VA reduced
4474-4142	Sham	332	Personal reasons
4474-4183	Sham	619	Personal reasons
4514-4381	Sham	133	Lack of efficacy
4514-4383	Sham	196	Lost to follow-up
4520-4445	Sham	540	Adverse event – macular edema
6413-4477	Sham	190	Personal reasons
6415-4486	Sham	813	Lost to follow-up
6417-4496	Sham	21	Other – patient refused to continue in the study
6418-4853	Sham	1119	Personal reasons
6654-4984	Sham	352	Lack of efficacy
6655-4665	Sham	544	Lost to follow-up
6655-4669	Sham	99	Personal reasons
6655-4748	Sham	925	Lack of efficacy
6685-4696	Sham	360	Other – patient has lost 20 letters since baseline visit, patients asked to exit study to test an alternative therapy
7871-4807	Sham	186	Lack of efficacy
7871-4851	Sham	561	Adverse event – subdural hematoma
7871-4895	Sham	126	Lost to follow-up
7871-4925	Sham	527	Adverse event – macular edema
8093-4712	Sham	34	Lost to follow-up
8093-4716	Sham	147	Personal reasons
8907-4730	Sham	192	Personal reasons
8907-4979	Sham	800	Other – early site closure

Study 206207-011: Patient Discontinuations (ITT Population)

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
0469-7659	DEX 700	907	Lack of efficacy
0469-7662	DEX 700	191	Lack of efficacy
0469-7672	DEX 700	931	Adverse event - pneumonia
1671-7396	DEX 700	189	Adverse event – detachment of RPE, macular degeneration
2707-7120	DEX 700	1110	Lost to follow-up
2707-7189	DEX 700	368	Other – withdrew consent
2707-7200	DEX 700	1044	Lost to follow-up
2707-7360	DEX 700	217	Other – withdrew consent
2707-7362	DEX 700	623	Other – withdrew consent

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
2707-7594	DEX 700	731	Lack of efficacy
2707-7623	DEX 700	390	Lack of efficacy
2707-7889	DEX 700	84	Other – withdrew consent, patient relocated
2707-7917	DEX 700	987	Personal reasons
2707-7922	DEX 700	210	Other – patient moving from area
2793-8429	DEX 700	175	Personal reasons
3059-7458	DEX 700	543	Personal reasons
3361-8131	DEX 700	197	Lack of efficacy
4019-8411	DEX 700	225	Adverse event – macular edema
4044-7606	DEX 700	863	Lost to follow-up
4207-7013	DEX 700	596	Adverse event – acute respiratory failure, coma, hemorrhage intracranial
4217-7366	DEX 700	477	Adverse event - endophthalmitis
4217-7368	DEX 700	1149	Adverse event – vertigo positional
4217-7371	DEX 700	1083	Other – patient received escape therapy with juxtasellar injection of triamcinolone acetonide
4217-7373	DEX 700	2	Adverse event – road traffic accident
4220-7613	DEX 700	325	Lost to follow-up
4227-7054	DEX 700	505	Adverse event – retinal detachment
4230-7004	DEX 700	562	Adverse event – vitreous hemorrhage
4234-7191	DEX 700	961	Lack of efficacy
4242-7156	DEX 700	355	Other – patient lost >15 letters @ 2 consecutive visits
4242-7356	DEX 700	1011	Personal reasons
4242-7709	DEX 700	228	Lost to follow-up
4247-7344	DEX 700	624	Other – A1C continues to increase-PI wants patient to exit study
4276-7064	DEX 700	364	Lack of efficacy
4287-7078	DEX 700	686	Other – withdrew consent-subject declined to continue
4289-7038	DEX 700	354	Adverse event – victim of homicide
4303-8070	DEX 700	354	Adverse event - endophthalmitis
4313-7093	DEX 700	281	Adverse event – transitional cell carcinoma
4355-7484	DEX 700	369	Other – escape therapy
4355-7905	DEX 700	250	Lack of efficacy
4361-7442	DEX 700	420	Lost to follow-up
4380-7099	DEX 700	837	Protocol violation – patient was injected with intravitreal steroid during cataract surgery
4380-7102	DEX 700	274	Lack of efficacy
4393-7808	DEX 700	218	Adverse event – open angle glaucoma
4401-7381	DEX 700	753	Personal reasons
4406-7060	DEX 700	1	Other – randomization failure
4453-7737	DEX 700	653	Other – patient discontinued due to site close out
4454-7989	DEX 700	190	Lack of efficacy
4456-7112	DEX 700	47	Lack of efficacy
4523-7321	DEX 700	177	Adverse event – VA reduced

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4531-7556	DEX 700	752	Other – patient decided to withdraw
4533-7318	DEX 700	746	Lack of efficacy
4571-7284	DEX 700	495	Other – site closure as per sponsor
4571-7286	DEX 700	281	Other – site closure as per sponsor
4580-7519	DEX 700	906	Other – withdrawn consent
4582-7680	DEX 700	273	Adverse event – necrotizing retinitis
4618-7220	DEX 700	224	Adverse event – VA reduced
4618-7246	DEX 700	624	Adverse event – VA reduced
4618-7272	DEX 700	750	Adverse – diabetic retinal edema
5020-7213	DEX 700	548	Personal reasons
5099-7084	DEX 700	288	Other – patient withdrew consent
5942-8239	DEX 700	736	Adverse event – VA reduced
6682-7691	DEX 700	811	Adverse event - cataract
6682-7862	DEX 700	696	Adverse event - cataract
6683-7865	DEX 700	336	Personal reasons
6683-7869	DEX 700	883	Adverse event – hemorrhagic stroke
6683-7875	DEX 700	701	Adverse event – macular fibrosis
8271-8036	DEX 700	486	Adverse event – diabetic retinal edema
8295-8125	DEX 700	365	Lack of efficacy
9095-7726	DEX 700	974	Adverse event – macular edema
9132-8438	DEX 700	683	Lack of efficacy
0469-7658	DEX 350	238	Lack of efficacy
0469-7706	DEX 350	179	Lack of efficacy
0469-7776	DEX 350	366	Lack of efficacy
0469-7856	DEX 350	1	Other – patient withdrew consent
0469-7871	DEX 350	529	Lack of efficacy
0914-7469	DEX 350	1091	Personal reasons
1671-7330	DEX 350	581	Lack of efficacy
1671-7395	DEX 350	980	Personal reasons
2707-7181	DEX 350	827	Lost to follow-up
2707-7187	DEX 350	595	Lost to follow-up
2707-7218	DEX 350	377	Lack of efficacy
2707-7358	DEX 350	650	Lost to follow-up
2707-7624	DEX 350	827	Adverse event – arrhythmia, cardiac arrest
3059-7457	DEX 350	281	Adverse event – myocardial infarction
3059-7460	DEX 350	906	Other – patient was not under social welfare
3361-8130	DEX 350	401	Lack of efficacy
4044-7686	DEX 350	862	Adverse event – gastric cancer
4207-7014	DEX 350	565	Other – patient non-compliant missed month 15, month 18 and retreatment for month 12
4220-7615	DEX 350	659	Adverse event – cerebrovascular accident
4220-7618	DEX 350	288	Adverse event – retinal neovascularization
4227-7049	DEX 350	104	Protocol violation – prohibited medications
4227-7053	DEX 350	677	Other – withdrew consent
4242-7010	DEX 350	532	Adverse event – macular edema

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4242-7355	DEX 350	1098	Lost to follow-up
4242-7678	DEX 350	1083	Adverse event – cardiac arrest, myocardial infarction
4247-7345	DEX 350	371	Adverse event – macular fibrosis, vitreous hemorrhage
4255-7137	DEX 350	311	Adverse event – cardiac failure congestive
4265-7428	DEX 350	398	Adverse event – pulseless electrical activity
4276-7063	DEX 350	324	Lack of efficacy
4276-7066	DEX 350	122	Lost to follow-up
4287-7077	DEX 350	575	Adverse event – respiratory distress
4298-7027	DEX 350	848	Protocol violation – prohibited procedure
4298-7028	DEX 350	298	Other – prohibited medication
4313-7091	DEX 350	1018	Lost to follow-up
4338-7072	DEX 350	729	Adverse event – vitreous hemorrhage
4348-7463	DEX 350	637	Other – ocular hypertension
4355-7906	DEX 350	1031	Adverse event – VA reduced
4355-7950	DEX 350	366	Adverse event – ocular hypertension
4364-7033	DEX 350	361	Lack of efficacy
4379-8006	DEX 350	366	Lack of efficacy
4401-7379	DEX 350	554	Adverse event - cataract
4401-7409	DEX 350	597	Personal reasons
4408-7498	DEX 350	1075	Adverse event – diabetic retinal edema
4453-7736	DEX 350	731	Other – patient discontinued due to site close out
4454-7988	DEX 350	225	Adverse event – macular fibrosis
4498-7511	DEX 350	1129	Personal reasons
4531-7553	DEX 350	1134	Lost to follow-up
4569-7331	DEX 350	183	Other – patient wishes to withdraw from study
4571-7285	DEX 350	452	Other – site closure as per sponsor
4580-7520	DEX 350	562	Other – patient withdraw consent
4618-7221	DEX 350	154	Adverse event – VA reduced
4618-7281	DEX 350	393	Adverse event – diabetic retinal edema OS, VA reduced OD (study eye)
5020-7212	DEX 350	554	Adverse event – renal failure
5099-7160	DEX 350	83	Other – patient was not eligible for randomization-patient was using 2 IOP lowering drugs
5941-8189	DEX 350	463	Adverse event – macular fibrosis
5941-8193	DEX 350	736	Adverse event – diabetic nephropathy, hyperkalemia, hypotension, ventricular fibrillation
5941-8225	DEX 350	448	Adverse event – cardiac arrest, diabetic nephropathy, hypovolemic shock, pleural effusion, tuberculosis
5942-8237	DEX 350	617	Personal reasons
6682-7690	DEX 350	624	Adverse event - cataract
6682-7863	DEX 350	536	Lack of efficacy

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
6682-7958	DEX 350	1067	Adverse event – sudden death
6683-7866	DEX 350	176	Personal reasons
6687-7925	DEX 350	576	Protocol violation – patient has taken systemic steroid for herpes on the face
6689-8090	DEX 350	191	Other – patient withdraw consent
8271-8163	DEX 350	183	Adverse event – vitreous hemorrhage
8295-8124	DEX 350	515	Adverse event – choroidal neovascularization
9095-7815	DEX 350	1065	Adverse event – VA reduced
9095-7907	DEX 350	701	Adverse event – macular edema
9095-7976	DEX 350	708	Adverse event – macular hole
0469-7653	Sham	368	Other – patient discontinued due to site close out
0469-7660	Sham	371	Lack of efficacy
0469-7661	Sham	190	Lack of efficacy
0469-7777	Sham	373	Lack of efficacy
0469-7861	Sham	182	Lack of efficacy
0469-7872	Sham	179	Lack of efficacy
0914-7470	Sham	1065	Lost to follow-up
1671-7327	Sham	1259	Lost to follow-up
1671-7394	Sham	887	Lost to follow-up
1671-7637	Sham	589	Lack of efficacy
1671-7763	Sham	700	Lack of efficacy
2707-7104	Sham	346	Other – withdrew consent
2707-7108	Sham	140	Lack of efficacy
2707-7119	Sham	155	Lack of efficacy
2707-7123	Sham	646	Lack of efficacy
2707-7188	Sham	479	Lack of efficacy
2707-7201	Sham	395	Lack of efficacy
2707-7217	Sham	373	Lack of efficacy
2707-7359	Sham	282	Other – non-compliance with study visit
2707-7363	Sham	391	Lack of efficacy
2707-7387	Sham	504	Lack of efficacy
2707-7577	Sham	190	Lack of efficacy
2707-7593	Sham	373	Lack of efficacy
2707-7621	Sham	702	Other – patient left to Mexico and did not know when she would return
2707-7627	Sham	359	Lost to follow-up
2707-7818	Sham	818	Other – possible prohibited (exclusionary) procedure (vitrectomy)
2707-7916	Sham	590	Lack of efficacy
3361-8129	Sham	302	Lack of efficacy
4019-8413	Sham	521	Lack of efficacy
4044-7478	Sham	405	Other – orthopedic problems
4044-7605	Sham	234	Personal reasons
4207-7015	Sham	197	Adverse event – diabetic retinal edema
4217-7364	Sham	183	Personal reasons

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4217-7369	Sham	28	Other – withdrew informed consent
4217-7370	Sham	19	Personal reasons
4217-7374	Sham	44	Lack of efficacy
4220-7729	Sham	371	Lack of efficacy
4220-7839	Sham	669	Other – withdrew consent
4224-7260	Sham	978	Lost to follow-up
4227-7051	Sham	281	Lack of efficacy
4227-7052	Sham	172	Adverse event – VA reduced
4230-7001	Sham	561	Adverse event – myocardial ischemia
4242-7007	Sham	333	Other – VA loss of 15+ letters over 2 consecutive visits
4242-7155	Sham	1078	Adverse event –diabetic retinal edema
4247-7343	Sham	273	Adverse event - leukemia
4255-7136	Sham	254	Lack of efficacy
4265-7427	Sham	183	Lack of efficacy
4276-7065	Sham	175	Lack of efficacy
4303-7882	Sham	729	Lack of efficacy
4303-7883	Sham	645	Other – patient withdrew the consent form
4303-8069	Sham	1198	Adverse event – hepatic cirrhosis
4338-7069	Sham	192	Lack of efficacy
4338-7168	Sham	176	Lack of efficacy
4338-7382	Sham	524	Adverse event – breast cancer
4338-7629	Sham	555	Lack of efficacy
4348-7465	Sham	616	Lack of efficacy
4348-7466	Sham	560	Lack of efficacy
4355-7486	Sham	575	Lack of efficacy
4355-7949	Sham	309	Lost to follow-up
4364-7032	Sham	186	Lack of efficacy
4364-7034	Sham	194	Lack of efficacy
4379-7543	Sham	212	Adverse event – macular edema
4379-7544	Sham	226	Adverse event – macular edema
4380-7097	Sham	283	Lack of efficacy
4380-7403	Sham	424	Other – decline health
4401-7380	Sham	137	Personal reasons
4406-7056	Sham	78	Lack of efficacy
4406-7058	Sham	1220	Lost to follow-up
4408-7494	Sham	631	Lack of efficacy
4408-7496	Sham	289	Lack of efficacy
4453-7738	Sham	297	Other – patient discontinued due to the site close out
4473-7349	Sham	106	Adverse event – vision blurred
4498-7513	Sham	362	Adverse event – hepatic neoplasm malignant
4498-7514	Sham	599	Personal reasons
4498-7984	Sham	289	Adverse event – cerebrovascular accident
4523-7320	Sham	330	Adverse event – macular edema
4533-7302	Sham	79	Adverse event – macular edema

Subject	Treatment	Study Day on Exit ^a	Reason for Discontinuation
4533-7306	Sham	373	Adverse event – retinal neovascularization
4533-7312	Sham	237	Personal reasons
4571-7283	Sham	531	Other – site closure as per sponsor
4582-7684	Sham	57	Adverse event – retinal vein occlusion
4618-7222	Sham	120	Adverse event – VA reduced
4618-7255	Sham	232	Adverse event – diabetic retinal edema, retinal exudates
4618-7264	Sham	450	Personal reasons
4618-7266	Sham	485	Lack of efficacy
4618-7402	Sham	169	Adverse event – retinal neovascularization
5020-7211	Sham	828	Adverse event – macular fibrosis OD, macular fibrosis OS (study eye), vitreous adhesions OS
5020-7215	Sham	1024	Adverse event – myocardial infarction
5099-7082	Sham	456	Other – patient withdrew consent
6683-7876	Sham	170	Lack of efficacy
6683-8005	Sham	180	Personal reasons
6690-7940	Sham	83	Adverse event – hepatic neoplasm malignant
6690-7943	Sham	193	Personal reasons
6690-7947	Sham	788	Other – due to patient’s missed visit
7412-8423	Sham	101	Personal reasons
8271-8038	Sham	404	Lost to follow-up
8295-8123	Sham	858	Adverse event - cardiomyopathy
8295-8126	Sham	488	Lack of efficacy
9095-7725	Sham	316	Lack of efficacy
9095-7761	Sham	358	Lack of efficacy
9095-7908	Sham	183	Lack of efficacy
9095-7977	Sham	827	Lack of efficacy

Reviewer’s Comments:

The number of discontinuations was similar for the DEX 700 [70 (37%)] and DEX 350 [69 (38%)] treatment groups and higher for the Sham treatment group [103 (56%)]. A large number of discontinuations in the Sham treatment group were due to lack of efficacy.

7.3.4 Significant Adverse Events

Number (%) Patients with Significant Ocular Adverse Events in the Study Eye (Studies 206207-010 and 206207-011 Pooled, Safety Population)

Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Vitreous hemorrhage	24 (6.9)	45 (13.1)	25 (7.1)
Retinal tear	5 (1.4)	3 (0.9)	3 (0.9)
Retinal detachment	2 (0.6)	0 (0.0)	2 (0.6)
Endophthalmitis	2 (0.6)	0 (0.0)	0 (0.0)
Hypotony of eye	2 (0.6)	0 (0.0)	0 (0.0)
Vitreous loss	1 (0.3)	0 (0.0)	0 (0.0)
Necrotizing retinitis	1 (0.3)	0 (0.0)	0 (0.0)
Complication of device insertion	1 (0.3)	1 (0.3)	0 (0.0)

^aBased on MEDRA, version 15.0

Seven cases of vitreous hemorrhage adverse events led to discontinuation from the study: 2 in the DEX 700 treatment group and 5 in the DEX 350 group. One case of retinal detachment adverse event (Patient 4227-7054/DEX 700) led to discontinuation from the study. Both cases of endophthalmitis adverse events (Patient 4217-7366/DEX 700 and Patient 4303-8070/DEX700) led to discontinuation from the study. The one case of necrotizing retinitis adverse event (Patient 4582-7680/DEX 700) led to discontinuation of the study. None of the cases of retinal tear, vitreous loss, and complication of device insertion led to discontinuation of the study.

Reviewer's Comments:

The most common significant ocular adverse event in all three treatment groups was vitreous hemorrhage.

7.3.5 Submission Specific Primary Safety Concerns

Corticosteroids as a class are known to increase the risk of increased intraocular pressure in those patients who are steroid responders and of cataract development. Analyses of these risks are presented below.

Number of Subjects with Elevated IOP Adverse Events in the Study Eye (Studies 206207-010 and 206207-011 Pooled, Safety Population)

Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	125 (36.0)	117 (34.1)	18 (5.1)
Intraocular pressure increased	107 (30.8)	103 (30.0)	12 (3.4)
Ocular hypertension	21 (6.1)	17 (5.0)	5 (1.4)
Open angle glaucoma	3 (0.9)	3 (0.9)	2 (0.6)
Glaucoma	3 (0.9)	3 (0.9)	0 (0.0)
Angle closure glaucoma	1 (0.3)	0 (0.0)	0 (0.0)
Borderline glaucoma	0 (0.0)	1 (0.3)	0 (0.0)
Glaucomatous optic disc atrophy	0 (0.0)	1 (0.3)	0 (0.0)

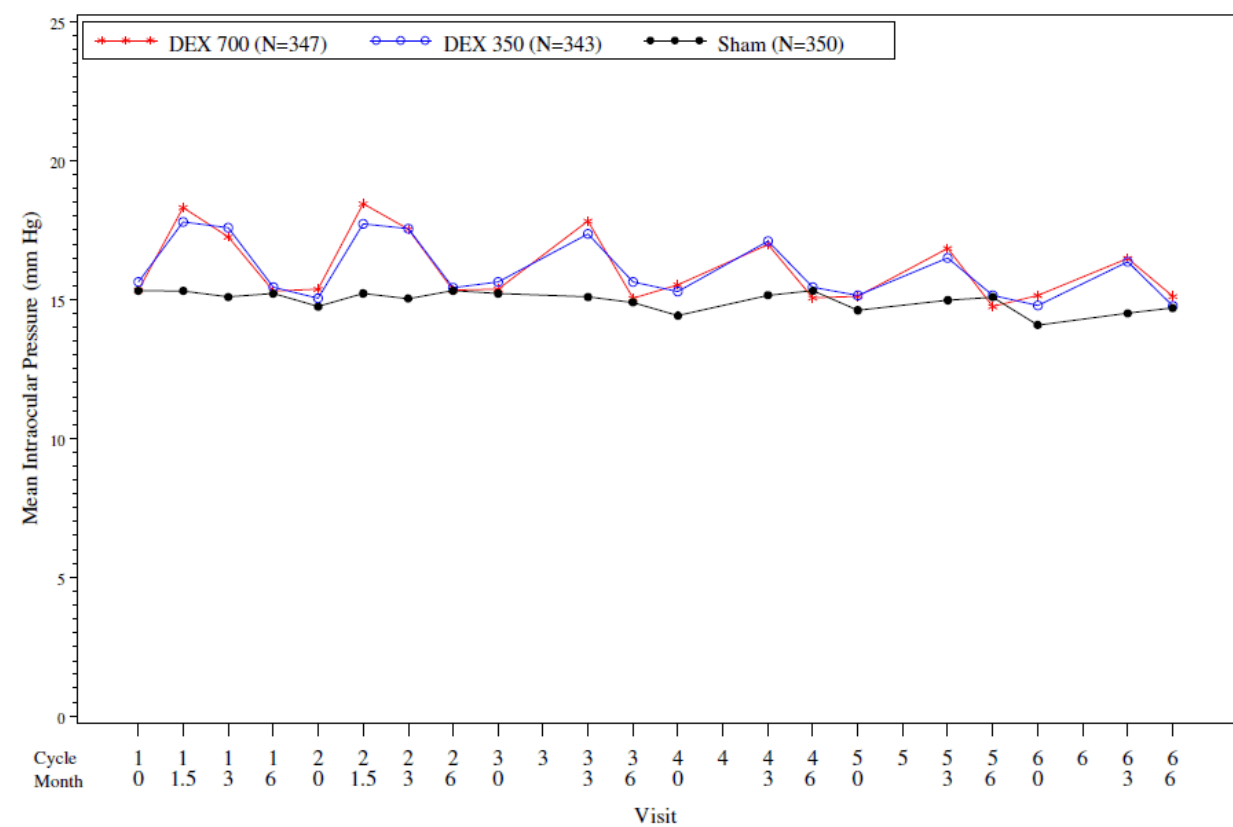
Note: Includes all adverse events with a MEDRA preferred term associated with elevated intraocular pressure which includes intraocular pressure increased, intraocular pressure fluctuation, ocular hypertension, angle closure glaucoma, borderline glaucoma, diabetic glaucoma, glaucoma, glaucoma traumatic, glaucomatous optic disc atrophy, open angle glaucoma, pigmentary glaucoma or normal tension glaucoma.

^aBased on MEDRA, version 15.0

Reviewer’s Comments:

Approximately 36% of patients treated with DEX 700 and 34% of patients treated with DEX 350 reported experiencing an elevated IOP adverse event as compared to 5% of patients treated with Sham.

**Mean Intraocular Pressure by Visit within Each Treatment Cycle
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**



Note: “Month” represents the number of months after each treatment.

Reviewer’s Comments:

For pooled Studies 206207-010 and 206207-011, the mean IOP increases at the beginning of each treatment cycle, peaks at 3 months post-treatment, and returns to baseline by month 6. The peak mean IOP appears to be higher in the earlier treatment cycles than in the later treatment cycles.

**Number (%) of subjects Using IOP-lowering Medications in the Study Eye
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

Visit	DEX 700 (N = 347)	DEX 350 (N = 343)	Sham (N = 350)	Total (N = 1040)
Baseline ^a	12/347 (3.5)	26/343 (7.6)	14/350 (4.0)	52/1040 (5.0)
Baseline to Month 12	114/347 (32.9)	99/343 (28.9)	23/350 (6.6)	236/1040 (22.7)
Month 12 to Month 24	90/305 (29.5)	89/314 (28.3)	11/241 (4.6)	190/860 (22.1)
Month 24 to Month 39/Final	75/261 (28.7)	75/269 (27.9)	12/176 (6.8)	162/706 (22.9)
Year 3/Final Visit ^b	56/261 (21.5)	49/269 (18.2)	6/176 (3.4)	111/706 (15.7)
Ever Used During the Study ^c	144/347 (41.5)	129/343 (37.6)	32/350 (9.1)	305/1040 (29.3)

IOP = intraocular pressure

Note: IOP-lowering medications included beta blocking agents, sympathomimetics, prostaglandins, carbonic anhydrase inhibitors, brimonidine, and combination agents.

^a Baseline refers to medications used prior to the first treatment.

^b Year 3/Final Visit includes only those medications marked as “ongoing” on the year 3 case report form.

^c Ever Used includes those who ever used IOP-lowering medications in the study eye at any time during the study.

Reviewer’s Comments:

Approximately 40% of patients in the DEX 700 and DEX 350 treatment group required IOP-lowering medications during the study as compared to 9% in the Sham treatment group.

Eight subjects (4 in the DEX 700 group, 3 in the DEX 350 group, and 1 in the Sham group) underwent a procedure for the treatment of IOP elevation.

In the DEX 700 group:

Subject 4341-4469 underwent a trabeculectomy in the study eye for worsening of elevated IOP on study day 476

Subject 4449-4759 underwent a trabeculectomy in the study eye for high IOP on study day 714 and an iridotomy on study day 719.

Subject 6654-4750 underwent an iridectomy in the study eye as part of cataract surgery (for worsening cataract) on study day 549.

Subject 4533-7318 underwent an iridotomy in both the study eye and non-study eye for narrow angle glaucoma on study day 322.

In the DEX 350 group:

Patient 7871-4970 underwent a trabeculectomy in the study eye on study day 857.

Patient 4353-4744 underwent trabeculoplasty in the study eye for increased IOP on study day 688.

Patient 9095-7742 underwent a trabeculoplasty in the study eye for ocular hypertension on study day 279.

Reviewer's Comments:

Two patients (0.6%) in the DEX 700 treatment group and one patient (0.3%) in the DEX 350 treatment group underwent trabeculectomy to control elevated IOP during the study period.

**Number of Phakic Subjects at Baseline with Cataract Adverse Events
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

Coded Adverse Event ^a	DEX 700 (N=262) n (%)	DEX 350 (N=256) n (%)	Sham (N=250) n (%)
Any cataract AE	178 (67.9)	164 (64.1)	51 (20.4)
Cataract	126 (48.1)	109 (42.6)	32 (12.8)
Cataract subcapsular	41 (15.6)	41 (16.0)	12 (4.8)
Cataract nuclear	18 (6.9)	15 (5.9)	8 (3.2)
Lenticular opacities	16 (6.1)	11 (4.3)	3 (1.2)
Cataract cortical	7 (2.7)	13 (5.1)	9 (3.6)

Note: Includes terms cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, lenticular opacities.

^aBased on MEDRA, version 15.0

Reviewer's Comments:

Approximately 68% of patients who were phakic at baseline in the DEX 700 treatment group and 64% of phakic patients at baseline in the DEX 350 treatment group reported a cataract adverse event as compared to 20% of patients in the Sham treatment group.

**Number (%) of Phakic Subjects at Baseline Who Had Cataract Surgery
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

Study visit	DEX 700 (N = 262)	DEX 350 (N = 256)	Sham (N = 250)
Month 6	9 (3.4)	8 (3.1)	5 (2.0)
Month 12	22 (8.4)	15 (5.9)	0 (0.0)
Month 18	41 (15.6)	31 (12.1)	5 (2.0)
Month 24	46 (17.6)	43 (16.8)	4 (1.6)
Month 30	32 (12.2)	29 (11.3)	1 (0.4)
Month 36	6 (2.3)	8 (3.1)	3 (1.2)
Month 39	1 (0.4)	0 (0.0)	0 (0.0)
Ever Had ^a	155 (59.2)	134 (52.3)	18 (7.2)

Note: Cataract surgery include: cataract operation, lens extraction, intraocular lens implant, lenticular operation, and phacocystectomy.

^a "Ever Had" includes those patients who had cataract surgery in the study eye at any time during the study.

Reviewer's Comments:

Approximately 59% of the patients treated with DEX 700 and 52% of the patients treated with DEX 350 had a cataract surgery performed during the study as compared to 7% for the patients treated with Sham. For the patients treated with DEX, the majority of the cataract surgeries were performed in the second and third years of the trial.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Common Adverse Events Occurring at an incidence 1% or Greater
(Studies 206207-010 and 206207-011 Pooled, Safety Population)**

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Overall	333 (96.0)	334 (97.4)	281 (80.3)
<u>Blood and lymphatic system disorders</u>			
Overall	18 (5.2)	21 (6.1)	15 (4.3)
Anemia	14 (4.0)	18 (5.2)	12 (3.4)
<u>Cardiac disorders</u>			
Overall	35 (10.1)	51 (14.9)	33 (9.4)
Atrial fibrillation	7 (2.0)	3 (0.9)	4 (1.1)
Coronary artery disease	6 (1.7)	9 (2.6)	8 (2.3)
Cardiac failure congestive	4 (1.2)	10 (2.9)	3 (0.9)
Angina pectoris	4 (1.2)	3 (0.9)	3 (0.9)
Myocardial infarction	2 (0.6)	11 (3.2)	5 (1.4)
Myocardial ischemia	1 (0.3)	3 (0.9)	5 (1.4)
<u>Ear and labyrinth disorders</u>			
Overall	10 (2.9)	10 (2.9)	4 (1.1)
Vertigo	4 (1.2)	6 (1.7)	2 (0.6)
<u>Endocrine disorders</u>			
Overall	8 (2.3)	6 (1.7)	2 (0.6)
Hypothyroidism	4 (1.2)	3 (0.9)	2 (0.6)
<u>Eye disorders</u>			
Overall	296 (85.3)	302 (88.0)	223 (63.7)
Cataract	141 (40.6)	125 (36.4)	44 (12.6)
Conjunctival hemorrhage	76 (21.9)	93 (27.1)	45 (12.9)
Macular edema	51 (14.7)	42 (12.2)	36 (10.3)
Cataract subcapsular	45 (13.0)	43 (12.5)	16 (4.6)
Vitreous hemorrhage	40 (11.5)	67 (19.5)	36 (10.3)
Visual acuity reduced	33 (9.5)	41 (12.0)	18 (5.1)
Macular fibrosis	30 (8.6)	43 (12.5)	18 (5.1)
Diabetic retinal edema	27 (7.8)	27 (7.8)	21 (6.0)
Dry eye	23 (6.6)	20 (5.8)	11 (3.1)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Ocular hypertension	23 (6.6)	17 (5.0)	6 (1.7)
Conjunctivitis	23 (6.6)	15 (4.4)	10 (2.9)
Retinal hemorrhage	22 (6.3)	28 (8.2)	16 (4.6)
Conjunctival hyperemia	21 (6.1)	30 (8.7)	20 (5.7)
Cataract nuclear	21 (6.1)	16 (4.7)	10 (2.9)
Retinal exudates	20 (5.8)	19 (5.5)	21 (6.0)
Diabetic retinopathy	20 (5.8)	19 (5.5)	13 (3.7)
Eye pain	19 (5.5)	25 (7.3)	16 (4.6)
Vitreous detachment	19 (5.5)	24 (7.0)	12 (3.4)
Posterior capsule opacification	17 (4.9)	18 (5.2)	8 (2.3)
Conjunctival edema	17 (4.9)	17 (5.0)	4 (1.1)
Vitreous floaters	17 (4.9)	12 (3.5)	10 (2.9)
Lenticular opacities	17 (4.9)	11 (3.2)	5 (1.4)
Punctate keratitis	14 (4.0)	11 (3.2)	11 (3.1)
Retinal aneurysm	13 (3.7)	16 (4.7)	7 (2.0)
Retinal neovascularization	12 (3.5)	23 (6.7)	21 (6.0)
Cataract cortical	11 (3.2)	17 (5.0)	11 (3.1)
Vitreous opacities	11 (3.2)	5 (1.5)	5 (1.4)
Blepharitis	10 (2.9)	6 (1.7)	20 (5.7)
Lacrimation increased	8 (2.3)	10 (2.9)	9 (2.6)
Foreign body sensation in eyes	8 (2.3)	7 (2.0)	5 (1.4)
Vitreous adhesions	7 (2.0)	6 (1.7)	5 (1.4)
Corneal erosion	7 (2.0)	4 (1.2)	3 (0.9)
Eyelid ptosis	7 (2.0)	3 (0.9)	2 (0.6)
Keratitis	6 (1.7)	7 (2.0)	3 (0.0)
Vision blurred	6 (1.7)	6 (1.7)	4 (1.1)
Anterior chamber inflammation	6 (1.7)	2 (0.6)	0 (0.0)
Eyelid edema	5 (1.4)	5 (1.5)	2 (0.6)
Macular hole	5 (1.4)	5 (1.5)	1 (0.3)
Eye irritation	5 (1.4)	4 (1.2)	7 (2.0)
Visual impairment	5 (1.4)	4 (1.2)	4 (1.1)
Retinal tear	5 (1.4)	3 (0.9)	3 (0.9)
Glaucoma	4 (1.2)	7 (2.0)	0 (0.0)
Iris neovascularization	4 (1.2)	5 (1.5)	4 (1.1)
Open angle glaucoma	4 (1.2)	3 (0.9)	2 (0.6)
Iritis	4 (1.2)	2 (0.6)	1 (0.3)
Blepharochalasis	4 (1.2)	1 (0.3)	2 (0.6)
Optic nerve cupping	3 (0.9)	6 (1.7)	1 (0.3)
Eye pruritus	3 (0.9)	4 (1.2)	8 (2.3)
Cystoid macular edema	3 (0.9)	4 (1.2)	1 (0.3)
Conjunctivitis allergic	3 (0.9)	1 (0.3)	4 (1.1)
Macular cyst	2 (0.6)	0 (0.0)	4 (1.1)
<u>Gastrointestinal disorders</u>			
Overall	50 (14.4)	57 (16.6)	42 (12.0)
Nausea	10 (2.9)	7 (2.0)	4 (1.1)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Diarrhea	7 (2.0)	9 (2.6)	3 (0.9)
Vomiting	6 (1.7)	8 (2.3)	3 (0.9)
Gastro-esophageal reflux disease	6 (1.7)	7 (2.0)	8 (2.3)
Gastritis	6 (1.7)	1 (0.3)	2 (0.6)
Constipation	5 (1.4)	8 (2.3)	5 (1.4)
Abdominal pain	4 (1.2)	2 (0.6)	3 (0.9)
Dyspepsia	3 (0.9)	2 (0.6)	4 (1.1)
Gastric ulcer	1 (0.3)	4 (1.2)	1 (0.3)
<u>General disorders and administration site conditions</u>			
Overall	30 (8.6)	34 (9.9)	25 (7.1)
Edema peripheral	9 (2.6)	13 (3.8)	8 (2.3)
Pyrexia	6 (1.7)	6 (1.7)	4 (1.1)
Non-cardiac chest pain	5 (1.4)	1 (0.3)	2 (0.6)
<u>Hepatobiliary disorders</u>			
Overall	4 (1.2)	7 (2.0)	7 (2.0)
Cholelithiasis	3 (0.9)	1 (0.3)	4 (1.1)
<u>Immune system disorders</u>			
Overall	8 (2.3)	19 (2.9)	3 (0.9)
Drug hypersensitivity	4 (1.2)	4 (1.2)	2 (0.6)
Seasonal allergy	1 (0.3)	4 (1.2)	1 (0.3)
<u>Infections and infestations</u>			
Overall	116 (33.4)	111 (32.4)	93 (26.6)
Nasopharyngitis	18 (5.2)	14 (4.1)	22 (6.3)
Bronchitis	15 (4.3)	10 (2.9)	10 (2.9)
Urinary tract infection	13 (3.7)	16 (4.7)	11 (3.1)
Influenza	13 (3.7)	12 (3.5)	11 (3.1)
Upper respiratory tract infection	10 (2.9)	19 (5.5)	17 (4.9)
Cellulitis	10 (2.9)	5 (1.5)	3 (0.9)
Sinusitis	7 (2.0)	4 (1.2)	1 (0.3)
Pneumonia	5 (1.4)	6 (1.7)	2 (0.6)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)
Gastroenteritis	4 (1.2)	4 (1.2)	2 (0.6)
Conjunctivitis viral	4 (1.2)	2 (0.6)	1 (0.3)
Hordeolum	2 (0.6)	6 (1.7)	1 (0.3)
Localized infection	2 (0.6)	1 (0.3)	5 (1.4)
Osteomyelitis	1 (0.3)	4 (1.2)	2 (0.6)
Tooth infection	0 (0.0)	5 (1.5)	0 (0.0)
<u>Injury, poisoning and procedural complications</u>			
Overall	62 (17.9)	55 (16.0)	29 (8.3)
Fall	11 (3.2)	14 (4.1)	7 (2.0)
Corneal abrasion	10 (2.9)	11 (3.2)	6 (1.7)
Ligament sprain	5 (1.4)	6 (1.7)	0 (0.0)
Foreign body in eye	5 (1.4)	1 (0.3)	0 (0.0)
Laceration	4 (1.2)	2 (0.6)	0 (0.0)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Procedural pain	4 (1.2)	1 (0.3)	2 (0.6)
Foot fracture	3 (0.9)	5 (1.5)	0 (0.0)
Contusion	0 (0.0)	5 (1.5)	1 (0.3)
<u>Investigations</u>			
Overall	142 (40.9)	136 (39.7)	46 (13.1)
Intraocular pressure increased	116 (33.4)	113 (32.9)	23 (6.6)
Blood creatinine increased	13 (3.7)	11 (3.2)	11 (3.1)
Glycosylated hemoglobin increased	11 (3.2)	10 (2.9)	6 (1.7)
Blood glucose increased	4 (1.2)	3 (0.9)	3 (0.9)
Blood pressure increased	4 (1.2)	2 (0.6)	2 (0.6)
<u>Metabolism and nutrition disorders</u>			
Overall	54 (15.6)	71 (20.7)	43 (12.3)
Hypercholesterolemia	16 (4.6)	11 (3.2)	12 (3.4)
Diabetes mellitus	11 (3.2)	5 (1.5)	8 (2.3)
Dyslipidemia	7 (2.0)	8 (2.3)	5 (1.4)
Diabetes mellitus inadequate control	6 (1.7)	9 (2.6)	6 (1.7)
Hypoglycemia	6 (1.7)	8 (2.3)	7 (2.0)
Hyperlipidemia	5 (1.4)	6 (1.7)	2 (0.6)
Type 2 diabetes mellitus	5 (1.4)	6 (1.7)	2 (0.6)
Gout	4 (1.2)	2 (0.6)	0 (0.0)
Hyperkalemia	2 (0.6)	6 (1.7)	1 (0.3)
Dehydration	1 (0.3)	6 (1.7)	3 (0.9)
Hyponatremia	0 (0.0)	5 (1.5)	0 (0.0)
<u>Musculoskeletal and connective tissue disorders</u>			
Overall	51 (14.7)	44 (12.8)	41 (11.7)
Osteoarthritis	9 (2.6)	3 (0.9)	4 (1.1)
Arthritis	8 (2.3)	5 (1.5)	2 (0.6)
Back pain	7 (2.0)	8 (2.3)	4 (1.1)
Pain in extremity	7 (2.0)	4 (1.2)	5 (1.4)
Musculoskeletal pain	4 (1.2)	4 (1.2)	3 (0.9)
Arthralgia	3 (0.9)	5 (1.5)	4 (1.1)
Muscle spasms	2 (0.6)	2 (0.6)	6 (1.7)
Spinal column stenosis	2 (0.6)	2 (0.6)	4 (1.1)
<u>Neoplasms benign, malignant and unspecified (includes cysts and polyps)</u>			
Overall	24 (6.9)	16 (4.7)	15 (4.3)
<u>Nervous system disorders</u>			
Overall	60 (17.3)	50 (14.6)	37 (10.6)
Headache	12 (3.5)	11 (3.2)	9 (2.6)
Dizziness	6 (1.7)	8 (2.3)	7 (2.0)
Transient ischemic attack	6 (1.7)	3 (0.9)	1 (0.3)
Cerebrovascular accident	5 (1.4)	3 (0.9)	4 (1.1)
Syncope	4 (1.2)	6 (1.7)	2 (0.6)
Carpal tunnel syndrome	4 (1.2)	3 (0.9)	1 (0.3)
Paraesthesia	4 (1.2)	1 (0.3)	2 (0.6)

System Organ Class Coded Adverse Event^a	DEX 700 (N=347) n (%)	DEX 350 (N=343) n (%)	Sham (N=350) n (%)
Convulsion	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic neuropathy	1 (0.3)	5 (1.5)	2 (0.6)
Carotid artery stenosis	1 (0.3)	4 (1.2)	2 (0.6)
<u>Psychiatric disorders</u>			
Overall	22 (6.3)	19 (5.5)	15 (4.3)
Depression	8 (2.3)	12 (3.5)	8 (2.3)
Insomnia	8 (2.3)	3 (0.9)	2 (0.6)
Anxiety	7 (2.0)	4 (1.2)	3 (0.9)
<u>Renal and urinary disorders</u>			
Overall	31 (8.9)	41 (12.0)	14 (4.0)
Renal failure chronic	6 (1.7)	11 (3.2)	3 (0.9)
Renal failure acute	6 (1.7)	9 (2.6)	3 (0.9)
Renal failure	6 (1.7)	7 (2.0)	3 (0.9)
Renal impairment	4 (1.2)	0 (0.0)	0 (0.0)
Diabetic nephropathy	0 (0.0)	4 (1.2)	1 (0.3)
<u>Reproductive system and breast disorders</u>			
Overall	12 (3.5)	6 (1.7)	4 (1.1)
Benign prostatic hyperplasia ^b	6 (2.9)	2 (1.0)	2 (0.9)
<u>Respiratory, thoracic and mediastinal disorders</u>			
Overall	28 (8.1)	49 (14.3)	16 (4.6)
Cough	4 (1.2)	13 (3.8)	2 (0.6)
Oropharyngeal pain	4 (1.2)	5 (1.5)	1 (0.3)
Sleep apnea syndrome	3 (0.9)	8 (2.3)	2 (0.6)
Dyspnea	3 (0.9)	5 (1.5)	4 (1.7)
Pleural effusion	0 (0.0)	4 (1.2)	3 (0.9)
<u>Skin and subcutaneous tissue disorders</u>			
Overall	24 (6.9)	22 (6.4)	20 (5.7)
Skin ulcer	4 (1.2)	4 (1.2)	2 (0.6)
<u>Surgical and medical procedures</u>			
Overall	5 (1.4)	3 (0.9)	1 (0.3)
<u>Vascular disorders</u>			
Overall	63 (18.2)	70 (20.4)	35 (10.0)
Hypertension	52 (15.0)	50 (14.6)	27 (7.7)
Hypotension	1 (0.3)	2 (0.6)	4 (1.1)

^aBased on MEDRA, version 15.0

^bPercentages based on the male population

Reviewer's Comments:

The most common ocular adverse events were cataracts (68%), increased intraocular pressure/glaucoma (36%), conjunctival hemorrhage (22%), macular edema (15%), and vitreous hemorrhage (12%).

The most common non-ocular adverse events were hypertension (15%), hypercholesterolemia (5%), nasopharyngitis (5%), anemia (4%), bronchitis (4%), headache (4%), increased blood creatinine (4%), influenza (4%), and urinary tract infection (4%).

7.4.2 Laboratory Findings

Glycosylated hemoglobin (HbA1c) and adjusted glomerular filtration rate (GFR) data was collected during studies 206207-010 and 206207-011. No clinically significant changes in laboratory values over time were observed within any of the treatment groups.

7.4.3 Vital Signs

Mean systolic blood pressure, diastolic blood pressure, and pulse rate data was collected during studies 206207-010 and 206207-011. There were no clinically significant changes from study baseline for any of the vital signs at any visit within each treatment group.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in the trials.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted for this supplement.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted for this supplement.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Two doses of the dexamethasone implant were studied, 700 µg and 350 µg. Overall, the adverse event profile between the DEX 700 and DEX 350 were similar.

7.5.2 Time Dependency for Adverse Events

See section 7.3.5

7.5.3 Drug-Demographic Interactions

Adverse events were analyzed by demographic parameters (age, sex, and race). Based on these analyses, the overall adverse event profile seen across treatment groups were similar for age 45-65 years vs. >65 years, male vs. female, and Caucasian vs. non-Caucasian. The adverse event rates were higher with DEX than Sham, and were comparable between DEX 700 and DEX 350.

7.5.4 Drug-Disease Interactions

This implant is contained within the vitreous cavity; hence, systemic drug-disease interactions are not expected.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not studied for this supplement.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Adequate studies have not been conducted in animals to determine whether dexamethasone intravitreal implant or dexamethasone have the potential for carcinogenesis.

No new studies were performed to investigate the mutagenicity, carcinogenicity, or reproductive effects due to the well-established profile of dexamethasone, and the published literature and clinical experience with dexamethasone.

7.6.2 Human Reproduction and Pregnancy Data

Safety for use in pregnancy and lactation has not been established. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical administration.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of dexamethasone intravitreal implant in pediatric patients has not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose with DEX PS DDS has not been reported in clinical trials. Overdose is unlikely as the applicator system is administered by a physician.

7.7 Additional Submissions / Safety Issues

The 120 day safety update did not raise any new safety concerns.

8 Postmarket Experience

DEX 700 was first approved on June 17, 2009 in the US for the treatment of macular edema following retinal vein occlusion. The drug product is currently approved for this indication in 56 countries and marketed in 37 countries. On September 26, 2010, the indication for DEX 700 was extended in the US to include the treatment non-infectious uveitis affecting the posterior segment of the eye. The drug product is approved for this additional indication in 46 countries worldwide

The cumulative postmarketing distribution from June 17, to January 31, 2013 for DEX 700 is (b) (4) units.

Since June 17, 2009, a total of 503 postmarketing case reports have been received for DEX 700 involving 832 adverse events. Ninety seven percent of the cases (488 cases) were medically confirmed and three percent (15

cases) were consumer reports. Of the total 503 cases, 284 were serious reports (473 serious events). Of the serious case reports, there were 4 deaths. Below are narratives of the deaths.

Case 1112994US: A 92-year-old male received Ozurdex implantation while enrolled in a Special Access Scheme Study for Ozurdex (a compassionate use program). The procedure went well and the patient had some improvement in vision and less macular edema post procedure. It was reported that the patient died about 4 months later. The cause of death was not reported.

Case 1016651US: A 90-year-old male with a medical history of diabetes, limb amputation and frequent hospitalization in recent years, experienced mild IOP increased in the treated eye following the implantation of Ozurdex in a compassionate use program. The event resolved and was reported as such at the 7 day follow-up visit. Sometime thereafter, the patient was hospitalized and subsequently died from renal failure and respiratory impairment.

Case 1107954US: A 90-year-old female with significant history of cardiovascular disease, bilateral vein occlusion and “bad vessels”, experienced cerebrovascular accident (reported as “stroke”), after receiving Ozurdex implantation for BRVO. After receiving Ozurdex and while in the ophthalmologist’s office, the patient complained of a headache, later passed out and became unresponsive. Cardiopulmonary resuscitation was initiated to revive the patient but was unsuccessful. The patient expired.

Case 1103857US: A 73-year-old male with past history of bilateral primary open angle glaucoma and IOP above normal range, experienced ocular hypertension 44 days after receiving Ozurdex implant (OD) for the treatment of macular edema due to CRVO. While the IOP was responding to oral Diamox treatment and unspecified IOP-lowering eye drops (IOP decreased from 40 to 27-30 mm Hg), the patient committed suicide and died. No known history of depression or psychological disorders was reported.

Reviewer’s Comments:

The postmarketing adverse events are consistent with the events seen in the clinical trials and do not change the safety profile for this product.

9 Appendices

9.1 Literature Review/References

N/A - an independent literature review was not conducted for this supplement.

9.2 Advisory Committee Meeting

An advisory committee meeting is scheduled to convene in late January, 2014.

9.3 Financial Disclosure Form

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 22-315 SE1-009

Submission Date(s): June 13, 2013

Applicant: Allergan, Ltd

Product: Ozurdex (dexamethasone intravitreal implant 0.7 mg)

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

Date of Review: December 1, 2013

Covered Clinical Study (Name and/or Number): Study 206207-010, Study 206207-011

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>134</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>1</u></p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>NA</u>		

Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
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Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Description of Financial Interests and Arrangements Study 206207-010

Principal Investigator Name (Site/PI Number), Address	Description
Dirk Sander, M.D. (12509/8092)	(b) (6) (sub-investigator) at this site completed a Financial Disclosure Form on 14-Jun-2007, indicating a financial interest in the form of a grant from Allergan in 2004. However, (b) (6) then completed another form on 17-Jun-2007 indicating no financial interest and also did the same on 2 later forms dated 30-Aug-2007 and 09-Mar-2009. No other record of such a grant being paid to (b) (6) can be located; however (b) (6) has since left the site, so it is impossible to follow-up for clarification.

9.4 Labeling Recommendations

See labeling recommendations which follow in the attached label.

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

¹ See [web address].

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

/s/

LUCIOUS LIM
03/18/2014

WILLIAM M BOYD
03/18/2014

CLINICAL FILING CHECKLIST FOR NDA 22-315/SE1-009

NDA/BLA Number: 22315

Applicant: Allergan, Ltd.

Stamp Date: June 13, 2013

Drug Name: Ozurdex
(dexamethasone intravitreal
implant)

NDA/BLA Type: Supplement
SE1-009

On initial overview of the Supplement application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				Efficacy supplement 505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	The drug product is an extended release implant
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 206207-010	X			

CLINICAL FILING CHECKLIST FOR NDA 22-315/SE1-009

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 206207-011 Indication: treatment of diabetic macular edema				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 22-315/SE1-009

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ YES ____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

No comments.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issues.

CLINICAL FILING CHECKLIST FOR NDA 22-315/SE1-009

Lucious Lim, MD, MPH	7/8/13
Reviewing Medical Officer	Date
William Boyd, MD	7/8/13
Clinical Team Leader	Date

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

/s/

LUCIOUS LIM
07/19/2013

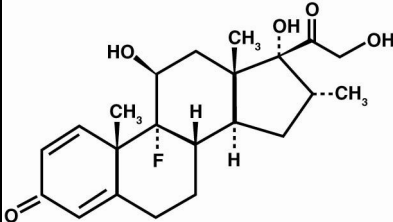
WILLIAM M BOYD
07/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

CHEMISTRY REVIEW(S)

CMC REVIEW	1. ORGANIZATION		2. NDA NUMBER	
	ONDQA, DNDQA II, Branch VI		22-315	
3. NAME AND ADDRESS OF APPLICANT			4. COMMUNICATION, DATE	
Allergan 2525 DuPont Drive, P.O. Box 19534 Irvine, CA 92623.			S-009, dated June 12, 2013 Efficacy Supplement User Fee Date is April 13, 2014	
5. PROPRIETARY NAME		6. NAME OF THE DRUG		7. AMENDMENTS, REPORT, DATE
Ozurdex		Dexamethasone intravitreal implant		009 dated June 12, 2013
8. SUPPLEMENT PROVIDES FOR:				
clinical data that demonstrate the safe and effective use of OZURDEX in the treatment of diabetic macular edema (DME).				
9. PHARMACOLOGICAL CATEGORY		10. HOW DISPENSED		11. RELATED IND, NDA, DMF
Ophthalmic		Rx		
12. DOSAGE FORM		13. POTENCY		
Intravitreal implant		0.7 mg		
14. CHEMICAL NAME AND STRUCTURE				
Chemical name: Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11 β ,16 α)- C ₂₂ H ₂₉ FO ₅ MW = 392.47 Structure:				
				
15. COMMENTS				
This efficacy supplement provides for inclusion of an additional indication, treatment of diabetic macular edema. The company, per 21 CFR 25.31 (b) claims categorical exclusion from the requirement to prepare an Environmental Assessment for Ozurdex™ (dexamethasone intravitreal implant). Per their request, approval of a supplemental NDA, will not increase the use of the active moiety and no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action. The applicant's request for categorical exclusion from environmental assessment is acceptable. There are no CMC changes in this supplement.				
16. CONCLUSION AND RECOMMENDATION				
Recommend approval from CMC perspective.				
17. NAME		18. REVIEWERS SIGNATURE		19. DATE COMPLETED
Balajee Shanmugam		In DARRTS		01-Nov-2013
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE				

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/s/

BALAJEE SHANMUGAM
11/25/2013

THOMAS F OLIVER
11/26/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22315/S-009
Supporting document/s: 211
Applicant's letter date: 6-13-13
CDER stamp date: 6-13-13
Product: OZURDEX®
Indication: Diabetic Macular Edema
Applicant: Allergan, Inc.
Review Division: DTOP
Reviewer: Ilona Bebenek, PhD
Supervisor/Team Leader: Lori E. Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Michael Puglisi

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 22315/009 are owned by Allergan, Inc. or are data for which Allergan, Inc. has obtained a written right of reference.

Any information or data necessary for approval of NDA# 22315/009 that Allergan, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 22315/009.

The purpose of the efficacy supplement for NDA 22315 (S-009) is to provide clinical data to demonstrate the safe and effective use of OZURDEX in the treatment of diabetic macular edema. The intravitreal implant contains dexamethasone 0.7 mg in a NOVADUR® solid polymer drug delivery system. No new nonclinical studies were submitted with this supplemental NDA; however label recommendations are provided below.

1.3 Recommendations

1.3.1 Approvability

The application is approvable from a Pharmacology/Toxicology perspective.

1.3.2 Labeling (Applicant's version)

Applicant-Proposed Label - The following sections of the applicant's proposed labeling are relevant to the Pharmacology/Toxicology discipline.

(b) (4)

Reviewer-recommended changes to Applicant's Label

The literature indicates that teratogenic effects in lower species are generally more severe than those reported in the monkey, and occur at significantly lower doses. Although effects in these species were mentioned in the Applicant's label, no study

details were provided regarding the doses at which these effects were produced. As such, essential context is lacking. Furthermore, the Applicant's proposed label indicates that the listed malformations are caused by "topical" administration. This appears to be erroneous, as the most of the listed malformations are not produced by topical administration, but rather by systemic administration. Additionally, it is unclear why study details regarding teratogenesis following topical ocular administration were not discussed in label, as these data are available and would appear to be most relevant to the proposed route of administration.

The following label changes are recommended:

1. Included specific details of animal studies which show teratogenesis following ocular exposure. This edit was included to provide dose information, and an accurate list of malformations associated with topical ocular exposure.
2. The sponsor was asked to provide exposure data to derive exposure multiples in nonclinical sections of the label (7-9-13). The sponsor responded that adequate animal exposure data are not available for dexamethasone. In the absence of such data, doses included in the label were scaled to the human based on mg/m^2 conversion to derive dose multiples. This scaling method is appropriate since dexamethasone is metabolized by the liver.
3. Provided information regarding the lack of fertility data

8 USE IN SPECIFIC POPULATIONS

(b) (4)

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

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/s/

ILONA G BEBENEK
03/12/2014

LORI E KOTCH
03/12/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:
22315/SE1-009

Applicant: Allergan Inc

Stamp Date: 6-13-2013

Drug Name: Ozurdex

NDA Type: Supplemental

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	<i>It is preferable that the sponsor provide exposure multiples based on systemic AUC data in nonclinical section 8. If adequate pharmacokinetic/ toxicokinetic data are available, it is recommended that the sponsor calculate exposure multiples based on systemic AUC data for label section 8.</i>
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? *Yes*

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

No nonclinical studies were submitted with this supplemental NDA. There are no nonclinical filing issues.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **(to be communicated to sponsor)**

It is preferable to provide exposure multiples based on systemic AUC data in nonclinical section 8. If adequate pharmacokinetic/ toxicokinetic data are available, please calculate exposure multiples based on systemic AUC data, and submit the dataset(s) and assumptions used to make these calculations.

If systemic AUC data are not available, but other estimates of systemic exposure are available, it is recommended that all available data be used to estimate systemic exposure and that the package insert describe the method used to estimate the exposure multiple.

Ilona G Bebenek, PhD

7/19/2013

Reviewing Pharmacologist

Date

Lori E Kotch, PhD

7/19/2013

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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ILONA G BEBENEK
07/19/2013

LORI E KOTCH
07/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

SECONDARY REVIEW

NDA/BLA #: 22-315/S-009

Drug Name: OZURDEX (dexamethasone intravitreal implant 700 µg)
Indication(s): Treatment of Diabetic Macular Edema
Applicant: ALLERGAN INC.
Date(s): Stamp date: June 13, 2013
PDUFA date: July 13, 2014
Review Priority: Standard

Biometrics Division: Division of Biometrics IV
Statistical reviewer: Abel Tilahun Eshete, Ph.D.
Secondary reviewer: Yan Wang, Ph.D.
Medical Division: Division of Transplant and Ophthalmology Products
Clinical Team: Medical reviewer: Lucious Lim, M.D.
Clinical team leader: William Boyd, M.D.
Deputy Division Director: Wiley Chambers, M.D.
Project Manager: Michael Puglisi

Keywords: Best corrected Visual Acuity, Intraocular Pressure, and cataract surgery.

Table of Contents

1	SUMMARY AND CONCLUSION.....	3
2	INTRODUCTION	5
3	REVIEW.....	6
3.1	STUDY DESIGN AND PRIMARY ENDPOINT.....	6
3.2	STATISTICAL ANALYSIS METHODS.....	6
3.3	PRIMARY EFFICACY RESULTS OF PROPORTION OF SUBJECTS WITH BCVA IMPROVEMENT ≥ 15 LETTERS.....	7
3.4	EFFICACY RESULTS OF MEAN BCVA CHANGE FROM BASELINE AND CONFOUNDING EFFECT OF CATARACT-RELATED ADVERSE EVENTS	8
3.5	EFFICACY RESULTS OF MEDIAN BCVA CHANGE FROM BASELINE	10
3.6	STATISTICAL ISSUES	11
3.6.1	<i>Subjects who Received Escape Therapy</i>	<i>11</i>
3.6.2	<i>Definition of the Primary Endpoint.....</i>	<i>12</i>
3.6.3	<i>Multiplicity Issue.....</i>	<i>14</i>
4	CONCLUSIONS	14

LIST OF TABLES

Table 1: Categorical Summary of BCVA Change from Baseline at Month 39 (ITT LOCF)	10
Table 2: Number of Subjects with BCVA Measurement at Month 36 and Month 39 and	16

LIST OF FIGURES

Figure 1: Mean BCVA Change from Baseline by Lens Status (Study 10 and Study 11).....	4
Figure 2: Primary Efficacy Results of Proportion of Subjects with BCVA Improvement ≥ 15 Letters at Month 36 and Month 39 (Study 10 and Study 11)	7
Figure 3: Proportion of Subjects with BCVA Improvement ≥ 15 Letters from Baseline by Study Visit (Study 10 and Study 11).....	8
Figure 4: Results of Mean BCVA Change from Baseline by Study Visit (Study 10 and Study 11).....	9
Figure 5: Results of Median BCVA Change from Baseline by Visit (Study 10 and Study 11).....	11
Figure 6: Efficacy Results for Site 2707, Study 11 before and after Excluding Site 2707	18

LIST OF APPENDICES

Appendix A: Information Regarding Masking, Escape Therapy, Retreatment Criteria, and Key Inclusion Criteria ..	15
Appendix B: Estimating the Percentage of Subjects with Missing Data for the Endpoint at Month 39	16
Appendix C: Efficacy Results for Site 2707, Study 11 before and after Excluding Site 2707	18

1 SUMMARY AND CONCLUSION

Modest efficacy of Ozurdex (DEX700) for the treatment of diabetic macular edema was demonstrated in two phase 3, three-arm, sham-controlled studies (Study 10 and Study 11). For the primary endpoint of proportion of subjects who had an improvement of 15 letters or more in best-corrected visual acuity (BCVA) from baseline at Month 39, the Ozurdex-treated subjects had a net gain of approximately 9% [95% CI: (1%, 17%)] in Study 10 and 8% [95% CI: (1%, 16%)] in Study 11 compared to the sham-treated subjects. However, the results of the analyses of the mean change from baseline in BCVA were not fully supportive of the results of the primary endpoint. While Ozurdex-treated subjects on average gained 3 [95% CI: (1, 6)] more letters in BCVA compared to sham-treated subjects in Study 10, there was no gain in Study 11. In fact, the treatment difference was -1 [95% CI: (-4, 3)] letter in Study 11. This non-supportive result appeared to be due to the confounding effect of the cataract formation and the need for surgery in phakic subjects treated with Ozurdex. There were a larger number of Ozurdex-treated phakic subjects experiencing cataract adverse events and subsequently needing a cataract surgery; and the majority of the cataract surgeries occurred from Month 18 to Month 30.

As shown in the graphs (Figure 1) of the mean BCVA change from baseline over time, the negative effect of cataracts in phakic subjects appeared approximately from Month 18 to Month 30 and Month 9 to Month 39 in Study 10 and Study 11, respectively. In phakic subjects, the treatment difference in mean BCVA change from baseline at Month 39 was 2 [95% CI: (-1, 5)] letters and -1 [95% CI: (-6, 3)] letter in Study 10 and Study 11, respectively.

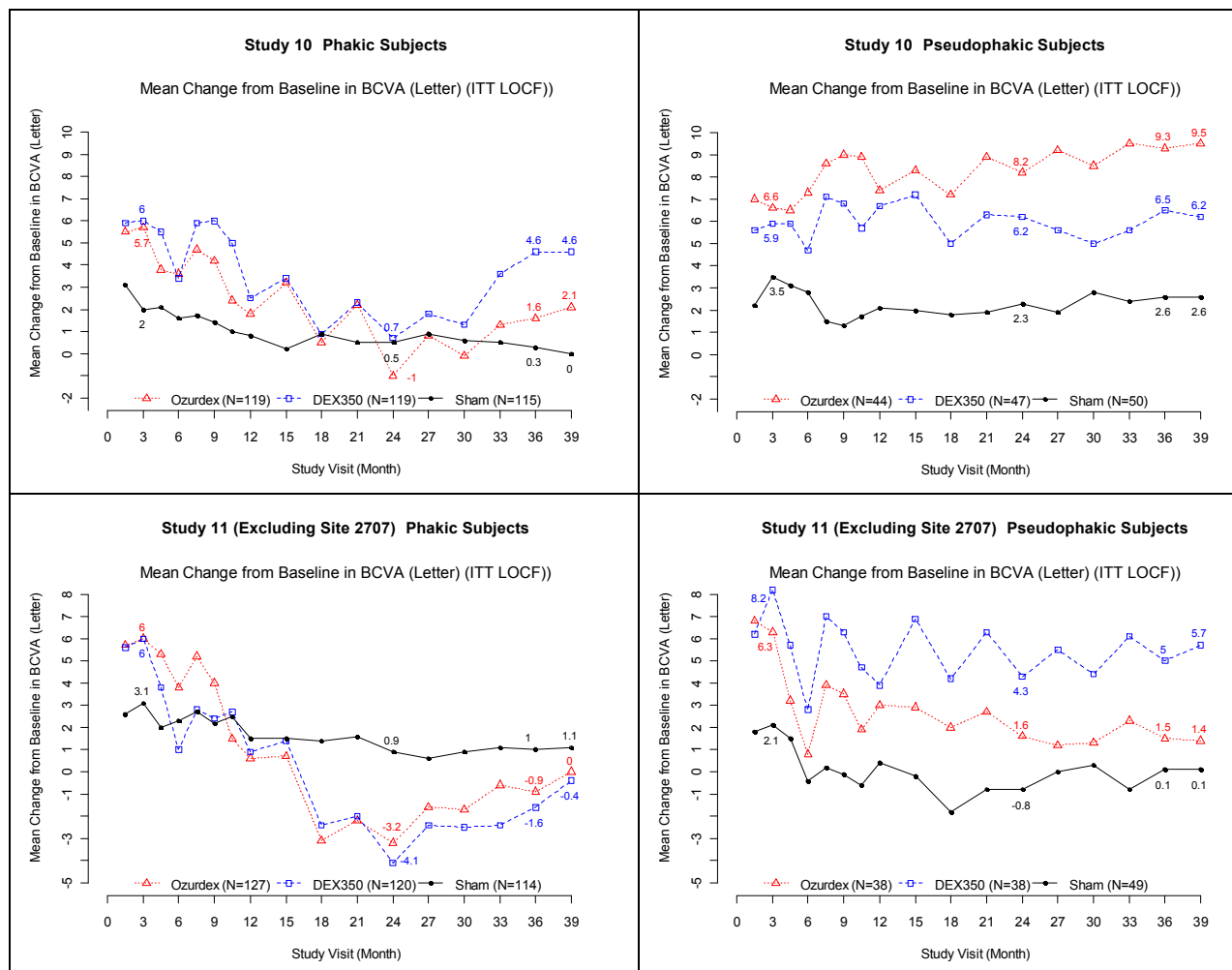
In pseudophakic subjects, who are not susceptible to cataract formation, both studies showed a positive trend in BCVA improvement for Ozurdex throughout the study course, though the effect in Study 11 was still modest. The treatment difference in mean BCVA change from baseline at Month 39 was 7 [95% CI: (3, 11)] letters in Study 10, and 1 [95% CI: (-4, 7)] letter in Study 11, and was 4 [95% CI: (1, 8)] letters for the two studies combined. Note that the sample size was small for pseudophakic subjects, approximately 25% of study subjects were pseudophakic.

Moreover, in pseudophakic subjects, both studies (Figure 1) showed a positive trend in BCVA improvement in the low dose arm (DEX350) throughout the study course. The treatment difference in mean BCVA change from baseline at Month 39 was 4 [95% CI: (-1, 8)] letters in Study 10, and 6 [95% CI: (0, 11)] letters in Study 11, and was 5 [95% CI: (1, 8)] letters for the two studies combined. These positive results in the low dose arm provided additional support to the efficacy of Ozurdex.

With respect to safety of Ozurdex, significantly increased risks of cataract formation (subsequently leading to cataract surgery) and elevated intraocular pressure (IOP) were observed in both studies. For phakic subjects, the risk of cataract formation was three times higher in Ozurdex-treated subjects than sham-treated subjects (68% vs. 21%), and the net risk was 47% [95% CI: (39%, 55%)]; the risk of cataract surgery was seven times higher (61% vs. 8%), with a net risk of 53% [95% CI: (46%, 60%)]. For both phakic and pseudophakic subjects, the risk of elevated IOP was six times higher (37% vs. 6%), with a net risk of 32% [95% CI: (26%, 37%)]. Note that these safety results were based on the data from the two studies combined.

In summary, based on the totality of findings, this review concludes that there is evidence to support the efficacy of Ozurdex in pseudophakic subjects provided the observed treatment effect is deemed clinically meaningful and outweighs the safety risks. Because of the confounding effect of cataract formation and surgery, the treatment effect in phakic subjects needs to be interpreted with the associated safety risks taken into consideration.

Figure 1: Mean BCVA Change from Baseline by Lens Status (Study 10 and Study 11)



DEX350 stands for the low dose treatment arm containing a total dose of 350 µg of dexamethasone; Ozurdex (DEX700) was the high dose treatment arm containing a total dose of 700 µg of dexamethasone.

2 INTRODUCTION

Ozurdex, an intravitreal biodegradable implant containing a total dose of 700 µg of dexamethasone, was approved for the treatment of macular edema following branch or central retinal vein occlusion on June 17, 2009, and for the treatment of non-infectious uveitis on September 24, 2010. The current application contained the results of two phase 3 studies (Study 10 and Study 11) to support the indication of diabetic macular edema (DME).

The primary statistical review was conducted by Dr. Abel Eshete and finalized on March 10, 2014. His review found evidence of modest efficacy of Ozurdex in both studies while it identified significant risks of elevated IOP and cataract formation and surgery.

Recently, because evidence of fraud was found at Site 2707 in Study 11, the Office of Scientific Inspection (OSI) recommended that the data from this site be excluded from efficacy and safety analyses. Note that this site enrolled the most domestic subjects [12% (68/554)] of the study population in Study 11 and reported much better efficacy results than the overall study population (Appendix C),

Dr. Eshete wrote an addendum (finalized on June 26, 2014) based on his analyses excluding Site 2707 and concluded the following:

“Because both studies revealed that DEX 700 had only a very modest treatment effect and that there was substantially higher risk of cataract surgery and intraocular pressure in the DEX 700 arm, this reviewer does not recommend the approval of this drug for the (b) (4) treatment of Diabetic Macular Edema (DME). From a safety perspective, the agency’s proposed limited indication, the treatment of DME for subjects who are either Pseudophakic or Phakic subjects who are scheduled for cataract surgery, is acceptable. However, because there was no statistically significant difference between DEX 700 and Sham in the proportion of subjects with a 15 letter or more gain from baseline BCVA at Month 36 and that there was no data in the submission to support the efficacy and safety of subjects who are scheduled to undergo cataract surgery, the subsequent recommendation for approval of the limited indication should be made based on clinical grounds.”

I agree with Dr. Eshete’s conclusion regarding the modest efficacy of Ozurdex and the significant risks of elevated IOP, cataract formation and surgery. This secondary review will describe my interpretation of the efficacy findings and provide my perspective on the statistical issues raised during the review process: (1) handling of subjects who received escape therapy, (2) definition of the primary efficacy endpoint, and (3) multiplicity related to the efficacy results in pseudophakic subjects.

3 REVIEW

3.1 Study Design and Primary Endpoint

Study 10 and Study 11 were identical in design. They were multi-center, randomized, double-blind studies, comparing two doses, 700 µg (DEX700) and 350 µg (DEX350), of dexamethasone implant to sham treatment (needleless injection). Subjects were randomized into one of the three treatment arms in a 1:1:1 ratio. For subjects with both eyes eligible for the study, the eye with shorter duration of DME was selected as the study eye. Only the study eye was treated with the assigned study drug during the study and received the first treatment at the randomization visit (Day 0). Subjects were evaluated for retreatment eligibility at a study-scheduled visit every 3 months starting from Month 6 through Month 33 or Month 36, but could not receive successive treatments more often than approximately a 6-month interval. Retreatment criteria were based on physician's discretion after examination including optical coherence tomography (OCT). Subjects may have been treated with escape therapy (defined as any therapy for macular edema in the study eye other than the assigned study drug). Subjects who received escape therapy in the study eye were considered study treatment failures and were withdrawn from the study. Details regarding masking, escape therapy, retreatment criteria, and inclusion criteria are provided in Appendix A.

Efficacy outcome assessment visits occurred every 1.5 months during the first year and every 3 months thereafter until Month 36 or 39. The primary efficacy outcome was BCVA in the study eye and assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) method.

The protocol-defined primary efficacy endpoint was the proportion of subjects who had an improvement of 15 letters or more in BCVA from baseline in the study eye at final assessment visit (Month 36 for those not retreated at Month 36 or Month 39 for those retreated at Month 36, or final visit for subjects who exited the study earlier) referred to simply as Month 39 in the remainder of the review. There were a number of secondary efficacy endpoints, including the mean BCVA change from baseline at each post-baseline visit.

Note that the initial timing of the primary endpoint was at 24 months with a final follow-up visit at 36 months. In a protocol amendment that occurred after the majority of the study subjects already exited the study at or prior to Month 36, the primary endpoint was changed to occur at Month 36 for those not needing retreatment at 36 months or at Month 39 for those needing retreatment at 36 months. However, due to the fact that prior to the amendment the study ended at Month 36 and retreatment was not available to subjects at that point, the post-amendment primary endpoint could not be fully assessed on all subjects and, therefore, there was potential difficulty in the interpretation of the primary endpoint at Month 39 (discussed in detail in Section 3.6). For this reason, the endpoint at Month 36 was considered as well.

3.2 Statistical Analysis Methods

The primary efficacy analysis was performed on the intent-to-treat (ITT) population including all randomized subjects. The between-treatment comparison was performed using the chi-square test, and the 95% CI for the treatment difference was calculated using the normal approximation

for a binomial endpoint. A gate keeping procedure was used to control the overall type I error rate at 5% for the two between-treatment comparisons (DEX700 vs. Sham and DEX350 vs. Sham): the comparison between DEX700 and Sham was tested first at the significance level of 0.05, and followed by the comparison between DEX350 and Sham. Missing data were imputed using the last observation carried-forward (LOCF) method.

In the analysis of mean BCVA change from baseline at each visit, treatment difference was tested using an analysis of covariance (ANCOVA) with treatment arm as a fixed effect, and baseline BCVA as a covariate on the ITT population; the 95% CI for the treatment difference was calculated using the least square means and assuming equal variances for treatment arms.

Note that for subjects who received escape therapy, their BCVA measurements were set as missing at all study visits after the receipt of escape therapy.

3.3 Primary Efficacy Results of Proportion of Subjects with BCVA Improvement ≥ 15 Letters

The results of the primary endpoint at Month 39 (Figure 2) demonstrated evidence of modest efficacy in both studies (excluding Site 2707). In Study 10, approximately 21% and 12% of subjects had BCVA improvement ≥ 15 letters in the DEX700 and sham arms, respectively, with a treatment difference of 9% [95% CI: (1%, 17%)]. In Study 11 (excluding Site 2707), approximately 18% and 10% subjects had BCVA improvement ≥15 letters in the DEX700 and sham arms, respectively, with a treatment difference of 8% [95% CI: (1%, 16%)]. Compared with Month 39, however, the results at Month 36 were less favorable, showing a reduction in the treatment difference of approximately 1% in Study 10 and 3% in Study 11. It is noted that the treatment difference at Month 36 was not statistically significant. This non-statistically significant result, however, is not an indication of lack of efficacy; instead, it reflects the nature of the modest effect of DEX700.

The modest effect of DEX700 was also seen in the graphs of the efficacy results over time (Figure 3). In both studies, the DEX700 arm had a higher proportion of subjects with BCVA improvement ≥ 15 letters at all study visits compared to the sham arm. The treatment differences ranged from 2% to 10%, and were not statistically significant at almost all visits between Month 6 and Month 27 in Study 11.

Figure 2: Primary Efficacy Results of Proportion of Subjects with BCVA Improvement ≥ 15 Letters at Month 36 and Month 39 (Study 10 and Study 11)

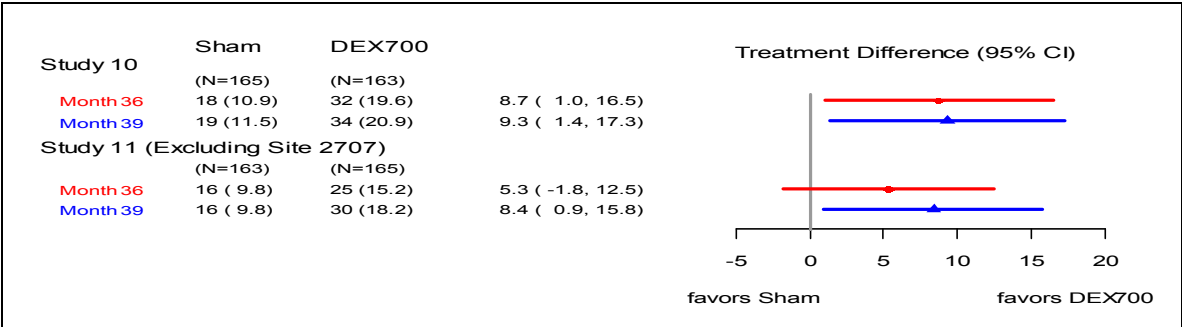
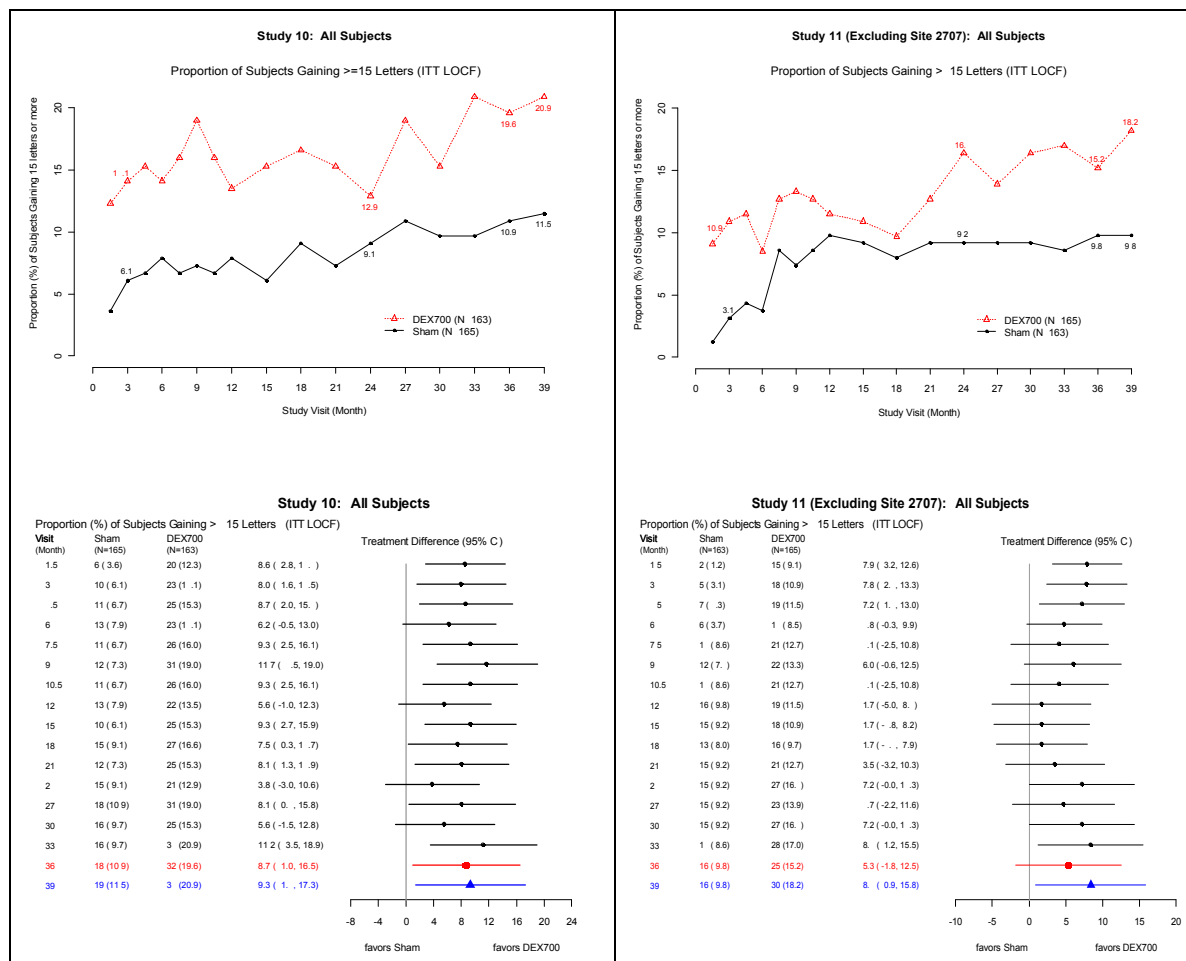


Figure 3: Proportion of Subjects with BCVA Improvement ≥ 15 Letters from Baseline by Study Visit (Study 10 and Study 11)



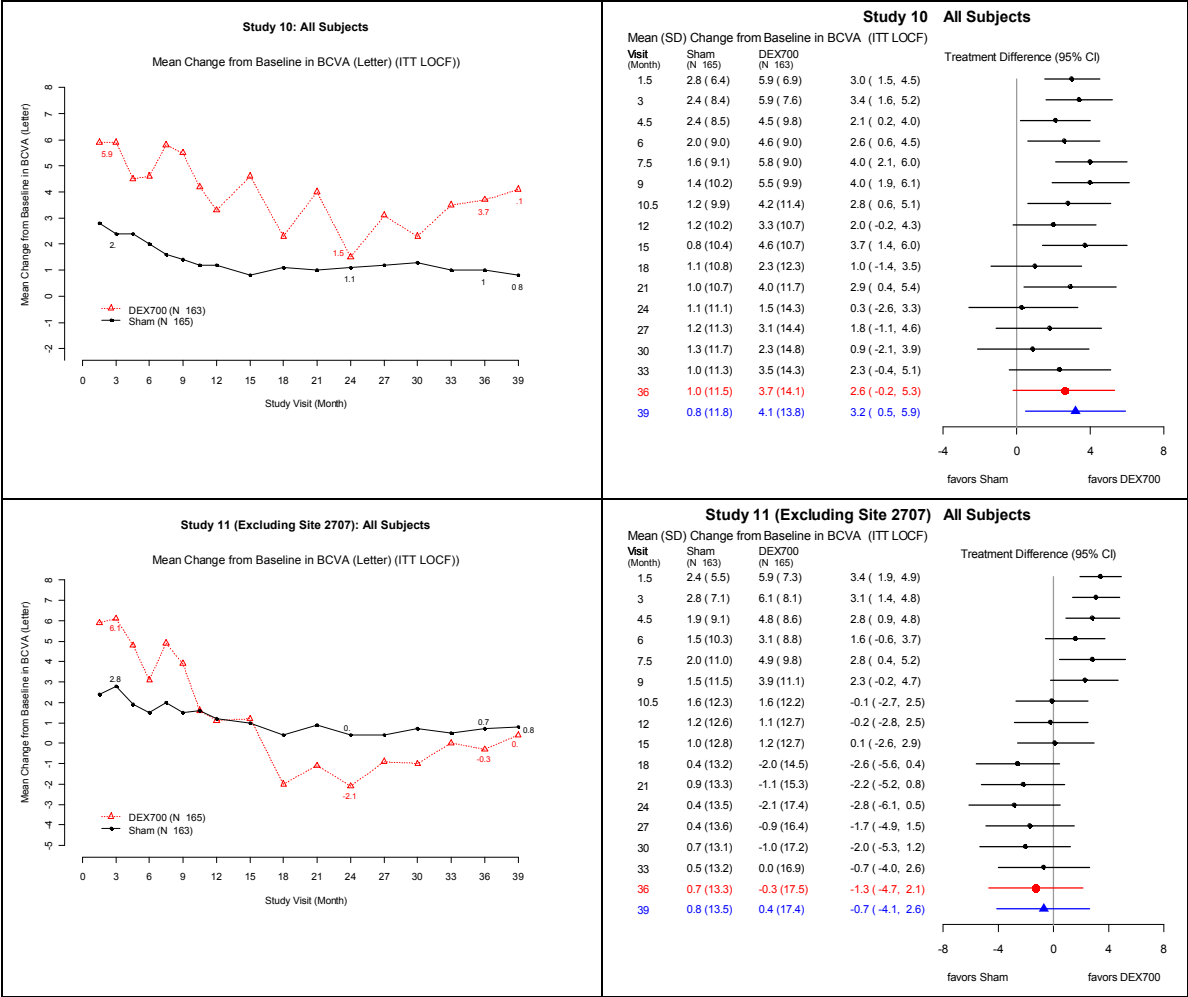
3.4 Efficacy Results of Mean BCVA Change from Baseline and Confounding Effect of Cataract-related Adverse Events

Mean BCVA changes from baseline at all post-baseline visits were considered as secondary endpoints in the protocol. These endpoints are clinically relevant because, unlike the dichotomous endpoints, they take into account the magnitude of the BCVA values for all subjects and provide insight into whether, on average, subjects treated with DEX700 achieve more gain in vision improvement than subjects treated with sham. The results of these endpoints were presented in Figure 4. While the results in Study 10 were supportive of the results of the dichotomous endpoints, the results in Study 11 were not supportive.

In Study 10, subjects in the DEX700 arm had more gain in BCVA at all study visits compared to the sham though the treatment differences were not numerically impressive, ranging from 0.3 to 4 letters; the treatment difference was 3 [95% CI: (0.5, 5.9)] letters at Month 39. In Study 11, however, there was no consistent separation between the DEX700 and sham arms. Starting from approximately Month 10 to Month 39, subjects in the DEX700 arm were performing worse than

subjects in the sham arm; the treatment difference was -1 [95% CI: (-4, 3)] letters at Month 39. The applicant attributed these non-supportive results to the confounding effect of cataract formation and the need for surgery in phakic subjects in the DEX700 arm. Note that as presented in Dr. Eshete’s review, based on the data from two studies combined, approximately 68% of Ozurdex-treated phakic subjects experienced cataract-related adverse events and 60% of Ozurdex-treated phakic subjects needed a cataract surgery. The majority of the cataract surgeries occurred from Month 18 to Month 30. The median time to first reported cataract adverse event and to cataract surgery were 15 months and 21 months, respectively.

Figure 4: Results of Mean BCVA Change from Baseline by Study Visit (Study 10 and Study 11)



The confounding effect of cataract formation was apparent in the graphs of mean BCVA change from baseline by baseline lens status (Figure 1). In phakic subjects, the effect of cataracts was seen from approximately Month 18 to Month 30 in Study 10 and Month 9 to Month 39 in Study 11, with the greatest mean negative change occurring around Month 24. Compared with Study 10, cataracts appeared to cause vision loss at a much faster rate and the recovery after surgery was much slower in Study 11. At Month 39, the DEX700-treated subjects in Study 11 were still doing worse than the sham-treated subject, with a net loss of -1 [95% CI: (-6, 3)] letter. On the other hand, a net gain of 2 [95% CI: (-1, 5)] letters was seen at Month 39 in Study 10.

In pseudophakic subjects, who are not susceptible to cataract formation, both studies (Figure 1) showed a positive trend in BCVA improvement for DEX700 throughout the study course, though the effect in study 11 was still modest. The treatment difference in mean BCVA change from baseline at Month 39 was 7 [95% CI: (3, 11)] letters in Study 10, and 1 [95% CI: (-4, 7)] letter in Study 11, and was 4 [95% CI: (1, 8)] letters for the two studies combined.

Moreover, in pseudophakic subjects, both studies (Figure 1) showed a positive trend in BCVA improvement in the DEX350 arm throughout the study course. The treatment difference in mean BCVA change from baseline at Month 39 was 4 [95% CI: (-1, 8)] letters in Study 10, and 6 [95% CI: (0, 11)] letters in Study 11, and was 5 [95% CI: (1, 8)] letters for the two studies combined. These positive results in the DEX350 arm provided additional support to the efficacy of Ozurdex in this subgroup.

3.5 Efficacy Results of Median BCVA Change from Baseline

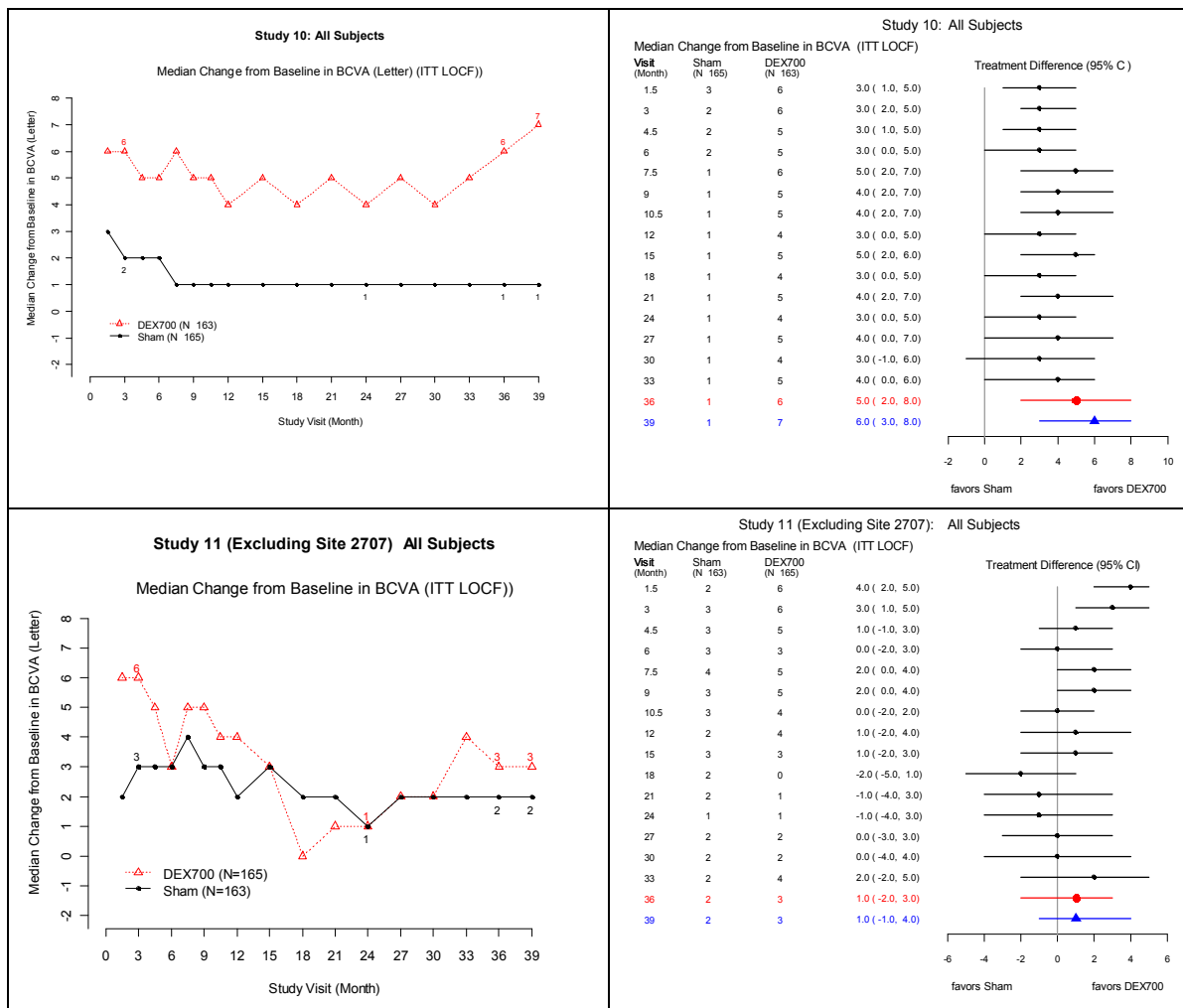
It is known that a numerical variable such as mean BCVA change from baseline is sensitive to outliers. Subjects who either had a large gain or loss (say more than 15 letters) in BCVA would have much more impact on the mean variable than those who had a gain or loss of no more than 5 letters. As shown in Table 1, the two DEX arms in Study 11 had approximately as many subjects who lost ≥ 15 letters as those who gained ≥ 15 letters in BCVA at Month 39. Because the median BCVA change from baseline is not sensitive to outliers, this endpoint was analyzed to further examine the treatment effect of DEX700 (Figure 5). In Study 10, there was a consistent separation between the DEX700 and sham arms through the study course. At Month 39, the median BCVA change from baseline was 7 and 1 letters in the DEX700 and sham arms, respectively, with a net gain of 6 [95% CI: (3, 8)] letters. In Study 11, however, there was no consistent separation, and the DEX700 arm was performing worse than the sham arm between Month 15 and Month 18. At Month 39, the median BCVA change from baseline was 3 and 2 letters in the DEX700 and sham arms, respectively, with a net gain of 1 [95% CI: (-1, 4)] letter.

Table 1: Categorical Summary of BCVA Change from Baseline at Month 39 (ITT LOCF)

BCVA Change	Study 10			Study 11		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163
≥ 15 Letters Improvement	34(20.9)	31(18.7)	19(11.5)	30(18.2)	24(15.2)	16(9.8)
≥ 10 and < 15 Letters Improvement	26(16)	22(13.3)	15(9.1)	15(9.1)	19(12)	21(12.9)
≥ 5 and < 10 Letters Improvement	29(17.8)	31(18.7)	16(9.7)	18(10.9)	29(18.4)	14(8.6)
No Change (-5 to +5 Letters)	39(23.9)	55(33.1)	74(44.8)	52(31.5)	39(24.7)	71(43.6)
≥ 5 and < 10 Letters Worsening	13(8)	9(5.4)	14(8.5)	15(9.1)	9(5.7)	17(10.4)
≥ 10 and < 15 Letters Worsening	7(4.3)	8(4.8)	10(6.1)	5(3)	15(9.5)	6(3.7)
≥ 15 Letters Worsening	15(9.2)	10(6)	17(10.3)	30(18.2)	23(14.6)	18(11)

Source: Table 6 in Dr. Eshete's review.

Figure 5: Results of Median BCVA Change from Baseline by Visit (Study 10 and Study 11)



The 95% CI was calculated using a bootstrap method.

3.6 Statistical Issues

3.6.1 Subjects who Received Escape Therapy

A total of 132 subjects received escape therapy in the two studies combined; of those subjects, 129 subjects received escape therapy prior to Month 36 and 3 subjects received therapy at Month 36. The applicant's and statistical reviewer's primary analyses differed in how these subjects were handled. According to the applicant's statistical analysis plan, the efficacy data for these subjects would be set as missing for all visits after the receipt of escape therapy and imputed using LOCF; consequently, 12 of these subjects were treated as success in the applicant's analysis at the visits after the receipt of escape therapy.

According to the applicant's protocol, however, subjects who received escape therapy would be considered as study treatment failures. The statistical review team agreed with the protocol and treated these 12 subjects as treatment failures in their reviews.

It is noted that among these 12 subjects, 5 (2 DEX700, 0 DEX350, and 3 Sham) were in Study 10, and 7 (4 DEX700, 2 DEX350, and 1 Sham) were in Study 11. Therefore, treating these subjects as treatment failures had no negative impact on the primary efficacy results of Study 10, but reduced the treatment effect by approximately 2% in Study 11 at Month 36 and Month 39.

3.6.2 Definition of the Primary Endpoint

The original study design was a 36-month trial and subjects were evaluated for retreatment eligibility every 3 months starting from Month 6 through Month 33. The primary efficacy endpoint was evaluated at Month 24. On May 8, 2010, four major changes were incorporated in protocol Amendment 4: (1) retreatment criteria were modified, including revising the requirement of OCT >225 μm to OCT >175 μm ; (2) an additional treatment was allowed at Month 36; (3) a visit at Month 39 was added to provide efficacy and safety assessment for subjects who received retreatment at Month 36; and (4) the assessment time point for the primary efficacy endpoint was revised from Month 24 to the final assessment visit (Month 36 for those not retreated at Month 36 or Month 39 for those retreated at Month 36, or final visit for subjects who exited the study earlier). This endpoint was labeled by the applicant in four different ways: 3-year endpoint, Month 36 endpoint, Month 36/39 endpoint, and Month 39/final endpoint. This review referred it to as the endpoint at Month 39 for simplicity.

According to the applicant, by the time all sites received ethics committee approval to initiate Amendment 4, approximately 52% of subjects had exited the study at or prior to Month 36.

Dr. Eshete's review included the results at both Month 36 and Month 39, but gave more emphasis to the results at Month 36 because of missing data at Month 39 and the concern with the timing of the amendment. Dr. Eshete's review stated that evaluating the primary efficacy endpoint at Month 39 would artificially create missing data for nearly 84% of study subjects (Section 1.2 and Section 2.3.4 of Dr. Eshete's review). I agree with Dr. Eshete's concern about the timing of the amendment, but I have a different opinion regarding the percentage of subjects with missing data.

In general, changing any key element of the study design after the majority of subjects had already exited the study is strongly discouraged because this practice will cast doubt on the integrity of the study outcomes and often cause difficulty in interpreting the study results. In Study 10 and Study 11, there is additional concern because the post-amendment endpoint (endpoint at Month 39) could not be assessed for the majority (approximately 52%) of the study subjects.

By contrast, the endpoint at Month 36, preferred in Dr. Eshete's review as the primary endpoint, could be assessed for all study subjects (if not withdrawn from the study). Additionally, it is more straightforward to explain this endpoint because it was assessed at the same time point for every subject. On the other hand, it seems difficult to explain the endpoint at Month 39 because

it was assessed at different time point for different subjects depending on the retreatment status at Month 36, capturing the “peak” effect at two time points as describe below.

The efficacy data showed that for most subjects the treatment effect peaked approximately 3 months and waned approximately 6 months after each treatment. Using the endpoint at Month 36 appeared to capture the “average” effect – including the “waning” effect in patients who needed retreatment at Month 36 and the “peak” effect in patients who did not need retreatment at Month 36. On the other hand, the endpoint at Month 39 kept the “peak” effect at Month 36 for subjects who did not need retreatment at Month 36 and replaced the “waning” effect at Month 36 with the “peak” effect at Month 39 for subjects who needed retreatment at Month 36. As a result, using the endpoint at Month 39 appeared to capture the “peak” effect for every subject. Consequently, the slightly better observed treatment effect at Month 39 compared to Month 36 was not surprising.

Regarding the missing data for the endpoint at Month 39, a high percentage (nearly 84%) of subjects with missing data was noted in Dr. Eshete’s review. However, I found the percentage of subjects with missing data could be estimated using a different approach. This approach was based on two considerations: (1) subjects who received escape therapy would not be treated as having missing data because they were treated as treatment failures; (2) subjects who did not need retreatment at Month 36 would not be treated as having missing data at Month 39 because by definition of the endpoint at Month 39, they did not have a visit at Month 39. Using this approach, the percentage of subjects with missing data at Month 39 is approximately 53% (Appendix B). This number shows that though the amount of missing data for the new primary endpoint at Month 39 is still large (53%), it should not be considered as large as originally reported in the statistical review (nearly 84%). A difference of 31% in these two percentages (84% vs. 53%) of missing data indicates that many of these 84% subjects who were originally reported as having missing data for the endpoint at Month 39 had reached the primary endpoint at Month 36.

Note that although the 53% missing data for the endpoint at Month 39 is lower than what was originally reported, it is still excessive compared to the 35% missing data at Month 36 (Appendix B). This increase in missing data is driven by the fact that the majority of the study subjects had exited the study and could not be assessed for the endpoint at Month 39 because of the timing of the amendment. Therefore, despite being less than originally reported, the fact that there is an additional 18% missing data within 3 months is concerning in its magnitude. However, because the endpoint at Month 39 is intended to capture the “peak” effect and that the BCVA values at Month 36 which reflect “average” effects were imputed for the additional 18% subjects with missing data at Month 39, I do not believe the estimated treatment effect at Month 39 has been inflated.

In summary, although the statistical team preferred the endpoint at Month 36 as the primary endpoint because of the concerns regarding the timing of the amendment and consequently the potential difficulty of interpreting the endpoint at Month 39, if the endpoint at Month 39 which captures the “peak” treatment effect, is deemed clinically meaningful, and can be clearly described in the drug labeling, I do not have objection to the use of this endpoint as the primary endpoint.

3.6.3 Multiplicity Issue

This secondary review concluded that evidence of modest effect existed in both studies for the overall population. This conclusion was based on the totality of findings. First, both studies met the primary endpoint at Month 39, though the treatment effect was very modest, especially in Study 11. Second, the results at Month 36 and Month 39 were similar, though the result at Month 36 was not statistically significant in Study 11. Finally, the treatment effect over time showed consistent trends favoring the test product. Therefore, this review concluded that the test product had modest treatment effect in the full population (after excluding Site 2707 due to fraud).

A concern about multiplicity has been raised because the Division's proposed indication is for subjects who are either pseudophakic or phakic subjects who are scheduled for cataract surgery. As multiplicity refers to situations where a study has multiple ways to claim success for treatment efficacy, one should clearly define the success criteria when discussing multiplicity.

The reason for limiting the indication is based on the toxicity of the test product. More specifically the reason for limiting the indication is to mitigate the risk of cataract formation and the need for cataract surgery, and it is not based on any statistical claim regarding the comparison of the treatment effects in the subgroup and in the overall population.

One might argue that by approving the limited indication, we are inexplicitly making a claim that the test product had treatment effect in the pseudophakic subjects. Would this claim lead to a multiplicity issue; in other words, is this claim likely due to chance? In my opinion, the answer is "No" because it is concluded that the test product had treatment effect for the overall population and the observed efficacy results in the pseudophakic subjects were consistent with the overall study results; consequently there is sufficient evidence to conclude that the test product had treatment effect in the pseudophakic subjects.

4 CONCLUSIONS

Based on the totality of findings, this review concludes that there is evidence to support the efficacy of Ozurdex in pseudophakic subjects provided the observed treatment effect is deemed clinically meaningful and outweighs the safety risks. Because of the confounding effect of cataract formation and surgery, the treatment effect in phakic subjects needs to be interpreted with the associated safety risks taken into consideration.

Appendix A: Information Regarding Masking, Escape Therapy, Retreatment Criteria, and Key Inclusion Criteria

Masking: The following statements are excerpted from the study report (section 9.4.6):

Patients were masked to the study treatments for the duration of the trial.

The study treatment procedure and postinjection safety evaluations (except BCVA) were performed by the treating investigator. The treating investigator also evaluated the quality of the OCT prints, fundus photographs, and/or fluorescein angiograms obtained during the qualification/baseline visit. He/she had overall responsibility for the safety of the patient, and did not participate in the efficacy procedures. Treating investigators were to keep study medication information confidential unless sharing this information was in the best interest of the patient for safety reasons.

The follow-up investigator did not participate in study treatment procedures. The treating investigators and follow-up investigators were to maintain their roles throughout the study. Any unscheduled visits necessary within 30 days after a study treatment procedure were performed by the treating investigator. All other unscheduled visits were performed by the follow-up investigator.

Individuals collecting BCVA, contrast sensitivity, OCT, fundus photographs, and fluorescein angiography data were masked to patient treatments. BCVA technicians only performed BCVA, manifest refraction, and contrast sensitivity.

A central reading center was used to evaluate OCT, fundus photographs, and fluorescein angiography and the grader was masked from study treatments.

Escape Therapy: The following statements are excerpted from the protocol (section 5.5.2).

A patient may be treated with escape therapy (defined as any therapy for macular edema in the study eye other than the assigned study therapy) at the investigator's discretion at any point during the study. Escape therapy may include

- *Intravitreal steroids other than the study medication in the study eye*
- *Periocular steroids to the study eye*
- *Laser and/ or surgical treatments for macular edema in the study eye*
- *Intravitreal anti-VEGF therapy in the study eye*
- *Systemic anti-VEGF therapy*
- *Other pharmacologic therapies for macular edema in the study eye*

Patients who receive escape therapy for the study eye will be considered study treatment failures, will no longer be eligible to receive study treatment, and will be withdrawn from the study based on when they last received study treatment.

Patients will be withdrawn from the study and the exit procedures should be performed prior to the administration of escape therapy. If the last study treatment is < 3 months prior to the escape therapy, the patient should be followed up for adverse event information 3 months after the last treatment as well.

Retreatment Criteria: The following statements are excerpted from the protocol (section 4.1).

Patients will be assessed for retreatment eligibility every 3 months at a study-scheduled visit starting from month 6 through month 36. Patients are eligible for retreatment if

Retinal thickness in the 1 mm central macular subfield by optical coherence tomography is >175 μ m (determined by the site, not the central reading center),

OR

Upon Investigator interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield).

Key Inclusion Criteria: The following information is from protocol (section 5.3).

- a) Diabetic macular edema in the study eye defined as clinically observable macular edema involving the center of the macula (fovea) associated with diabetic retinopathy with any of the following characteristics:
 - Prior medical therapy for diabetic macular edema
 - Prior macular laser(s) for diabetic macular edema with the most recent laser at least months prior to Baseline/ Qualification where, in the

opinion of the investigator, the patient will be able improve 15 or more letters in BCVA from baseline with the resolution of the macular edema despite the presence of macular laser scars

- In the investigator's opinion the patient would not benefit from macular laser treatment
 - The patient refuses laser treatment
- b) BCVA score between 34 letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye measured by the ETDRS method at qualification/baseline
- c) Retinal thickness of ≥ 300 μm by OCT in the 1 mm central macular subfield of the study eye at qualification/baseline as determined by the investigator

Appendix B: Estimating the Percentage of Subjects with Missing Data for the Endpoint at Month 39

Step 1: Estimating the number and percentage of subjects with missing data at Month 36

As shown in Table 2, 52% (517/980) of subjects had BCVA measurements at Month 36, but this does not mean that the remaining subjects (48%) had missing data for the endpoint at Month 36. In fact, 129 subjects who received escape therapy prior to Month 36 were treated as treatment failures and as such should not be counted as having missing data at Month 36, thus the number of subjects with missing data at Month 36 is 334 (=980-517-129), and the percentage of subjects with missing data at Month 36 is approximately 35% (334/980).

Table 2: Number of Subjects with BCVA Measurement at Month 36 and Month 39 and Number of Subjects with Retreatment at Month 36
(Based on pooled data from Study 10 and Study 11 excluding Site 2707)

	DEX 700 N=328	DEX 350 N=324	Sham N=328	Total N=980
Number of Subjects Who had BCVA measurement				
Month 36	199(60.7%)	191(59%)	127(38.7%)	517 (52.8%)
Month 39	55(16.8%)	63(19.4%)	40(12.2%)	158 (16.1%)
Number of Subjects Who Received Retreatment				
Month 36	52 (15.8%)	56 (17.3%)	45 (13.7%)	153 (32.6%)

Source: Table 18 and Table 63 in Dr. Eshete's review. . * Out of the 158 subjects with BCVA at Month 39, 137 were re-treated at Month 36 while the remaining 21 were not retreated at Month 36.

Step 2: Estimating the number and percentages of subjects with missing data at Month 39

Let R_{m39} denote the percentage of subjects with missing data for the endpoint at Month 39. All subjects considered to have missing data for the Month 36 analysis would also be considered as having missing data for the Month 39 analysis (334). For subjects who remained in the study after Amendment 4, let $N_{\text{after_amendment}}$ denote the number of subjects who received retreatment at Month 36 and did not have outcome measurement at Month 39. These subjects are considered as missing. For subjects who already exited the study, let $N_{\text{before_amendment_reatreatment}}$ denote the number of subjects who would have received retreatment at Month 36 if they were offered the opportunity to be evaluated for retreatment eligibility at Month 36. Since there are no values for these subjects at Month 39, these subjects are also considered to have missing data for their Month 39 value. Then R_{m39} can be written as $(334 + N_{\text{after_amendment}} + N_{\text{before_amendment_reatreatment}})/980$.

Among the subjects (approximately $470=980*(1-0.52)$) who remained in the study after Amendment 4, a total of 153 (32.6%) subjects received retreatment at Month 36. Of those subjects, 137 subjects had BCVA measurement at Month 39, and thus 16 ($=153-137$) subjects had missing BCVA at Month 39. Therefore, $N_{\text{after_amendment}}$ is 16.

Though the sponsor reported that approximately 52% of the subjects had exited the study by the time Amendment 4 was implemented, we do not have data on individual subjects regarding who were included in Amendment 4. For this reason we will need to estimate $N_{\text{before_amendment_reatreatment}}$. Among the 470 subjects who remained in the study after Amendment 4, 153 (32.6%) of them received retreatment at Month 36. If we approximate the number of subjects who exited the study prior to Amendment 4 as 510 ($980*0.52$) and then apply the same percentage of those would have received retreatment at Month 36 as those who remained in the study (32.6%), $N_{\text{before_amendment_reatreatment}}$ could be estimated as $32.6\%*510 = 166$. This estimation was based on the assumption that the subjects who remained in the study after Amendment 4 are representative of the study population.

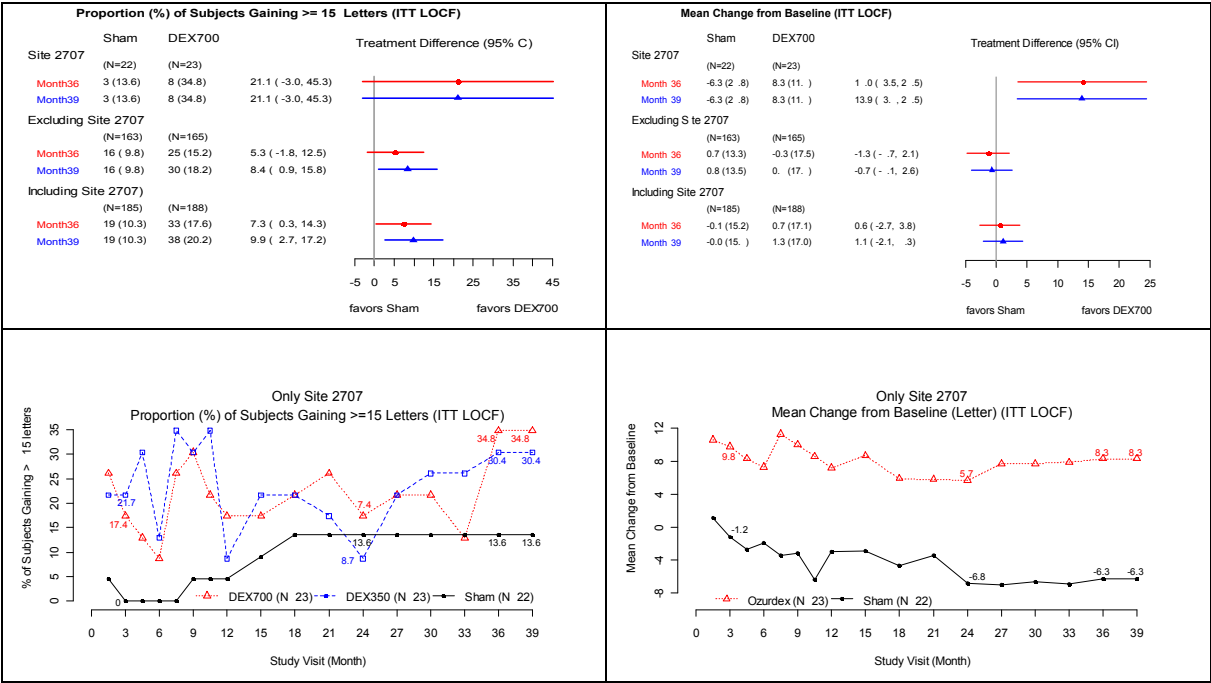
Thus, the estimated percentage of subjects who had missing data at Month 39 would be approximately 53% [$R_{m39} = (334 + N_{\text{after_amendment}} + N_{\text{before_amendment_reatreatment}})/980 = (334+16+166)/980 = 53\%$].

Appendix C: Efficacy Results for Site 2707, Study 11 before and after Excluding Site 2707

Site 2707 enrolled the most domestic subjects in Study 11, accounting for 12% (68/554) of the study population (23 in DEX700 arm, 23 in DEX350 arm, and 22 in sham arm). OSI recommended that the data from this site be excluded from efficacy and safety analyses because evidence of fraud was found at this site. The efficacy results based on the data from this site (Figure 6) were much better than the overall study results: at Month 39, this site had a net gain of 21% in the binary endpoint, and a net gain of 14 letters in BCVA, compared to a net gain of 8% for the binary endpoint and a net loss of 1 letter in BCVA for the rest of the study sites.

Compared to the results including Site 2707, the treatment effect after excluding the data from this site was reduced by approximately 2% for the binary endpoint, and 2 letters in mean BCVA change from baseline at Month 36 and Month 39.

Figure 6: Efficacy Results for Site 2707, Study 11 before and after Excluding Site 2707



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/s/

YAN WANG

06/28/2014

DIONNE L PRICE

06/28/2014

Concur with overall conclusion



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 22-315/S-009

Drug Name: OZURDEX: Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)

Indication(s): Treatment of Diabetic Macular Edema

Applicant: ALLERGAN INC.

Date(s): Stamp date: June 13, 2013
PDUFA date: July 14, 2014

Review Priority: Standard

Biometrics Division: DBIV

Statistical Reviewer: Abel Tilahun Eshete

Concurring Reviewers: Yan Wang

Medical Division: Ophthalmology

Clinical Team: Medical Reviewer: Lucious Lim

Project Manager: Michael Puglisi

Keywords: Best corrected Visual Acuity, Intraocular Pressure and cataract surgery.

Table of Contents

1	EXECUTIVE SUMMARY	6
1.1	INTRODUCTION	6
1.2	STATISTICAL ISSUES	6
1.3	SUMMARY OF MAIN FINDINGS	7
1.4	CONCLUSIONS AND RECOMMENDATIONS	8
2	RESULTS AND CONCLUSIONS	9
2.1	STATISTICAL METHODS	9
2.2	DEMOGRAPHIC AND BASELINE CHARACTERISTICS AND SUBJECT DISPOSITION.....	9
2.2.1	<i>Demographic and Baseline Characteristics</i>	<i>9</i>
2.2.2	<i>Subject Disposition</i>	<i>12</i>
2.3	EFFICACY RESULTS	13
2.3.3	<i>Summary of Site 2707</i>	<i>18</i>
2.3.4	<i>Month 36 versus Month 39/final visits</i>	<i>21</i>
2.3.5	<i>Confounding effect of cataract related AE and Surgery</i>	<i>23</i>
2.4	EVALUATION OF SAFETY	25
3	RISK BENEFIT ANALYSIS.....	32
3.1	RISK-BENEFIT ANALYSIS AT SUBJECT LEVEL	32
3.2	RISK-BENEFIT ANALYSIS AT POPULATION LEVEL.....	33
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	38
4.1	AGE GENDER RACE AND COUNTRY	38
4.2	OTHER SPECIAL/SUBGROUP POPULATIONS.....	42
5	SUMMARY AND CONCLUSIONS	45
5.1	STATISTICAL ISSUES	45
5.2	COLLECTIVE EVIDENCE	46
5.3	CONCLUSIONS AND RECOMMENDATIONS	46
6	APPENDIX A: EFFICACY AND SAFETY SUMMARY EXCLUDING SITE 2707	47
7	APPENDIX B: EFFICACY AND SAFETY SUMMARY WITHOUT EXCLUDING SITE 2707	80

LIST OF TABLES

Table 1: Baseline and Demographics: Study 206207-010 (ITT population)	10
Table 2: Baseline and Demographics: Study 206207-011 (ITT population)	10
Table 3: Patient Disposition.....	12
Table 4: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by Visit (ITT LOCF)	13
Table 5: Categorical Summary of BCVA Change from Baseline at Month 36(ITT LOCF)	14
Table 6: Categorical Summary of BCVA Change from Baseline at Month 39/final (ITT LOCF).....	14
Table 7: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)	15
Table 8: Summary of Area under the Curve (AUC) of the Change from Baseline BCVA (ITT LOCF).....	16
Table 9: Summary of Change from Baseline Retinal Thickness at Center field (OCT) (ITT LOCF)	17
Table 10: Summary of Efficacy without before and after excluding Site 2707 (ITT LOCF)	20
Table 11: Summary of Efficacy Excluding Subjects from Site 2707 Whose BCVA was measured before (b) (4) (ITT LOCF)	20
Table 12: BCVA summary of the 21 subjects who had a BCVA measurement at Month 39 but were not re-treated at Month 36 (ITT LOCF).....	21
Table 13: Mean Change from Baseline BCVA at Month 39/final Visit (ITT LOCF)	22
Table 14: Proportion of subjects with ≥ 15 letters gain from Baseline at Month 39/final Visit (ITT LOCF).....	22
Table 15: Proportion of subjects with ≥ 15 letters from Baseline at Month 36 for subgroups based on lens status and cataract (ITT LOCF).....	23

Table 16: Mean Change from Baseline BCVA at Month 36 for Subgroups based on Lens and Cataract Status (ITT LOCF).....	24
Table 17: Summary of Number of Injections	25
Table 18: Summary of Subjects Who Received Retreatment by Visit	26
Table 19: Summary of First Time Retreatment	26
Table 20: Summary of Adverse Events (AE) (Pooled: All Treated Subjects).....	27
Table 21: Summary of time-to-first reported Cataract-related AE among Baseline Phakic Subjects.....	28
Table 22: Summary of Cataract surgery among Baseline Phakic Subjects.....	28
Table 23: Summary of Subjects who had Cataract surgery among baseline Phakic subjects who reported Cataract AE	28
Table 24: Summary of time (Month) between first reported Cataract related AE and Surgery.....	29
Table 25: Summary of time-to-first IOP-Related AE	29
Table 26: Summary of number of reported IOP related AE by study visit.....	29
Table 27: Cross-tabulation of Cataract –related AE and IOP-related AE.....	30
Table 28: Summary of Adverse Events (AE) (Pooled: Psuedophakic Subjects)	30
Table 29: Summary of Adverse Events (AE) (Pooled: Phakic Subjects)	31
Table 30: Summary of time (Month) to first reported Cataract related AE, IOP and Surgery	32
Table 31: Summary of Risk-Benefit Analysis (Safety Population)	35
Table 32: Summary of Risk-Benefit Analysis for Psuedophakic subjects.....	37
Table 33: Summary of Population level Risk-Benefit Measures (Safety Population).....	38
Table 34: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by study Visit (ITT LOCF)	47
Table 35: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)	48
Table 36: Summary of Mean Change from baseline for sites with at least 10 subjects per arm.....	50
Table 37: Summary of proportion of subjects with a 15 letter or more improvement from baseline at Month 36 for sites with at least 10 subjects per arm.....	50
Table 38: Summary OCT at Baseline for sites with at least 10 subjects per arm	51
Table 39: Summary of Mean OCT change from Baseline at Month 36 for sites with at least 10 subjects per arm.....	51
Table 40: Summary of Study duration by number of Injection by treatment arm (Month)	53
Table 41: Summary of reason for discontinuation by # of injections	53
Table 42: Proportion of subjects with ≥ 15 letters from baseline at Month 39/final for subgroups based on lens status and cataract.....	59
Table 43: Mean change from baseline at baseline at Month 39/final for subgroups based on lens status and cataract	59
Table 44: Proportion of Phakic Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at Month 36 grouped by Cataract Surgery and AE status	60
Table 45: Mean Change from baseline BCVA at Month 36 for Phakic subjects by cataract surgery and AE status ...	60
Table 46: Summary of proportion of subjects with a ≥ 15 letter gain from baseline at Month 36 by number of injection (by study).....	61
Table 47: Summary of Adverse Events (AE) (Study 10: All Treated Subjects).....	62
Table 48: Summary of Adverse Events (AE) (Study 11: All Treated Subjects).....	63
Table 49: Summary of selected adverse events by number of Injections	63
Table 50: Summary of Adverse Events (AE) (for subjects with only one Injection)	63
Table 51: Summary of Adverse Events (AE) (One or two injections)	64
Table 52: Summary of Adverse Events (AE) (3-4 injections)	65
Table 53: Summary of Adverse Events (AE) (Five or more injections).....	65
Table 54: Summary of Adverse Events (AE) (Subjects who lost 15 letters or more at Month 36.....	66
Table 55: Summary of Adverse Events (AE) (Subjects who lost 15 letters or more at Month 36 by # of injections)..	66
Table 56: Summary of Cross tabulation of Number of Injections and study duration.....	67
Table 57: Summary of Adverse Events (AE) by study duration.....	67
Table 58: Summary of disposition for subjects with 15 letters or more worsening.....	68
Table 59: Summary of Risk-Benefit Analysis (Safety Population: DEX 350 vs. Sham)	70
Table 60: Summary of Risk-Benefit Analysis for Psuedophakic subjects (DEX 350 vs. Sham)	72
Table 61: Summary of Population level Risk-Benefit Measures (Safety Population: DEX 350 vs. Sham)	73
Table 62: The 22 subjects with BCVA at Month 39 without re-treatment at Month 36.....	76
Table 63: Number of subjects with a BCVA measurement by Visit	76

Table 64: Number of who remained in the study by Visit	77
Table 65: Number of Subjects who remained in the study and with BCVA outcomes by Visit (Site 2707)	78
Table 66: Definition of visit Window	78

LIST OF FIGURES

Figure 1: Plot proportion of subjects with BCVA change from Baseline \geq BCVA cutoff (ITT LOCF)	15
Figure 2: Plot of Mean Change from Baseline BCVA (Study 206207-010; ITT LOCF)	16
Figure 3: Plot of Mean Change from Baseline BCVA (Study 206207-011; ITT LOCF)	16
Figure 4: Plot of Mean Change from Baseline Retinal Thickness (Study 206207-010; ITT LOCF)	17
Figure 5: Plot of Mean Change from Baseline Retinal Thickness (Study 206207-011; ITT LOCF)	18
Figure 6: Plot of Individual Change from Baseline BCVA (Site 2707) (ITT LOCF)	19
Figure 7: Plot of Mean Change from Baseline BCVA (Site 2707) (ITT LOCF)	19
Figure 8: Summary plot for Risk-Benefit Analysis (Safety Population)	34
Figure 9: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Pooled)	39
Figure 10: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 10)	39
Figure 11: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 11)	40
Figure 12: Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (pooled)	40
Figure 13: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Study 10)	41
Figure 14: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Study 11)	41
Figure 15: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Pooled)	42
Figure 16: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 10)	43
Figure 17: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 11)	43
Figure 18: Additional Subgroup Analysis by Baseline Disease Characteristics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Pooled)	44
Figure 19: Additional Subgroup Analysis by Baseline Disease Characteristics for the Mean Change from Baseline BCVA at 3 Years: DEX 700 vs. Sham (Study 10)	44
Figure 20: Additional Subgroup Analysis by Baseline Disease Characteristics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Study 11)	45
Figure 21: Plot of the proportion of subjects with a 15 letter or more gain from baseline (.....	49
Figure 22: Summary of Mean change from baseline for the top 6 largest sites	50
Figure 23: Plot of Mean Change from Baseline BCVA (Phakic: Study 206207-010; ITT LOCF)	51
Figure 24: Plot of Mean Change from Baseline BCVA (Phakic: Study 206207-011; ITT LOCF)	52
Figure 25: Plot of Mean Change from Baseline BCVA (Pseudophakic: Study 206207-010; ITT LOCF)	52
Figure 26: Plot of Mean Change from Baseline BCVA (Pseudophakic: Study 206207-011; ITT LOCF)	52
Figure 27: Proportion of Pseudophakic subjects with a 15 letter or more gain from Baseline	53
Figure 28: Mean BCVA plot for baseline Phakic Subjects Who Underwent Cataract Surgery	55
Figure 29: Mean BCVA plot for baseline Pseudophakic subjects and Phakic Subjects Who Underwent Cataract Surgery	56
Figure 30: Mean BCVA plot for Phakic Subjects Who did not report Cataract related AE	57
Figure 31: Mean BCVA plot for baseline Pseudophakic subjects and Phakic Subjects Who did not report Cataract related AE	58
Figure 32: Summary of Median Study duration by number of Injections	61
Figure 33: Summary of Median Study duration by number of Injections by treatment	61
Figure 34: Summary plot for Risk-Benefit Analysis (Safety Population: DEX 350 vs. Sham)	69
Figure 35: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 350 vs. Sham (pooled)	74
Figure 36: Mean Change from Baseline BCVA at Month 36: DEX 350 vs. Sham (Pooled)	74

Figure 37: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a \geq 15 Letter Gain in BCVA from Baseline at Month 36: DEX 350 vs. Sham (Pooled).....75

Figure 38: Additional Mean Change from Baseline BCVA at Month 36: DEX 350 vs. Sham (Pooled)75

1 EXECUTIVE SUMMARY

1.1 Introduction

This review was initiated following the recommendation of the Office of Scientific Inspection (OSI) who had inspected four sites involved in this NDA. Three of the investigated sites had no significant regulatory violations. Evidence of fraud was reported in the third site (Site 2707), which was chosen for inspection because it was the highest domestic enroller in Study 2062070-11. At this site, substitution of OCT scans to ensure that subjects met inclusion criteria as well as falsification of BCVA values by an employee was suspected. Because the reliability of the data at this site cannot be verified, OSI recommended that the data from this site be excluded from safety and efficacy analysis. The efficacy and safety analyses in this review are therefore performed after excluding all subjects from site 2707. The original review is uploaded to DARRTS (see DARRTS entry for Eshete on 03/10/2014) and summary results from the original review are presented in Appendix B in this review.

1.2 Statistical Issues

Besides the removal of the 68 subjects from site 2707 in Study 2062070-11, and the presence of substantial missing data in both studies, two major statistical issues were encountered in this review. The first was regarding subjects who received a rescue (escape) therapy. During the study period, a total of 132 subjects received escape therapy (Table 20). Among these 132 subjects, 12 subjects (6 in the DEX 700, 2 in DEX 350 and 4 in the Sham arm) were treated as treatment successes in the primary efficacy analysis in contradiction with section 5.2.2 of the study protocol. Section 5.2.2 of the study protocol clearly stated that subjects who received a rescue therapy would be treated as treatment failures.

The second statistical issue was related to the definition of the primary efficacy endpoint. Amendment 4 of the study protocol (08 May 2010) allowed a possible re-treatment at Month 36 visit and included an additional visit at a Month 39 to provide assessment of efficacy and safety for subjects who received a re-treatment at Month 36 visit. Consequently, the applicant re-defined the primary efficacy endpoint as the proportion of subjects who had a 15 letter or more gain in BCVA from baseline at final study visit (Month 39 or earlier). However, only 172 (17.5%) of the 980 randomized subjects had completed the Month 39 visit, and only 158 (16.1%) had a BCVA measurement at the Month 39 visit. Thus, evaluating the primary efficacy endpoint at Month 39 will artificially create a missing data for nearly 84% of study subjects. It should also be noted that by the time this amendment was implemented, 549 (52.4%) of the originally randomized 1048 study subjects had either prematurely exited the study or completed the Month 36 visit and exited the study. At the End-of-Phase 2 meeting in September 2003, the agency recommended that any study that includes diabetic patients will require a 3-year study to establish *efficacy* and *safety*. Additionally, at the Type C meeting in September 2011, the agency argued that, an earlier treatment success is not necessarily a good indicator of a later success. Consequently, the agency recommended that for indication of DME, the treatment effect of a test product be demonstrated at a time point of at least *36 month or later*. Thus, technically, the applicant's re-defined primary efficacy endpoint is in line with the agency's recommendation. However because of the aforementioned missing data problem and the concern with the timing of the amendment, in this

review, efficacy results evaluated at both Month 36 and Month 39/final (Month 39-or-earlier) will be presented with slightly more emphasis given to the results at Month 36.

1.3 Summary of main findings

Because site 2707 was from Study 2062070-11, the primary efficacy results for Study 2062070-10 remain unchanged. After the 68 subjects from site 2707 were excluded from the analysis, there was no statistically significant difference between the two DEX arms and Sham in the proportion of subjects with a 15 letter or more gain from baseline BCVA at Month 36 in Study 2062070-11. The treatment differences were 5.3% (95% CI: -1.8%, 12.5%) for DEX 700 vs. Sham and 3.5% (95% CI: -3.5%, 10.5%) for DEX 350 vs. Sham (Table 4). In both studies, the DEX 700 arm had statistically significantly higher proportion of subjects with at least 15 letters gain from baseline at Month 39 /final visit. For Study 2062070-11, the proportion of subjects who lost at least 15 letters was higher than those who gained at least 15 letters in the two DEX arms both at Month 36 and the Month 39/final visits (Table 5 and Table 6). Consequently, in Study 2062070-11, the mean change from baseline BCVA, was not statistically significant and negative (favoring Sham). The treatment differences at the Month 36 visit were -1.01 (95% CI: -4.4, 2.4) letters for DEX 700 vs. Sham and -0.7 (95% CI: -3.9, 2.5) letters for DEX 350 vs. Sham (Table 7). The significant decline in the efficacy estimates in Study 2062070-11 when site 2707 was excluded was not surprising. In addition to enrolling the largest number of subjects, this site had the highest mean change from baseline for the DEX 700 arm and the lowest mean change from baseline for the Sham arm among the 6 top sites (3 sites for each study) which enrolled at least 10 subjects per study arm (Table 37 and Figure 22).

With respect to safety, there is a slight increase in the difference between the two DEX arms and the Sham arm in the proportion of subjects who reported AEs. For example, the difference between DEX 700 and Sham in the proportion of subjects who reported intraocular pressure related AEs increased from 30.9% (when all subjects were considered) to 31.5% (when the 68 subjects from site 2707 were excluded from the analysis). Similarly, the proportion of subjects who underwent cataract surgery increased from 51.9 to 53.1% (Table 20). After exclusion of site 2707 from the analyses, the risk-benefit analyses for both DEX arms showed a slight increase in the proportion of subjects with the worst case scenario (failure to achieve a 15 letter or more improvement while reporting an AE) and slight decline in the proportion of subjects with the best case scenario (achieving a 15 letter or more improvement without an AE) when IOP related AE and cataract surgery for baseline Phakic subjects were considered as important risks (Table 33 and Table 59).

Following the original review, the agency proposed a limited indication to the applicant. The limited indication was for the treatment of DME for subjects who are either Pseudophakic or Phakic subjects who are *scheduled* for cataract surgery. Based on a subgroup analysis for baseline Pseudophakic subjects, there was no statistically significant difference between the two DEX arms and the Sham with respect to the proportion of subjects with at least 15 letters gain from baseline at Month 36 in either of the two studies. The difference between Pseudophakic subjects randomized to DEX 700 and Sham in the mean BCVA change from baseline at Month 36 was statistically significant in Study 2062070-10 but not in Study 2062070-11 (Table 15 and Table 16). There was no data in the submission to support the efficacy for subjects who are *scheduled* for cataract surgery. With respect to safety, compared to the Phakic subjects, Pseudophakic

subjects had lower risk of serious ocular AE and IOP related adverse events (Table 28 and Table 29).

1.4 Conclusions and recommendations

Because both studies revealed that DEX 700 had only a very modest treatment effect and that there was substantially higher risk of cataract surgery and intraocular pressure in the DEX 700 arm, this reviewer does not recommend the approval of this drug for the (b) (4) treatment of Diabetic Macular Edema (DME). From a safety perspective, the agency's proposed limited indication, the treatment of DME for subjects who are either Pseudophakic or Phakic subjects who are scheduled for cataract surgery, is acceptable. However, because there was no statistically significant difference between DEX 700 and Sham in the proportion of subjects with a 15 letter or more gain from baseline BCVA at Month 36 and that there was no data in the submission to support the efficacy and safety of subjects who are *scheduled* to undergo cataract surgery, the subsequent recommendation for approval of the limited indication should be made based on clinical grounds.

2 Results and Conclusions

2.1 Statistical Methods

The two DEX arms were compared against the Sham arm with respect to the primary efficacy outcome using the chi-square test. Confidence intervals for the treatment differences were computed using the normal approximation for binomial distribution. For the mean change from baseline BCVA, the t-test was used to compare the two DEX arms against the Sham arm. Confidence intervals for the mean difference between each DEX arm and the Sham arm were conducted assuming unequal variance for each arm and without adjusting for baseline measurements. For the mean change from baseline, the applicant used an ANCOVA model with treatment study and baseline BCVA as covariates. The confidence interval for the mean difference was computed using the least square means assuming equal variances for both treatment arms. Slight differences in the confidence limits between the applicant's analysis and the reviewer's analysis might be observed.

Unless stated otherwise, all efficacy analyses were conducted on the ITT population, defined as all randomized subjects; and subjects were analyzed in the arm to which they were randomized. For the primary analysis, the Last Observation Carried Forward (LOCF) approach was used as a main tool to impute missing values. The applicant used different range of days to define visit windows for different variables. To ease the comparison of the results across different variables, in this review, unless stated otherwise, the visit window definition used for the BCVA outcome was used for all variables (see Table 66). Consequently slight differences in some summary measures might be observed for some variables. One such difference is observed in the timing of cataract surgery.

The reviewer conducted risk-benefit analyses both at the subject and population levels. The subject level risk-benefit analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best case scenario, is the case in which a pre-specified level of BCVA improvement was observed without incurring an AE. The worst case scenario is incurring an AE without achieving a pre-specified level of improvement in BCVA from baseline at 3 years. The other two scenarios are having benefit with AE, and no benefit and no AE. For the risk-benefit analysis at the population level, the unadjusted number needed to treat (NNT) and adverse event adjusted number needed to treat (NNTadj), Number Needed to Harm (NNH), together with the Benefit-Risk Ratio (BRR) = NNH/NNT were computed for each benefit and risk combination.

2.2 Demographic and baseline characteristics and subject disposition

2.2.1 Demographic and Baseline Characteristics

There were no significant baseline imbalances among the three arms in the demographics of age, gender, race or study eye iris color. The mean age of participants in Study 206207-010 was slightly higher than those in Study 206207-011. In both studies, there were more male participants than female participants; and most of the study subjects were Caucasian. The

percentage of participants with dark iris was higher than those with light iris (Table 1 and Table 2).

Table 1: Baseline and Demographics: Study 206207-010 (ITT population)

	DEX 700 (N=163)	DEX 350 (N=166)	Sham (N=165)	Total (N=494)	P-value
Age(years)					0.696
Mean (SD)	63.1 (8.01)	63.3 (9.01)	62.6 (9.10)	63.0 (8.71)	
Range	33-84	27-82	26-83	26-84	
<45	4 (2.5%)	5(3.0%)	7(4.2%)	16 (3.2%)	
45-65	89 (54.6%)	97 (58.4%)	95 (57.6%)	281 (56.9%)	
>65	70 (42.9%)	64 (38.6%)	63 (38.2%)	197 (39.9%)	
Sex					0.906
Male	102 (62.6%)	100 (60.2%)	102 (61.8%)	304 (61.5%)	
Female	61 (37.4%)	66 (39.8%)	63 (38.2%)	190 (38.5%)	
Race					0.649
Caucasian	138 (84.7%)	140 (84.3%)	134 (81.2%)	412 (83.4%)	
Non-Caucasian	25 (15.3%)	26 (15.7%)	31 (18.8%)	82 (16.6%)	
Black	7 (4.3%)	7 (4.2%)	13 (7.9%)	27 (5.5%)	
Asian ^a	12 (7.4%)	14 (8.4%)	13 (7.9%)	39 (7.9%)	
Hispanic	1 (0.6%)	2 (1.2%)	2 (1.2%)	5 (1.0%)	
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	5 (3.1%)	3 (1.8%)	3 (1.8%)	11 (2.2%)	
Iris Color					0.907
Light	69 (42.3%)	74 (44.6%)	73 (44.2%)	216 (43.7%)	
Dark	94 (57.7%)	92 (55.4%)	92 (55.8%)	278 (56.3%)	
Baseline Lens Status					0.799
Phakic	119 (73.0%)	119 (71.7%)	115 (69.7%)	353 (71.5%)	
Pseudophakic	47 (28.3%)	47 (28.3%)	50 (30.3%)	141 (28.5%)	
Prior DME Treatment					
Laser	115 (70.6%)	116 (69.9%)	122 (73.9%)	353 (71.5%)	
Steroid Injection	28 (17.2%)	30 (18.1%)	23 (13.9%)	81 (16.4%)	
Anti-VEGF	17 (10.4%)	20 (12.0%)	13 (7.9%)	50 (10.1%)	
No prior treatment	40 (24.5%)	40 (24.1%)	38 (23.0%)	118 (23.9%)	
Weight (Kg)					0.337
Mean (SD)	84.3 (17.8)	85.1 (20.4)	82.2 (16.9)	83.8 (18.5)	
Range	48 -144	43 - 155	50 - 150	43 - 155	
Height (cm)					0.957
Mean (SD)	167.2 (9.3)	167.3 (10.1)	167.0 (8.8)	167.1 (9.4)	
Range	146 -188	139 -191	142- 188	139- 191	
Diabetes Duration ^b					0.142
Mean (SD)	17.2 (9.2)	16.2 (9.2)	15.3 (8.3)	16.2 (8.9)	
Median (Range)	16 (2-51)	15.5 (2-57)	15.5 (1-37)	16 (1-57)	
DME Duration ^c					0.582
Mean (SD)	24.0 (26.2)	24.9 (29.3)	27.2 (29.6)	25.4 (28.3)	
Median (Range)	15 (0-160)	14 (0-191)	16 (0-152)	15 (0-191)	
HbA1c					0.987
Mean (SD)	7.5 (1.1)	7.5 (1.1)	7.5 (1.1)	7.5 (1.1)	
Median (Range)	7.4 (5-10)	7.4 (5-10)	7.4 (5-10)		

Source: Tables 10.1 and 10.2 of Applicant's submitted Study Reports. ^aAsian race excludes Japanese. ^b Years ^c Months

Table 2: Baseline and Demographics: Study 206207-011 (ITT population)

	DEX 700 (N=165)	DEX 350 (N=158)	Sham (N=163)	Total (N=486)	P-value
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Age(years)					0.327	
Mean (SD)	62.4(8.4)	61.8(8.9)	63.3(9.6)	61.9 (9.26)		
Range	46-85	36-83	31-88	25-88		
<45	0 (0.0%)	6(3.8%)	4(2.5%)	10(2.1%)		
45-65	100(60.6%)	93(58.9%)	108 (55.8%)	284(58.4%)		
>65	65(39.4%)	59(37.3%)	71 (41.7%)	192(39.5%)		
Sex					0.367	
Male	61(37%)	91(57.6%)	106(65%)	301(61.9%)		
Female	104(63%)	67(42.4%)	57(35%)	185(38.1%)		
Race					0.891	
Caucasian	95(57.6)	91(57.6%)	96(58.9)	282(58%)		
Non-Caucasian	70(42.4)	67(42.4)	67(41.1%)	204(42%)		
Asian	41(24.8%)	40(25.3%)	39(23.9%)	120(24.7%)		
Black	9(5.5%)	9(5.7%)	7(4.3%)	25(5.1%)		
Hispanic	13(7.9%)	91(57.6%)	96(58.9%)	282(58%)		
Japanese	1(0.6%)	14(8.9%)	13(8.0%)	40(8.2%)		
Other	6(3.6%)	2(1.3%)	1(0.6%)	4(0.8%)		
Iris Color						0.492
Dark	108(65.5%)	113(71.5%)	113(69.3%)	334(68.7%)		
Light	57(34.5%)	45(28.5%)	50(30.7%)	152(31.3%)		
Baseline Lens Status					0.293	
	Phakic	127(77%)	120(75.9%)	114(69.9%)		361(74.3%)
	Pseudophakic	38(23%)	38(24.1%)	49(30.1%)		125(25.7%)
Prior DME Treatment						
Laser	110(66.7%)	99(62.7%)	115(70.6%)	324(66.7%)		
Steroid Injection	30(18.2%)	39(24.7%)	37(22.7%)	106(21.8%)		
Anti-VEGF	8(4.8%)	19(12%)	13(8.0%)	40(8.2%)		
No prior treatment	47(28.5%)	44(27.8%)	35(21.5%)	126(25.9%)		
Weight (Kg)						0.158
Mean (SD)	81.7(23.5)	77.3(18.6)	79.1(18.6)	79.7 (20.4)		
Range	41 -204	43 - 141	45 - 135	41 - 204		
Height (cm)					0.510	
Mean (SD)	164.8(9.2)	164.7(9.8)	165.8(9.4)	164.4 (9.5)		
Range	137 -196	135 -186	133- 190	133- 196		
Diabetes Duration ^b					0.788	
Mean (SD)	15.8(9.1)	15.9(9.7)	16.5(10.1)	15.9 (9.4)		
Median (Range)	15 (1-43)	16 (1-61)	15 (1-54)	15 (1-61)		
DME Duration ^c					0.506	
Mean (SD)	24(25.7)	27.6(34.7)	25.4(22.1)	24.5 (28.2)		
Median (Range)	15 (0-163)	20 (0-299)	21 (0-136)	17 (0-299)		
HbA1c					0.391	
Mean (SD)	7.6(1.2)	7.5(1.2)	7.4(1)	7.5 (1.1)		
Median (Range)	7.5 (4-10)	7.5 (5-10)	7.2 (5-10)	7.5 (4-10)		

Source: Reviewer's Analysis. ^a Asian race excludes Japanese. ^b Years, ^c Months

2.2.2 Subject Disposition

The percentage of subjects in the two DEX arms who terminated the study was lower than those in the Sham arm. Most people terminated the study due to lack of efficacy (Sham arm) and adverse events (DEX arms) (Table 3). Note that in the protocol, a subject was considered to have completed the study if he/she completed the Month 36 or 39 visits.

Table 3: Patient Disposition

	DEX 700	DEX 350	Sham	Total
Study 206207-010				
Subjects Randomized	163 (100%)	166 (100%)	165 (100%)	494
Subjects Who completed the Study	107/163 (65.6%)	118/166 (71.1%)	70/165 (42.4%)	
Completed the Study at Month 36	77/163(47.2%)	78/166(47%)	48/165(29.1%)	
Completed the Study at Month 39	30/163(18.4%)	40/166(24.1%)	22/165(13.3%)	
Reason for Discontinuation				
Adverse Events	20/163(12.3%)	18/166(10.8%)	16/165(9.7%)	
Lack of Efficacy	9/163(5.5%)	14/166(8.4%)	37/165(22.4%)	
Lost-to-Follow-up	5/163(3.1%)	5/166(3%)	10/165(6.1%)	
Personal Reason	7/163(4.3%)	4/166(2.4%)	16/165(9.7%)	
Protocol Violations	2/163(1.2%)	4/166(2.4%)	16/165(9.7%)	
Other	13/163(8%)	7/166(4.2%)	16/165(9.7%)	
Study 206207-011				
	DEX 700	DEX 350	Sham	Total
Subjects Randomized	165 (100%)	158 (100%)	163 (100%)	486
Subjects Who completed the Study	105/165(63.6)	94/158(59.5)	76/163(46.6)	
Completed the Study at Month 36	79/165(47.9%)	68/158(43%)	50/163(30.7%)	
Completed the Study at Month 39	26/165(15.8%)	26/158(16.5%)	26/163(16%)	
Reason for Discontinuation				
Adverse Events	25/165(15.2%)	29/158(18.4%)	23/163(14.1%)	
Lack of Efficacy	12/165(7.3%)	10/158(6.3%)	36/163(22.1%)	
Lost-to-Follow-up	4/165(2.4%)	4/158(2.5%)	7/163(4.3%)	
Personal Reason	6/165(3.6%)	6/158(3.8%)	10/163(6.1%)	
Protocol Violations	1/165(0.6%)	3/158(1.9%)	1/163(0.6%)	
Other	12/165(7.3%)	12/158(7.6%)	10/163(6.1%)	
Pooled				
Subjects Randomized	328 (100%)	324 (100%)	328 (100%)	980
Subjects Who completed the Study	212/328(64.6%)	212/324(65.4%)	146/328(44.5%)	
Completed the Study at Month 36	156/328(47.6%)	146/324(45.1%)	98/328(29.9%)	
Completed the Study at Month 39	56/328(17.1%)	66/324(20.4%)	48/328(14.6%)	
Reason for Discontinuation				
Adverse Events	45/328(13.7%)	47/324(14.5%)	39/328(11.9%)	
Lack of Efficacy	21/328(6.4%)	24/324(7.4%)	73/328(22.3%)	
Lost-to-Follow-up	9/328(2.7%)	9/324(2.8%)	17/328(5.2%)	
Personal Reason	13/328(4%)	10/324(3.1%)	26/328(7.9%)	
Protocol Violations	3/328(0.9%)	3/324(0.9%)	1/328(0.3%)	
Other	25/328(7.6%)	19/324(5.9%)	26/328(7.9%)	

Source: Reviewer's Analysis.

The summary of subjects who had BCVA measures at each study visit and the number of subjects who remained in the study at each study visit are presented in Table 63 and Table 64 respectively. The number of subjects with observed BCVA measurements at Month 36 (not carried forward) was 104 (63.8%), 107 (64.4%) and 63 (38.2%) in the DEX 700, DEX 350 and

Sham respectively for Study 206207-010, and 95 (57.6%), 84 (53.2%) and 64 (39.3%) in the DEX 700, DEX 350 and Sham respectively for Study 206207-011.

2.3 Efficacy Results

2.3.1 Proportion of subjects with at least 15 letters gain from baseline

The summary of the proportion of subjects with a 15 letter or more improvement at selected months is given in Table 4. The summary for all measurement times is provided in Table 34 and Figure 21 in the appendix. In study 206207-10, the DEX 700 arm had significantly higher proportion of subjects with a 15 letter or more improvement from baseline at Month 36 compared to the Sham arm, whereas, non-significant differences were observed between both DEX arms and Sham in Study 206207-11. The DEX 700 arm had significantly higher proportion of subjects with a 15 letter or more improvement from baseline at the Month 39/final visit compared to the Sham arm in both studies.

For the remaining study visits, there were either borderline significant or non-significant differences in the proportion of subjects with a 15 letter or more gain from baseline. For example, at Month 24, there was no significant difference between the DEX 700 arm and Sham in Study 206207-10 and the difference was only slightly significant in Study 206207-11.

Table 4: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by Visit (ITT LOCF)

Visit	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010				
Month 6	23(14.1%)	17(10.2%)	13(7.9%)	6.2%(-0.5%, 13%)	2.4%(-3.8%, 8.5%)
Month 12	22(13.5%)	25(15.1%)	13(7.9%)	5.6%(-1%, 12.3%)	7.2%(0.4%,14%)
Month 18	27(16.6%)	16(9.6%)	15(9.1%)	7.5%(0.3%,14.7%)	0.5%(-5.7%, 6.8%)
Month 24	21(12.9%)	25(15.1%)	15(9.1%)	3.8%(-3%, 10.6%)	6%(-1%, 13%)
Month 30	25(15.3%)	33(19.9%)	16(9.7%)	5.6%(-1.5%, 12.8%)	10.2%(2.6%,17.7%)
Month 36	32(19.6%)	33(19.9%)	18(10.9%)	8.7%(1%,16.5%)	9%(1.3%,16.7%)
Month 39	34(20.9%)	31(18.7%)	19(11.5%)	9.3%(1.4%,17.3%)	7.2%(-0.5%, 14.8%)
	Study 206207-011				
	DEX 700 N=165	DEX 350 N=158	Sham N=163	DEX 700 vs. Sham	DEX 350 vs. Sham
Month 6	14(8.5%)	8(5.1%)	6(3.7%)	4.8%(-0.3%,9.9%)	1.4%(-3.1%,5.9%)
Month 12	19(11.5%)	15(9.5%)	16(9.8%)	1.7%(-5%,8.4%)	-0.3%(-6.8%,6.1%)
Month 18	16(9.7%)	13(8.2%)	13(8%)	1.7%(-4.4%,7.9%)	0.3%(-5.7%,6.2%)
Month 24	27(16.4%)	13(8.2%)	15(9.2%)	7.2%(0%,14.3%)	-1%(-7.1%,5.2%)
Month 30	27(16.4%)	14(8.9%)	15(9.2%)	7.2%(0%,14.3%)	-0.3%(-6.6%,5.9%)
Month 36	25(15.2%)	21(13.3%)	16(9.8%)	5.3%(-1.8%,12.5%)	3.5%(-3.5%,10.5%)
Month 39	30(18.2%)	24(15.2%)	16(9.8%)	8.4%(0.9%,15.8%)	5.4%(-1.8%,12.6%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy prior to a given visit were set as treatment failures in that and subsequent visits.

The summaries of the change from baseline BCVA at Month 36 and Month 39/final visits categorized into different levels of improvement and worsening are respectively given in Table 5 and Table 6. For all arms, the largest proportion of subjects fell in the “no change” category, which the applicant defined as a change in BCVA of between -5 to 5 letters from baseline. Compared to Sham, DEX 700 had higher proportion of subjects with a 15 letter or more improvement and lower proportion of subjects with no change in BCVA (BCVA of between -5 to 5 letters) from baseline. In Study 2062070-11, there were more subjects who lost at least 15 letters than those who gained 15 letters or more in all treatment arms and more so in the DEX 700 arm.

Table 5: Categorical Summary of BCVA Change from Baseline at Month 36(ITT LOCF)

BCVA Change	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163
≥15 Letters Improvement	32(19.6)	33(19.9)	18(10.9)	25(15.2)	21(13.3)	16(9.8)
≥10 and <15 Letters Improvement	27(16.6)	21(12.7)	15(9.1)	18(10.9)	16(10.1)	19(11.7)
≥5 and <10 Letters Improvement	27(16.6)	31(18.7)	20(12.1)	17(10.3)	31(19.6)	16(9.8)
No Change (-5 to +5 Letters)	40(24.5)	52(31.3)	70(42.4)	54(32.7)	39(24.7)	71(43.6)
>=5 and <10 Letters Worsening	13(8)	13(7.8)	16(9.7)	14(8.5)	11(7)	18(11)
>=10 and <15 Letters Worsening	9(5.5)	7(4.2)	9(5.5)	5(3)	15(9.5)	5(3.1)
>=15 Letters Worsening	15(9.2)	9(5.4)	17(10.3)	32(19.4)	25(15.8)	18(11)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy but fall into an “improvement” category were set to the “no change” category.

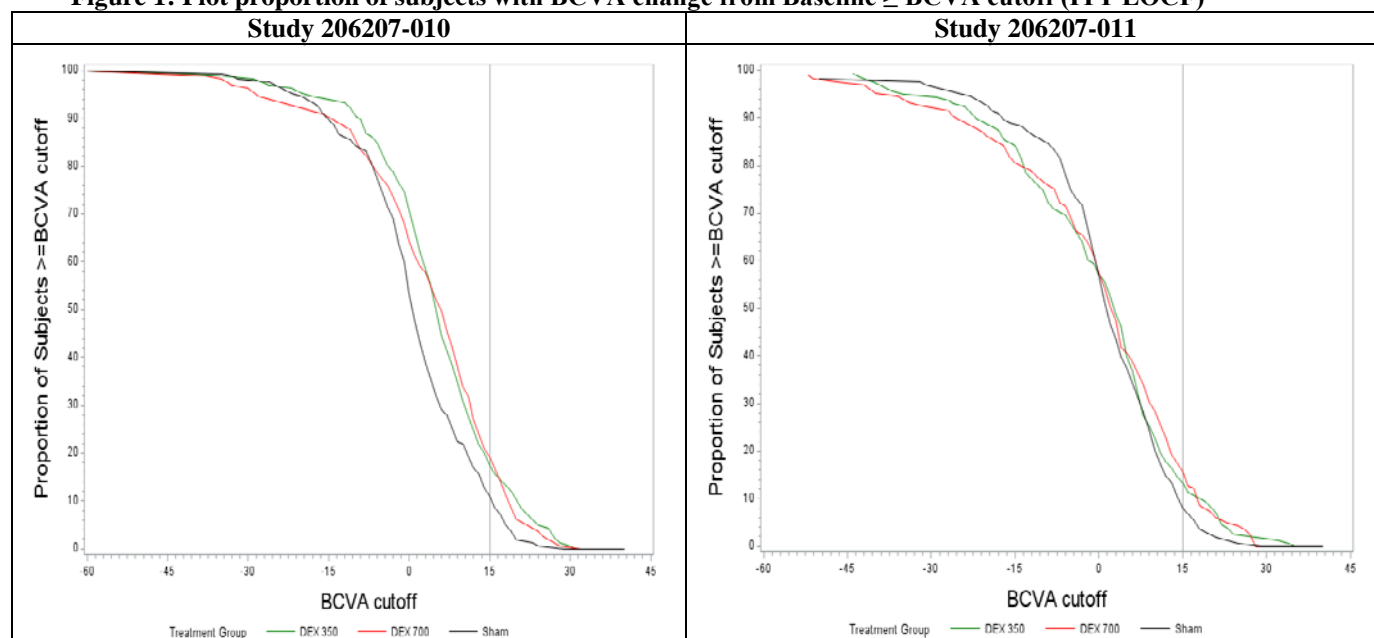
Table 6: Categorical Summary of BCVA Change from Baseline at Month 39/final (ITT LOCF)

BCVA Change	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163
≥15 Letters Improvement	34(20.9)	31(18.7)	19(11.5)	30(18.2)	24(15.2)	16(9.8)
≥10 and <15 Letters Improvement	26(16)	22(13.3)	15(9.1)	15(9.1)	19(12)	21(12.9)
≥5 and <10 Letters Improvement	29(17.8)	31(18.7)	16(9.7)	18(10.9)	29(18.4)	14(8.6)
No Change (-5 to +5 Letters)	39(23.9)	55(33.1)	74(44.8)	52(31.5)	39(24.7)	71(43.6)
>=5 and <10 Letters Worsening	13(8)	9(5.4)	14(8.5)	15(9.1)	9(5.7)	17(10.4)
>=10 and <15 Letters Worsening	7(4.3)	8(4.8)	10(6.1)	5(3)	15(9.5)	6(3.7)
>=15 Letters Worsening	15(9.2)	10(6)	17(10.3)	30(18.2)	23(14.6)	18(11)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy but fall into an “improvement” category were set to the “no change” category.

A plot of the proportions of subjects with BCVA gains from baseline above different cutoff points is given in Figure 1. The DEX 700 arm had consistently higher proportion of subjects with a positive change from baseline compared to Sham, especially in Study 206207-010.

Figure 1: Plot proportion of subjects with BCVA change from Baseline \geq BCVA cutoff (ITT LOCF)



Source: Reviewer's Analysis. LOCF was used for imputing missing data

2.3.2 Mean of change from baseline BCVA and Area under the curve (AUC)

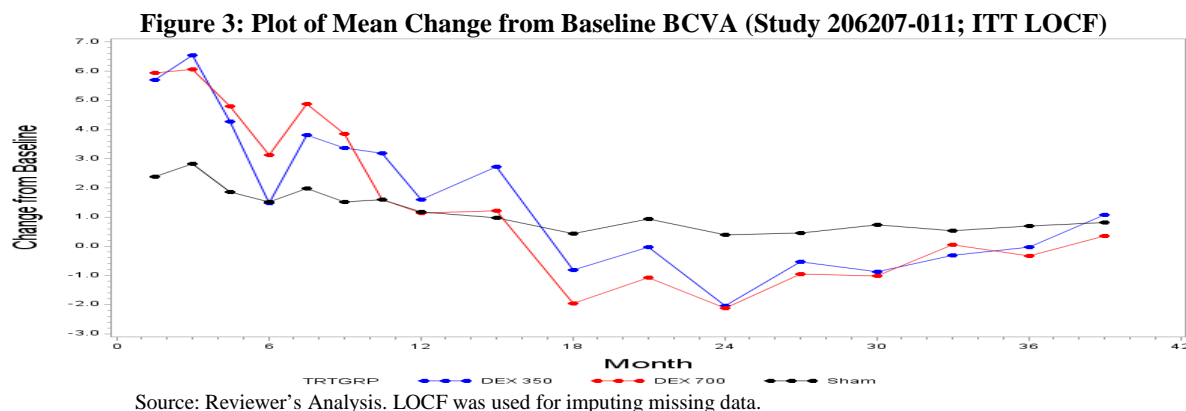
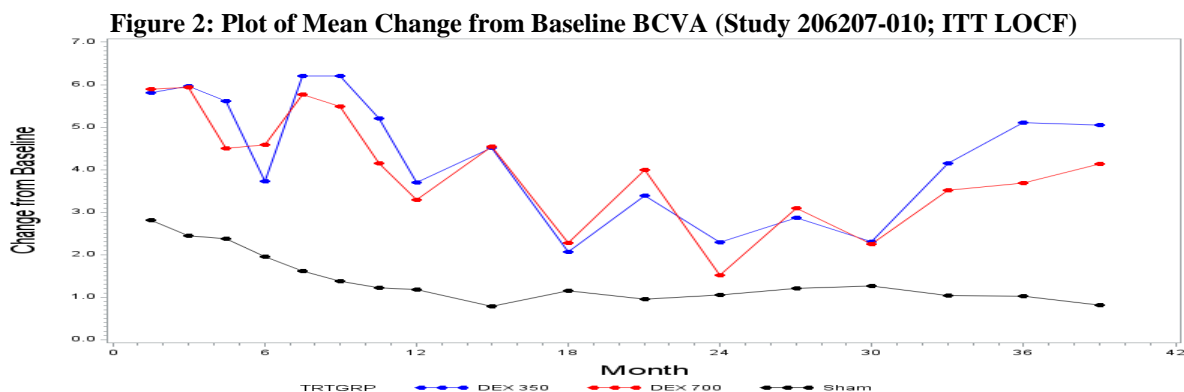
The summary of the mean change in BCVA and the mean plots of the change in BCVA from baseline over time are given in Table 7, Figure 2 and Figure 3. For Study 206207-010, the Sham arm had consistently lower mean change from baseline for all measurement times. For Study 206207-011, however, there was no noticeable separation among the three arms before Month 18, and it appears that the Sham arm had a higher mean change from baseline for the remainder of the study duration. The difference between the DEX 700 arm and Sham in the mean change from baseline at the Month 36 and the Month 39/final visits were in fact negative for Study 206207-011.

Table 7: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)

Visit	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Baseline*	56.2 (10.0)	55.9(9.6)	56.8(8.7)	-0.5 (-2.5, 1.5)	-0.9 (-2.9, 1.1)
Month 6	4.6(9)	3.7(9.1)	2(9)	2.6(0.7,4.6)	1.8(-0.2,3.7)
Month 12	3.3(10.7)	3.7(10.4)	1.2(10.2)	2.1(-0.2,4.4)	2.5(0.3,4.8)
Month 18	2.3(12.4)	2.1(11.3)	1.1(10.9)	1.1(-1.4,3.7)	0.9(-1.5,3.3)
Month 24	1.5(14.4)	2.3(14.7)	1.1(11.1)	0.5(-2.3,3.2)	1.2(-1.6,4.1)
Month 30	2.3(14.8)	2.3(15.2)	1.3(11.7)	1(-1.9,3.9)	1(-1.9,4)
Month 36	3.7(14.1)	5.1(12.3)	1(11.6)	2.7(-0.1,5.5)	4.1(1.5,6.7)
Month 39	4.1(13.9)	5(12)	0.8(11.9)	3.3(0.5,6.1)	4.2(1.7,6.8)
Study 206207-011					
Baseline*	55.2(9.9)	54.6(9.7)	56.3(8.8)	-1.1 (-3.2, 0.9)	-1.7 (-3.7, 0.3)
Month 6	3.1(8.8)	1.5(10.9)	1.5(10.3)	1.6(-0.5,3.7)	0(-2.4,2.3)
Month 12	1.1(12.8)	1.6(11.4)	1.2(12.6)	0(-2.8,2.7)	0.4(-2.2,3.1)
Month 18	-2(14.6)	-0.8(13.8)	0.4(13.2)	-2.4(-5.4,0.6)	-1.3(-4.2,1.7)
Month 24	-2.1(17.5)	-2(14.3)	0.4(13.5)	-2.5(-5.9,0.9)	-2.4(-5.5,0.6)
Month 30	-1(17.3)	-0.9(14.5)	0.7(13.2)	-1.7(-5.1,1.6)	-1.6(-4.7,1.4)

Month 36	-0.3(17.6)	0(15.7)	0.7(13.4)	-1(-4.4,2.4)	-0.7(-3.9,2.5)
Month 39	0.4(17.5)	1.1(15.2)	0.8(13.6)	-0.5(-3.9,2.9)	0.3(-2.9,3.4)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. * Baseline measurement. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.



The applicant used the mean area under the curve (AUC) of the change from baseline BCVA as the primary efficacy endpoint for other regulatory agencies. For each subject, the area under the curve was computed (see Table B27 in Appendix B). The mean AUC for each treatment arm was subsequently computed and compared using a t-test. Compared to the Sham arm, both DEX arms showed a significantly higher mean AUC of the change from baseline BCVA in Study 206207-010 but not in Study 206207-011. Additionally, the difference between DEX 700 and Sham in the mean AUC was negative in Study 206207-011 (Table 8).

Table 8: Summary of Area under the Curve (AUC) of the Change from Baseline BCVA (ITT LOCF)

Studies	Treatment : Mean AUC (std)			Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	4.11 (8.26)	4.33 (8.49)	1.89 (7.74)	2.22 (0.48, 3.96)	2.45 (0.69, 4.20)
011	2.24 (8.71)	2.53 (7.71)	2.28 (8.20)	-0.03 (-1.87, 1.80)	0.24 (-1.50, 2.00)
Pooled	3.17 (8.53)	3.46 (8.16)	2.08 (7.96)	1.08 (-0.17, 2.35)	1.37 (0.13, 2.61)

Source: Reviewer's Analysis.

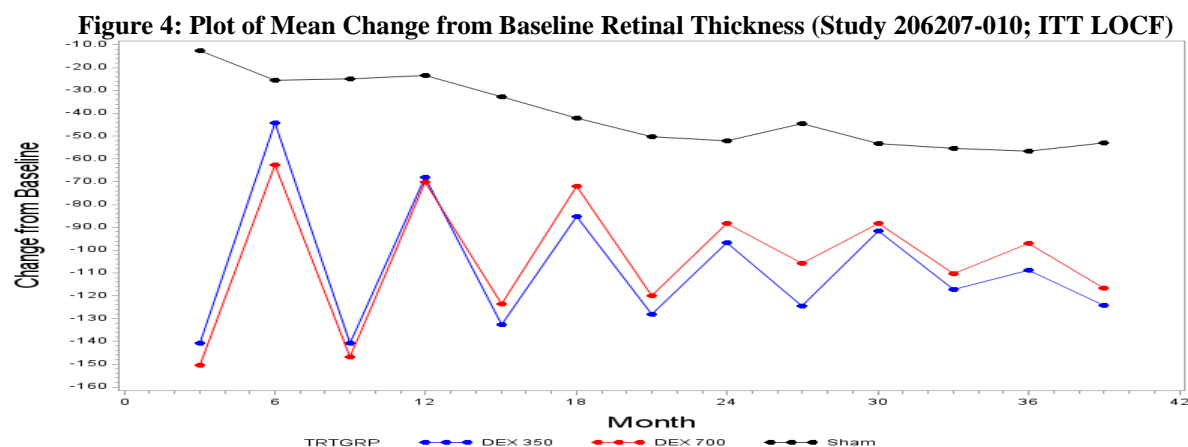
2.3.2.1 Retinal thickness at center field (OCT)

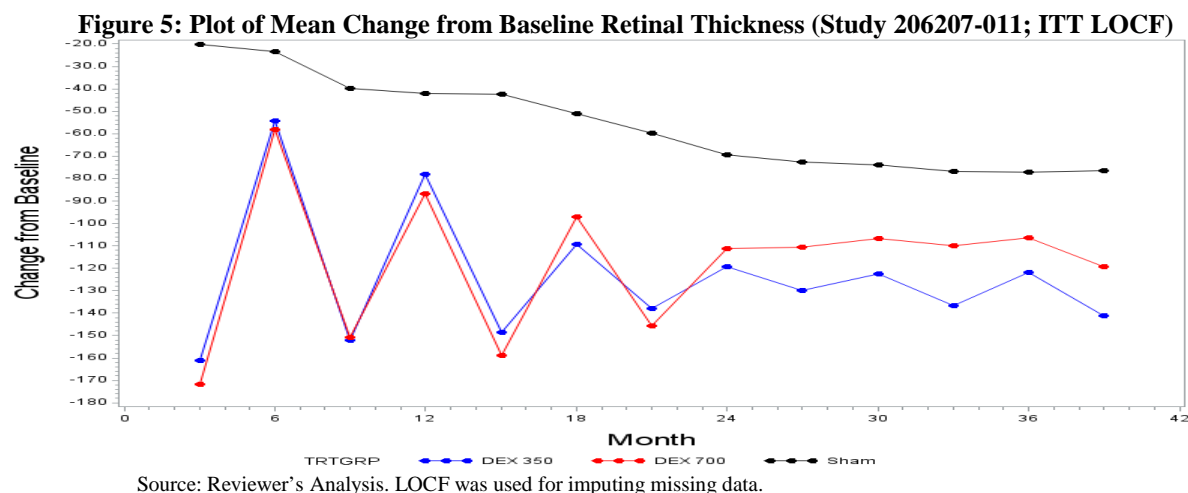
Retinal thickness in the central macular subfield by optical coherence tomography (OCT) was used to determine whether a subjects needs a re-treatment. Subjects in the DEX 700 arm had significantly higher decline in retinal thickness from baseline at both Month 36 and Month 39 compared to subjects in the Sham arm in Study 206207-010. There was however no significant difference between DEX 700 and Sham in Study 206207-011 (Table 9).

Table 9: Summary of Change from Baseline Retinal Thickness at Center field (OCT) (ITT LOCF)

Visit	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010				
Month 6	-62.6(123.5)	-44.2(135.5)	-25.5(120.1)	-37.1(-63.6,-10.6)	-18.7(-46.3,9)
Month 12	-70.3(147.4)	-68.2(157.5)	-23.5(146.3)	-46.8(-78.5,-15.2)	-44.8(-77.5,-12)
Month 18	-72.1(160.2)	-85.3(169.3)	-42.2(162.1)	-29.8(-64.7,5.1)	-43(-78.8,-7.2)
Month 24	-88.3(175.8)	-96.7(172.3)	-52(171.4)	-36.3(-74,1.3)	-44.7(-81.8,-7.6)
Month 30	-88.1(182)	-91.6(173.5)	-53.2(179.3)	-34.9(-74.1,4.3)	-38.4(-76.3,-0.5)
Month 36	-97.1(178.8)	-109(184.9)	-56.6(188)	-40.5(-80.2,-0.9)	-52.4(-92.6,-12.2)
Month 39	-116.7(184.6)	-124.1(188.5)	-53.1(179.5)	-63.6(-103.3,-24)	-71.1(-110.9,-31.2)
	Study 206207-011				
	DEX 700 N=165	DEX 350 N=158	Sham N=163	DEX 700 vs. Sham	DEX 350 vs. Sham
Month 6	-58.1(182.2)	-54.4(164.5)	-23.3(127.7)	-34.8(-68.8,-0.8)	-31.1(-63.3,1)
Month 12	-86.9(199.8)	-78.2(203.7)	-42.1(173.3)	-44.8(-85.4,-4.2)	-36.1(-77.7,5.5)
Month 18	-97.2(207.7)	-109.3(207.3)	-51.2(166.8)	-46(-87,-5.1)	-58.2(-99.4,-16.9)
Month 24	-111.1(245.9)	-119.4(212.7)	-69.2(172.4)	-41.8(-87.6,3.9)	-50.1(-92.8,-7.4)
Month 30	-106.8(236.1)	-122.6(205.3)	-74(186)	-32.8(-78.6,13.1)	-48.6(-91.8,-5.4)
Month 36	-106.4(235.3)	-121.7(206.1)	-77.3(180.9)	-29.1(-74.8,16.6)	-44.5(-87.3,-1.6)
Month 39	-119.4(233.9)	-141.1(207.1)	-76.3(185.3)	-43.1(-89.2,3.1)	-64.7(-108.2,-21.2)

Source: Reviewer's Analysis. LOCF was used for imputing missing data.





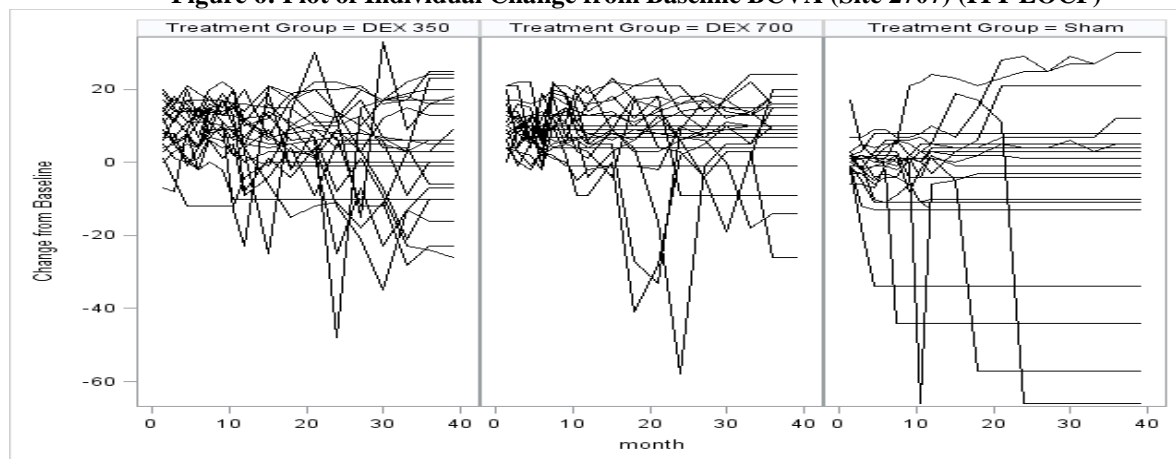
In both studies, the two treatment arms had consistently lower mean change from the baseline retinal thickness at all measurement times (Figure 4 and Figure 5).

2.3.3 Summary of Site 2707

Site 2707 was one of the sites inspected by the OSI. At this site, substitution of OCT scans to ensure that subjects met inclusion criteria as well as falsification of BCVA values by an employee was suspected. Consequently, OSI recommended that the data from this site be excluded from safety and efficacy analysis. This site enrolled a total of 68 subjects (23 subjects in each of the two DEX arms and 22 subjects in the Sham arm). The summary of the number of subjects from this site with BCVA outcomes at each visit and the number of subjects who remained in the study is presented in Table 65. Most subjects in the Sham arm left the study early. At Month 36, 12 (52.2%), 17 (73.9%) subjects from the DEX 700 and DEX 350 arms and only 4 (18.2%) subjects from the Sham arm had BCVA outcomes.

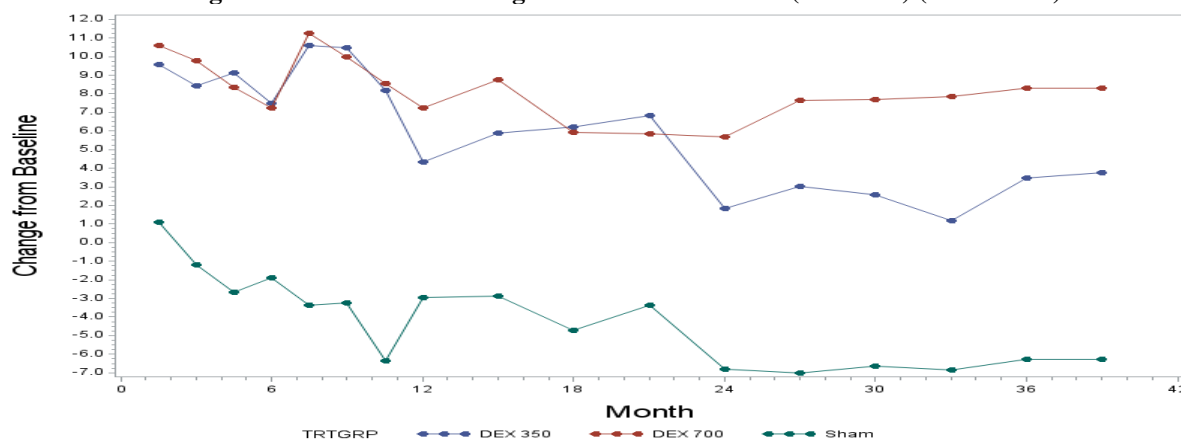
The plot of the individual change from baseline BCVA and the mean change from baseline BCVA by treatment for the 68 subjects from Site 2707 are presented in Figure 6 and Figure 7 respectively. Because most subjects in the Sham arm left the study early and the LOCF was used to impute their missing BCVA values, the BCVA values appear to be constant over time. Compared to Sham, the two DEX arms had consistently higher mean change from baseline BCVA for the whole study duration.

Figure 6: Plot of Individual Change from Baseline BCVA (Site 2707) (ITT LOCF)



Source: Reviewer's Analysis.

Figure 7: Plot of Mean Change from Baseline BCVA (Site 2707) (ITT LOCF)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

The summary of the mean change from baseline BCVA at Month 36 and the proportion of subjects with a 15 letter or more gain from baseline at Month 36 for the top 6 sites (3 sites from each of the two studies) which enrolled at least 10 subjects per arm are summarized in the appendix in Figure 22, Table 36 and Table 37. Site 2707 had the highest and the lowest mean change from baseline BCVA values among the top 6 sites for the DEX 700 and Sham arms respectively. Additionally, the difference between DEX 700 and Sham in the proportion of subjects with a 15 letter or more gain from baseline at Month 36 was the highest among the top 6 large sites. Consequently, when this site was excluded from the analysis, the overall treatment effect was lower than when the outcomes from this site were included in the analysis (Table 10).

The summary of baseline OCT and change from baseline OCT at Month 36 for the 6 largest sites including site 2707 are provided in Table 38 and Table 39. For all treatment arms, the baseline OCT in site 2707 was slightly lower compared to the other five sites which enrolled at least 10 subjects in each arm (Table 38). Additionally, subjects randomized to the DEX 700 arm in Site 2707 had the highest mean change from baseline OCT compared to subjects randomized to the same arm in the other top 5 sites (Table 39).

Table 10: Summary of Efficacy without before and after excluding Site 2707 (ITT LOCF)

Visit	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010 Study 206207-011 Including Site 2707				
Month 6	14(8.5%)	8(5.1%)	6(3.7%)	4.8%(-0.3%,9.9%)	1.4%(-3.1%,5.9%)
Month 12	19(11.5%)	15(9.5%)	16(9.8%)	1.7%(-5%,8.4%)	-0.3%(-6.8%,6.1%)
Month 18	16(9.7%)	13(8.2%)	13(8%)	1.7%(-4.4%,7.9%)	0.3%(-5.7%,6.2%)
Month 24	27(16.4%)	13(8.2%)	15(9.2%)	7.2%(0%,14.3%)	-1%(-7.1%,5.2%)
Month 36	27(16.4%)	14(8.9%)	15(9.2%)	7.2%(0%,14.3%)	-0.3%(-6.6%,5.9%)
Month 39	25(15.2%)	21(13.3%)	16(9.8%)	5.3%(-1.8%,12.5%)	3.5%(-3.5%,10.5%)
	Study 206207-011 Excluding Site 2707				
	DEX 700 N=165	DEX 350 N=158	Sham N=163	DEX 700 vs. Sham	DEX 350 vs. Sham
Month 6	16(8.5%)	11(6.1%)	6(3.2%)	5.3% (0.5%, 10%)	2.8%(-1.5%, 7.2%)
Month 12	23(12.2%)	17(9.4%)	17(9.2%)	3%(-3.2%, 9.3%)	0.2%(-5.7%, 6.2%)
Month 18	21(11.2%)	18(9.9%)	16(8.6%)	2.5%(-3.5%, 8.6%)	1.3%(-4.7%, 7.2%)
Month 24	31(16.5%)	15(8.3%)	18(9.7%)	6.8%(-0.1%, 13.6%)	-1.4%(-7.3%, 4.4%)
Month 36	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)
Month 39	38(20.2%)	31(17.1%)	19(10.3%)	9.9% (2.7%, 17.2%)	6.9%(-0.2%, 13.9%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

The person who allegedly falsified BCVA values worked at Site 2707 between (b) (6) and (b) (6). There were 41 subjects (13 from DEX 700, 10 from DEX 350 and 18 from Sham) whose Month 36 BCVA was recorded prior to (b) (6). Efficacy summary excluding these 41 subjects only is presented in Table 11. Although there was a slight improvement in the mean change from baseline BCVA at Month 36, the results were still lower than when all subjects from this site were included in the analysis.

Table 11: Summary of Efficacy Excluding Subjects from Site 2707 Whose BCVA was measured before (b) (6) (ITT LOCF)

Studies	Proportion of subjects with >=15 letters gain from baseline at Month 36				
	Treatment: N (%)			Treatment: N (%)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	32/163(19.6%)	33/166(19.9%)	18/165(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
011	30/175(17.1%)	27/171(15.8%)	19/167(11.4%)	5.8% (-1.6%, 13.1%)	4.4%(-2.9%, 11.7%)
Pooled	62/338 (18.3%)	60/337 (17.8%)	37/332 (11.1%)	7.2% (1.9%, 12.5%)	6.7% (1.3%, 12.0%)
Studies	Mean change from Baseline BCVA at Month 36				
	Treatment : Mean (std)			Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	3.7(14.1)	5.1(12.3)	1.0(11.6)	2.7(-0.1,5.5)	4.1(1.5,6.7)
011	0.2(17.5)	0.3(15.9)	0.8(14.6)	-0.6(-4.1,2.9)	-0.5(-2.6,3.7)
Pooled	1.8 (16.0)	2.6 (14.4)	0.9 (13.2)	0.9 (-1.3, 3.2)	1.7 (-0.3, 3.8)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

In conclusion, although the above summaries may not be sufficient to conclude that falsification of BCVA values and changes in OCT had taken place, there was a noticeably higher mean

change from baseline BCVA at Month 36 and a slightly lower baseline OCT in the DEX 700 arm in this site compared to the other five sites which enrolled at least 10 subjects per arm. The exclusion of this site has therefore resulted in a reduction in the observed treatment effect, especially when this effect was measured by the mean change from baseline BCVA at Month 36.

2.3.4 Month 36 versus Month 39/final visits

One of the differences between the applicant and this reviewer's analysis was the time at which the primary efficacy endpoint was defined. As per amendment 4 of the study protocol (08 May 2010), subjects were allowed to receive a study treatment at Month 36 as needed by treatment criteria, and a Month 39 visit was added to provide assessment of efficacy and safety for subjects who received a re-treatment at Month 36. Note that, by the time all sites received ethics committee approval to initiate Amendment 4, 52.4% (549/1048) of the originally randomized study subjects had either prematurely exited the study or completed the Month 36 visit and exited the study. Following this amendment, the applicant re-defined the primary efficacy endpoint as the proportion of subjects who had a 15 letter or more gain in BCVA from baseline at Month 39/final visit. However, only 172 (17.5%) of the 980 randomized subjects had completed the Month 39 visit, and only 158(16.0%) of the randomized subjects had BCVA measurements at the Month 39 visit. Thus, evaluating the primary efficacy endpoint at Month 39/final visit will artificially create a missing data for nearly 84% percent of study subjects.

Additionally, in contradiction with the intent of Amendment 04, out of the 158 subjects with BCVA measurements at Month 39, only 137/158 (86.7%) subjects were re-treated at Month 36. This implies that 21 subjects had BCVA outcomes at Month 39 without being re-treated at Month 36. Also note that, 16 subjects who were re-treated at Month 36 did not have a BCVA measure at Month 39; 5 of which did not even complete Month 39 visit.

Zooming on the 21 subjects who had BCVA measurements at Month 39 without being re-treated at Month 36, 10 were from DEX 350, 6 from DEX 700 and the remaining 5 from the Sham arm. Fifteen of these 21 subjects were baseline Phakic and 10 had cataract surgery. Two subjects had cataract surgery at Month 36; one had cataract surgery at Month 33 and the remaining at different times earlier. Ten of the 21 subjects had at least one cataract related AE and 12 had at least one IOP related AE. With respect to BCVA, out of these 21 subjects, 12 subjects (4 in DEX 700, 6 in DEX350 and 2 in Sham) had higher change from baseline BCVA values at Month 39 compared to Month 36 (Table 62).

The summary of the mean change from baseline BCVA at Month 36 and Month 39 for the 21 subjects discussed earlier is presented in the Table 12. For the two DEX arms, the mean change from baseline BCVA at Month 39 was higher than at Month 36, while a slight decline was observed for the Sham arm.

Table 12: BCVA summary of the 21 subjects who had a BCVA measurement at Month 39 but were not re-treated at Month 36 (ITT LOCF)

Treatment	# of subjects	Month 36			Month 39		
		Mean (Std)	Min	Max	Mean (Std)	Min	Max
DEX 350	10	-8.80 (23.6)	-44	30	0.2 (15.6)	-22	23

DEX 700	6	-3.67 (21.39)	-40	15	5.67 (7.86)	-6	15
Sham	5	2.00 (11.51)	-17	14	1.40 (8.68)	-9	15

Source: Reviewer's Analysis.

To understand the impact of the BCVA measures of these 21 subjects on the treatment differences at Month 39, the two DEX arms were compared with the Sham arm after replacing the Month 39 BCVA measurements by Month 36 values for the aforementioned 21 subjects. There was only a minor change in Study 206207-010. In Study 206207-011, the difference in the mean change from baseline BCVA between DEX 700 and Sham decreased from -0.5 to -0.83. A slightly more pronounced change was observed in the difference between DEX 350 and Sham (0.3 to -0.35). A similar analysis was performed for proportion of subjects with at least 15 letters gain from baseline. There was only a minor change in the proportion of subjects with at least 15 letters improvement at Month 39/final. This is because, although the BCVA change from baseline values at Month 39/final were higher in magnitude, almost equal number of subjects had values that changed from <15 letters to ≥ 15 letters from Month 36 to Month 39 and vice-versa (Table 62). Although there is no evidence to suggest that these subjects were re-evaluated at Month 39 because of their anticipated improved BCVA at Month 39, the above summary results indicate that the inclusion of these subjects had improved the treatment effect at Month 39, albeit only marginally in the primary efficacy endpoint.

Table 13: Mean Change from Baseline BCVA at Month 39/final Visit (ITT LOCF)

Studies	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	4.13(13.9)	5.06(12.1)	0.79(11.9)	3.34(0.53,6.16)	4.27(1.7,6.87)
011	0.02(17.8)	0.5(15.9)	0.85(13.6)	-0.83(-4.27,2.6)	-0.35(-3.6,2.9)
Pooled	2.06 (16.1)	2.83 (14.2)	0.82(12.7)	1.24 (-0.98, 3.47)	2.02 (-0.06,4.10)
Pseudophakic Subjects					
010	9.52(10.5)	6.15(10.3)	2.68(10.4)	6.84(2.56,11.13)	3.47(-0.7,7.65)
011	1.5(12.1)	5.71(10.9)	0.24(14)	1.26(-4.31,6.82)	5.47(0.1,10.78)
Pooled	5.80(11.8)	5.95(10.5)	1.47(12.3)	4.33(0.77,7.89)	4.48 (1.15,7.80)

Source: Reviewer's Analysis. Month 36 BCVA was used for the 22 subjects who had a BCVA measure at Month 39 Without being re-treated at Month 36. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

Table 14: Proportion of subjects with ≥ 15 letters gain from Baseline at Month 39/final Visit (ITT LOCF)

Studies	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	34 (20.9%)	31(18.7%)	18(10.9%)	9.9%(2.1%,17.8%)	7.8%(0.2%,15.4%)
011	30(18.2%)	24(15.2%)	16(9.8%)	8.4%(0.9%,15.8%)	5.4%(-1.8%,12.6%)
Pooled	64 (19.5%)	55 (17.0%)	34 (10.4%)	9.1% (3.7%, 14.6%)	6.6% (1.4%, 11.9%)
Pseudophakic Subjects					
010	14(31.8%)	7(14.9%)	8(16%)	15.8%(-1.3%,32.9%)	-1.1%(-15.5%,13.3%)
011	3(7.9%)	5(13.2%)	3(6.1%)	1.8%(-9.1%,12.7%)	7%(-5.6%,19.7%)
Pooled	17 (20.7%)	12 (14.1%)	11 (11.1%)	9.6% (-1.1%, 20.4%)	4.9% (-6.6%, 12.7%)

Source: Reviewer's Analysis. Month 36 BCVA was used for the 22 subjects who had a BCVA measure at Month 39 Without being re-treated at Month 36. Subjects who received a rescue therapy were treated as treatment failures

2.3.5 Confounding effect of cataract related AE and Surgery

The applicant argued that cataract formation had a confounding effect on BCVA. To evaluate this claim, ad-hoc subgroup analyses for subgroup of subjects formed based on baseline lens and cataract status was performed. For the complete summary of subjects who reported cataract related AE and subjects who underwent cataract surgery please refer to Section 2.4. The summaries of the proportion of subjects with at least 15 letters gain from baseline and the mean change from baseline BCVA at Month 36 visit for the different subgroups formed based on lens and cataract status is presented in Table 15 and Table 16 respectively. Similar summaries for the Month 39/final visit are provided in the appendix Table 42 and Table 43.

Table 15: Proportion of subjects with ≥ 15 letters from Baseline at Month 36 for subgroups based on lens status and cataract (ITT LOCF)

Subgroup	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010				
Phakic (0)	18/119(15.1%)	25/119(21%)	10/115(8.7%)	6.4%(-1.8%, 14.7%)	12.3% (3.4%, 21.3%)
Pseudophakic (1)	14/44(31.8%)	8/47(17%)	8/50(16%)	15.8%(-1.3%,32.9%)	1%(-13.8%,15.8%)
Phakic Subjects who had Cataract surgery (2)	13/72(18.1%)	16/72(22.2%)	2/8(25%)	-6.9%(-38.2%,24.3%)	-2.8%(-34.3%,28.7%)
(1)+ (2)	27/116(23.3%)	24/119(20.2%)	10/58(17.2%)	6%(-6.4%,18.4%)	2.9%(-9.2%,15%)
Phakic subjects with No Cataract related AE (3)	6/39(15.4%)	8/37(21.6%)	7/98(7.1%)	8.2%(-4.2%,20.7%)	14.5%(0.3%,28.7%)
(1)+(3)	20/83(24.1%)	16/84(19%)	15/148(10.1%)	14%(3.6%,24.4%)	8.9%(-0.8%,18.6%)
Study 206207-011					
Phakic (0)	22/127(17.3%)	17/120(14.2%)	13/114(11.4%)	5.9%(-2.9%, 14.7%)	2.8% (-5.8%, 11.3%)
Pseudophakic (1)	3/38(7.9%)	4/38(10.5%)	3/49(6.1%)	1.8%(-9.1%,12.7%)	4.4%(-7.4%,16.2%)
Phakic Subjects who had Cataract surgery (2)	14/76(18.4%)	13/53(24.5%)	1/10(10%)	8.4%(-12.1%,29%)	14.5%(-7.4%,36.4%)
(1)+ (2)	17/114(14.9%)	17/91(18.7%)	4/59(6.8%)	8.1%(-1%,17.3%)	11.9%(1.6%,22.2%)
Phakic subjects with No Cataract related AE (3)	8/41(19.5%)	4/52(7.7%)	10/83(12%)	7.5%(-6.5%,21.5%)	-4.4%(-14.4%,5.7%)
(1)+(3)	11/79(13.9%)	8/90(8.9%)	13/132(9.8%)	4.1%(-5.1%,13.2%)	-1%(-8.7%,6.8%)
Pooled					
Phakic (0)	40/246(16.3%)	42/239(17.6%)	23/229(10%)	6.2% (0.2%, 12.3%)	7.5% (1.3%,13.7%)
Pseudophakic (1)	17/82(20.7%)	12/85(14.1%)	11/99(11.1%)	9.6%(-1.1%,20.4%)	3%(-6.6%,12.7%)
Phakic Subjects who had Cataract surgery (2)	27/148(18.2%)	29/125(23.2%)	3/18(16.7%)	1.6%(-16.7%,19.9%)	6.5%(-12.2%,25.3%)
(1)+ (2)	44/230(19.1%)	41/210(19.5%)	14/117(12%)	7.2%(-0.6%,14.9%)	7.6%(-0.4%,15.5%)

Phakic subjects with No Cataract related AE (3)	14/80(17.5%)	12/89(13.5%)	17/181(9.4%)	8.1%(-1.2%,17.5%)	4.1%(-4.2%,12.4%)
(1)+(3)	31/162(19.1%)	24/174(13.8%)	28/280(10%)	9.1%(2.1%,16.1%)	3.8%(-2.4%,10%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures

Table 16: Mean Change from Baseline BCVA at Month 36 for Subgroups based on Lens and Cataract Status (ITT LOCF)

Subgroup	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010				
Phakic (0)	1.6(14.7)	4.6(13)	0.3(12)	1.3(-2.1,4.8)	4.2(1,7.5)
Pseudophakic (1)	9.3(10.8)	6.5(10.2)	2.6(10.4)	6.7(2.3,11)	3.8(-0.3,8)
Phakic Subjects who had Cataract surgery (2)	3.4(14.7)	6.1(12.5)	3.1(16.8)	0.2(-13.9,14.4)	2.9(-11.2,17)
(1)+(2)	5.6(13.6)	6.2(11.6)	2.7(11.3)	2.9(-0.9,6.7)	3.5(-0.1,7.1)
Phakic subjects with No Cataract related AE (3)	3(12)	4.9(11.9)	0.2(12)	2.8(-1.7,7.3)	4.8(0.2,9.4)
(1)+(3)	6.3(11.7)	5.8(10.9)	1(11.5)	5.3(2.2,8.5)	4.8(1.8,7.8)
Study 206207-011					
Phakic (0)	-0.9(18.9)	-1.6(16.8)	1(13.2)	-1.8(-6,2.3)	-2.6(-6.5,1.3)
Pseudophakic (1)	1.5(11.9)	5(10.7)	0.1(13.9)	1.4(-4.1,6.9)	4.9(-0.3,10.2)
Phakic Subjects who had Cataract surgery (2)	1.4(17.6)	2.8(16.3)	2.7(12.1)	-1.3(-10.5,8)	0.1(-9.4,9.5)
(1)+(2)	1.5(15.9)	3.7(14.2)	0.5(13.6)	0.9(-3.6,5.5)	3.2(-1.4,7.8)
Phakic subjects with No Cataract related AE (3)	0.7(16)	-1.4(15.4)	0.2(14.5)	0.6(-5.3,6.4)	-1.6(-6.9,3.7)
(1)+(3)	1.1(14.1)	1.3(13.9)	0.1(14.2)	1(-3,4.9)	1.2(-2.6,4.9)
Pooled					
Phakic (0)	0.3(17)	1.5(15.3)	0.6(12.6)	-0.3(-3,2.4)	0.8(-1.7,3.4)
Pseudophakic (1)	5.7(11.9)	5.8(10.4)	1.4(12.2)	4.3(0.8,7.9)	4.5(1.2,7.7)
Phakic Subjects who had Cataract surgery (2)	2.4(16.2)	4.7(14.2)	2.9(13.9)	-0.5(-7.8,6.8)	1.8(-5.5,9.1)
(1)+(2)	3.6(14.9)	5.1(12.8)	1.6(12.5)	2(-1,4.9)	3.5(0.7,6.4)
Phakic subjects with No Cataract related AE (3)	1.8(14.1)	1.2(14.3)	0.2(13.2)	1.7(-2,5.3)	1.1(-2.5,4.6)
(1)+(3)	3.8(13.2)	3.5(12.7)	0.6(12.8)	3.2(0.6,5.7)	2.9(0.5,5.3)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

Based on the above analyses, it appears that baseline Pseudophakic subjects or subjects who did not have cataract formation during the study had better BCVA outcomes. The applicant's assertion that the decline in the BCVA is due to cataract formation seems acceptable. However, subjects who developed cataract during the study, even after undergoing cataract surgery did not have a significant improvement in BCVA at the last measurement time (Month 36 or Month 39/final). Because in the above analyses some of the subgroups were formed based on post-randomization patient characteristics and had few subjects in each treatment arm, the results should be interpreted with caution.

Plots of the mean change from baseline BCVA over time for the different subgroups are provided in Figure 25 - Figure 31. First, the plot of the mean change from baseline BCVA for baseline Pseudophakic subjects only is presented in Figure 25 and Figure 26. There appears to be a noticeable separation in the mean change from baseline BCVA for both studies. The two DEX arms had relatively higher mean change from baseline BCVA at all study visits.

The second summary was for baseline Phakic subjects who underwent cataract surgery during the study period and is presented in Figure 28. From this plot, there does not appear to be any noticeable separation among the three treatment groups in either of the two studies. The DEX 700 arm had higher mean change from baseline BCVA compared to Sham between Months 12 to 24 and after Month 36 in Study 206207-010; and between baseline and Month 12 in Study 206207-011. After Month 12, the DEX arm had consistently lower mean change from baseline BCVA compared to Sham in Study 206207-011.

A similar mean plot for subgroup of subjects comprising of baseline Pseudophakic subjects and baseline Phakic subjects who underwent cataract surgery is presented in Figure 29. There was a relatively better separation between DEX 700 and Sham in Study 206207-010, but no noticeable difference was observed in Study 206207-011 until Month 30 after which the DEX arm had a relatively higher mean change from baseline compared to Sham. Because there was no separation among the three treatment arms for baseline Phakic subjects who underwent cataract surgery, it appears that, the relatively better separation seen when this group was combined with baseline Pseudophakic subjects is due to the better BCVA outcome for baseline Pseudophakic subjects. Two additional plots for the mean change from baseline BCVA were produced. The first was for subjects who did not report any cataract related AE only (Figure 30), and the second is for the combination of baseline Pseudophakic subjects and all Phakic subjects who did not report any cataract related AE (Figure 31). From Figure 30, we can see that there was a noticeable separation among the three treatment groups with the two DEX arms having higher mean change from baseline at all times in Study 206207-010 and after Month 18 in Study 206207-011. From Figure 31, in both studies, the two DEX arms had better mean change from baseline outcomes at all study visits.

2.4 Evaluation of Safety

After excluding the 68 subjects from site 2707, the safety population, subjects who received at least one injection, consisted of 972 subjects (324, 320 and 328 subjects in the DEX 700, DEX 350 and Sham arm respectively). Eighty-five of the 324 subjects in the DEX 700 arm and 95 of the 320 subjects in the DEX 350 arm received 6 injections during the course of the study (Table 17). Subjects in the two DEX arms had slightly higher average number of injections compared to subjects in the Sham arm.

Table 17: Summary of Number of Injections

# of Injections	Treatment: N (%)		
	DEX 700 N=324	DEX 350 N=320	Sham N=328
1	40(12.3%)	34(10.6%)	101(30.8%)
2	51(15.7%)	42(13.1%)	51(15.5%)
3	36(11.1%)	37(11.6%)	40(12.2%)
4	37(11.4%)	38(11.9%)	23(7%)

5	44(13.6%)	37(11.6%)	29(8.8%)
6	85(26.2%)	95(29.7%)	49(14.9%)
7	31(9.6%)	37(11.6%)	35(10.7%)
Mean (std)	4.15(1.97)	4.36 (1.95)	3.35 (2.18)
Median	4.0	5.0	3.0
Q1, Q3	2.0, 6.0	3.0, 6.0	1.0, 6.0

Source: Reviewer's analysis.

From Table 17, we can deduce that a total of 284, 286 and 227 subjects in the DEX 700, DEX 350 and Sham arm respectively, received at least one retreatment (2 or more injections). The summary of the number of subjects who received retreatment at a given study visit and the summary of the time at which the first retreatment was provided is presented in Table 18 and Table 19, respectively. In each treatment arm, over 75% of study subjects, received their first retreatment at Month 6, which corresponds to the protocol defined earliest possible time for retreatment.

Table 18: Summary of Subjects Who Received Retreatment by Visit

Time to First Re-treatment	Treatment: N (%)		
	DEX 700 N=284*	DEX 350 N=286*	Sham N=227*
Month 6	215(75.7%)	231(80.8%)	187(82.4%)
Month 7.5	23(8.1%)	17(5.9%)	12(5.3%)
Month 9	19(6.7%)	18(6.3%)	15(6.6%)
Month 10.5	5(1.8%)	4(1.4%)	1(0.4%)
Month 12	179(63%)	196(68.5%)	139(61.2%)
Month 15	38(13.4%)	29(10.1%)	23(10.1%)
Month 18	139(48.9%)	145(50.7%)	108(47.6%)
Month 21	41(14.4%)	50(17.5%)	22(9.7%)
Month 24	104(36.6%)	124(43.4%)	95(41.9%)
Month 27	54(19%)	43(15%)	24(10.6%)
Month 30	86(30.3%)	109(38.1%)	68(30%)
Month 33	65(22.9%)	53(18.5%)	32(14.1%)
Month 36	52(18.3%)	56(19.6%)	45(19.8%)
Month 39	1(0.4%)	0(0%)	0(0%)

Source: Reviewer's analysis. * # of subjects who received at least one retreatment.

Table 19: Summary of First Time Retreatment

Time to First Re-treatment	Treatment: N (%)		
	DEX 700 N=284*	DEX 350 N=279*	Sham N=227*
Month 6	215(75.7%)	231(80.5%)	187(82.4%)
Month 7.5	23(8.1%)	17(5.9%)	12(5.3%)
Month 9	19(6.7%)	18(6.3%)	15(6.6%)
Month 10.5	3(1.1%)	3(1%)	1(0.4%)
Month 12	13(4.6%)	7(2.4%)	3(1.3%)
Month 15	2(0.7%)	1(0.3%)	2(0.9%)
Month 18	4(1.4%)	3(1%)	3(1.3%)
Month 21	2(0.7%)	0(0%)	0(0%)
Month 24	2(0.7%)	3(1%)	3(1.3%)
Month 27	0(0%)	2(0.7%)	0(0%)
Month 30	0(0%)	1(0.3%)	0(0%)
Month 33	1(0.4%)	0(0%)	1(0.4%)

Source: Reviewer's analysis. * # of subjects who received at least one retreatment.

The summary of selected adverse events for the two studies combined is presented in Table 20. The safety summary for each study separately is presented in Table 47 and Table 48 in Appendix A. Similar summary for baseline Pseudophakic and baseline Phakic subjects is presented in Table 28 and Table 29 respectively. In the two studies combined, the proportion of subjects who reported at least one ocular AE in the study eye was 274/324 (84.6%), 282/320 (88.1%) and 190/328 (57.9%) in the DEX 700, DEX 350 and Sham arm respectively. Higher proportion of subjects in the DEX 700 (120/324; 37.0%) and DEX 350 (107/320; 33.4%) arms reported at least one IOP-related AE compared to Sham (18/328; 5.51%).

Among baseline Phakic subjects, a higher proportion in the DEX 700 (148/243, 60.9%) and DEX 350 (125/236, 53.0%) arms required cataract surgery in the study eye compared to only 18/231 (7.8%) in the Sham arm. A higher proportion of subjects reported at least one serious AE (ocular or non-ocular) in the DEX 700 arm (110/324, 34.0%) and the DEX 350 arm (113/320, 35.3%) compared to the Sham arm (79/328, 24.1%; Table 20).

Table 20: Summary of Adverse Events (AE) (Pooled: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=324	DEX 350 N=320	Sham N=328	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	310(95.7%)	311(97.2%)	260(79.3%)	16.4%(11.5%,21.3%)	17.9%(13.2%,22.7%)
Any Ocular AE	274(84.6%)	282(88.1%)	190(57.9%)	26.6%(20%,33.3%)	30.2%(23.8%,36.6%)
Any Serious AE	110(34%)	113(35.3%)	79(24.1%)	9.9%(2.9%,16.8%)	11.2%(4.2%,18.2%)
Any Ocular Serious AE	24(7.4%)	14(4.4%)	4(1.2%)	6.2%(3.1%,9.3%)	3.2%(0.6%,5.7%)
Any Severe AE	151(46.6%)	149(46.6%)	100(30.5%)	16.1%(8.7%,23.5%)	16.1%(8.7%,23.5%)
Any Ocular Severe AE	91(28.1%)	71(22.2%)	34(10.4%)	17.7%(11.8%,23.6%)	11.8%(6.2%,17.4%)
Any IOP Related AE	120(37%)	107(33.4%)	18(5.5%)	31.5%(25.7%,37.4%)	27.9%(22.2%,33.7%)
≥10 mm Hg IOP Change from Baseline at any visit	91(28.1%)	79(24.7%)	13(4%)	24.1%(18.8%,29.5%)	20.7%(15.5%,25.9%)
≥25 mm Hg IOP at any visit	106(32.7%)	86(26.9%)	15(4.6%)	28.1%(22.6%,33.7%)	22.3%(16.9%,27.7%)
≥35 mm Hg IOP at any visit	20(6.2%)	16(5%)	3(0.9%)	5.3%(2.4%,8.1%)	4.1%(1.5%,6.7%)
Glaucoma	4(1.2%)	3(0.9%)	1(0.3%)	0.9%(-0.4%,2.3%)	0.6%(-0.6%,1.8%)
IOP Lowering Procedures	4(1.2%)	1(0.3%)	1(0.3%)	0.9%(-0.4%,2.3%)	0%(-0.8%,0.9%)
Any Cataract Related AE Baseline Phakic Subjects	166(68.3%)	149(63.1%)	49(21.3%)	47%(39.1%,54.9%)	41.8%(33.7%,49.9%)
Cataract Surgery in Baseline Phakic Subjects	148(60.9%)	125(53%)	18(7.8%)	53.1%(46%,60.1%)	45.1%(37.9%,52.4%)
Death	9(2.8%)	14(4.4%)	5(1.5%)	1.3%(-1%,3.5%)	2.9%(0.2%,5.5%)
Escape Therapy	31(9.6%)	38(11.9%)	63(19.2%)	-9.6%(-15%,-4.3%)	-7.3%(-12.9%,-1.8%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Most subjects in all treatment arms reported their first cataract related AE within a year after randomization and had cataract surgery between months 15 and 27. The median time to first reported cataract related AE was 15 months for the two DEX arms and 12 for the Sham arm. The median time to cataract surgery was 21 months for the two DEX arms and 20 months after randomization for the Sham arm.

Table 21: Summary of time-to-first reported Cataract-related AE among Baseline Phakic Subjects

Time to First Cataract Related AE	Study 206207-010			Study 206207-011		
	DEX 700 N=117	DEX 350 N=118	Sham N=115	DEX 700 N=126	DEX 350 N=118	Sham N=115
≤Month 6	16(13.7%)	13(11%)	6(5.2%)	12(9.5%)	19(16.1%)	12(10.4%)
> Month 6 ≤ Month 12	17(14.5%)	19(16.1%)	1(0.9%)	26(20.6%)	19(16.1%)	9(7.8%)
Month 15	8(6.8%)	8(6.8%)	0 (0.0%)	6(4.8%)	2(1.7%)	2(1.7%)
Month 18	10(8.5%)	11(9.3%)	0 (0.0%)	19(15.1%)	8(6.8%)	2(1.7%)
Month 21	11(9.4%)	8(6.8%)	2(1.7%)	6(4.8%)	8(6.8%)	1(0.9%)
Month 24	4(3.4%)	9(7.6%)	4(3.5%)	6(4.8%)	5(4.2%)	1(0.9%)
Month 27	4(3.4%)	7(5.9%)	1(0.9%)	4(3.2%)	3(2.5%)	1(0.9%)
Month 30	3(2.6%)	2(1.7%)	2(1.7%)	6(4.8%)	3(2.5%)	1(0.9%)
Month 33	2(1.7%)	1(0.8%)	0 (0.0%)	1(0.8%)	0 (0.0%)	2(1.7%)
Month 36	5(4.3%)	2(1.7%)	1(0.9%)	0 (0.0%)	0 (0.0%)	1(0.9%)
Month 39	0 (0.0%)	2(1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's analysis. This is the first time a subject reported cataract related AE. Note some subjects report more than one cataract related AE.

Table 22: Summary of Cataract surgery among Baseline Phakic Subjects

Time to First Cataract Related AE	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=117	DEX 350 N=118	Sham N=115	DEX 700 N=126	DEX 350 N=118	Sham N=115
≤Month 6	4(3.4%)	3(2.5%)	0 (0.0%)	1(0.8%)	3(2.5%)	3(2.6%)
> Month 6 ≤ Month 12	10(8.5%)	7(5.9%)	1(0.9%)	10(7.9%)	5(4.2%)	1(0.9%)
Month 15	7(6%)	8(6.8%)	0 (0.0%)	5(4%)	2(1.7%)	3(2.6%)
Month 18	6(5.1%)	8(6.8%)	0 (0.0%)	14(11.1%)	9(7.6%)	1(0.9%)
Month 21	14(12%)	11(9.3%)	1(0.9%)	11(8.7%)	7(5.9%)	1(0.9%)
Month 24	7(6%)	15(12.7%)	2(1.7%)	14(11.1%)	8(6.8%)	0 (0.0%)
Month 27	12(10.3%)	6(5.1%)	1(0.9%)	8(6.3%)	7(5.9%)	0 (0.0%)
Month 30	5(4.3%)	7(5.9%)	0 (0.0%)	6(4.8%)	4(3.4%)	0 (0.0%)
Month 33	4(3.4%)	5(4.2%)	1(0.9%)	5(4%)	6(5.1%)	0 (0.0%)
Month 36	2(1.7%)	2(1.7%)	2(1.7%)	2(1.6%)	2(1.7%)	1(0.9%)
Month 39	1(0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's analysis.

The summary of baseline Phakic subjects who had cataract surgery among those who reported at least one cataract related adverse event is presented in Table 23. In both studies, between 75-80% subjects in the two DEX arms who reported at least one cataract related adverse event had undergone cataract surgery compared to 25-48% in the Sham arm.

Table 23: Summary of Subjects who had Cataract surgery among baseline Phakic subjects who reported Cataract AE

Cataract surgery	Study 206207-010			Study 206207-011		
	DEX 700 N=80	DEX 350 N=82	Sham N=17	DEX 700 N=86	DEX 350 N=67	Sham N=32
Yes	64 (80.0%)	65 (79.3%)	8 (47.1%)	69 (80.2%)	50 (74.6%)	8 (25.0%)
No	16 (20.0%)	17 (20.7%)	9 (52.9%)	17 (19.8%)	17 (25.4%)	24 (75.0%)

Source: Reviewer's analysis.

In the two studies combined, there were 264 subjects (133, 115 and 16 in the DEX 700, DEX 350 and Sham respectively) who reported at least one cataract related AE and had cataract surgery. The summary of the time between the first reported cataract related adverse event and cataract

surgery for subjects who had reported cataract AE and had surgery is presented Table 24. In Study 206207-011 the time between cataract surgery and first reported cataract related adverse event was longer compared to Study 206207-010 for the two DEX arms, while a relatively shorter time for the Sham arm.

Table 24: Summary of time (Month) between first reported Cataract related AE and Surgery

Treatment	Study 206207-010		Study 206207-011		Pooled	
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
DEX 350	6.3 (7.5)	6.0	8.1 (8.7)	6.0	7.1 (8.1)	6
DEX 700	6.5 (7.2)	6.0	6.9 (5.5)	6.0	6.7 (6.3)	6
Sham	12.9 (13.1)	6.7	7.3 (10.8)	3.0	10.1 (12.0)	3.75

Source: Reviewer's Analysis.

One of the reported consequences of cataract formation was the loss of BCVA from baseline. The summary of selected adverse events for subjects who lost 15 letters or more from baseline at Month 36 is summarized in Table 54. In the DEX 700 arm, 30 (71%) of baseline Phakic subjects who lost 15 letters or more had at least one cataract related AE, while only 20 (47.6%) had cataract surgery. The corresponding figures in the Sham arm were 4 (14.3%) and 3 (10.7%) respectively. This result appears to be in line with the applicant's argument that cataract formation had resulted in a BCVA loss.

The summary of the first time an IOP related AE is reported is presented in Table 25. Most subjects reported IOP related AE for the first time within 6 Month after randomization.

Table 25: Summary of time-to-first IOP-Related AE

Time to First Elevated IOP Related AE	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=160	DEX 350 N=165	Sham N=164	DEX 700 N=164	DEX 350 N=155	Sham N=164
≤Month 6	38(23.8%)	32(19.4%)	1(0.6%)	35(21.3%)	29(18.7%)	6(3.7%)
> Month 6 ≤ Month 12	19(11.9%)	20(12.1%)	1(0.6%)	12(7.3%)	10(6.5%)	4(2.4%)
Month 15	5(3.1%)	1(0.6%)	1(0.6%)	4(2.4%)	5(3.2%)	0 (0.0%)
Month 18	0 (0.0%)	1(0.6%)	1(0.6%)	0 (0.0%)	0 (0.0%)	1(0.6%)
Month 21	2(1.3%)	2(1.2%)	0 (0.0%)	2(1.2%)	1(0.6%)	0 (0.0%)
Month 24	0 (0.0%)	1(0.6%)	0 (0.0%)	0 (0.0%)	1(0.6%)	0 (0.0%)
Month 27	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1(0.6%)	1(0.6%)
Month 30	0 (0.0%)	0 (0.0%)	0 (0.0%)	2(1.2%)	0 (0.0%)	1(0.6%)
Month 33	0 (0.0%)	1(0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Month 36	0 (0.0%)	2(1.2%)	1(0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Month 39	0 (0.0%)	2(1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's analysis. This is the first time a subject reported cataract related AE. Note subjects report more than one cataract related AE.

The summary of the number of reported IOP related AE at each visit is presented in Table 26. A majority of IOP related AEs were reported within the first year after randomization.

Table 26: Summary of number of reported IOP related AE by study visit

Visit Month	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=160	DEX 350 N=165	Sham N=164	DEX 700 N=164	DEX 350 N=155	Sham N=164
1	12(7.5%)	15(9.1%)	0 (0.0%)	14(8.5%)	17(11)	2(1.2%)
1.5	21(13.1%)	12(7.3%)	0 (0.0%)	25(15.2%)	18(11.6)	2(1.2%)

3	16(10%)	12(7.3%)	0 (0.0%)	7(4.3%)	10(6.5%)	1(0.6%)
4.5	0 (0.0%)	2(1.2%)	1(0.6%)	0 (0.0%)	0 (0.0%)	1(0.6%)
6	10(6.3%)	6(3.6%)	0 (0.0%)	5(3%)	4(2.6%)	0 (0.0%)
7.5	20(12.5%)	20(12.1%)	1(0.6%)	14(8.5%)	8(5.2%)	3(1.8%)
9	12(7.5%)	12(7.3%)	0 (0.0%)	9(5.5%)	4(2.6%)	1(0.6%)
10.5	5(3.1%)	4(2.4%)	0 (0.0%)	5(3%)	2(1.3%)	3(1.8%)
12	12(7.5%)	16(9.7)	0 (0.0%)	8(4.9%)	3(1.9%)	5(3%)
15	16(10%)	8(4.8%)	2(1.2%)	16(9.8%)	8(5.2%)	2(1.2%)
18	4(2.5%)	7(4.2%)	1(0.6%)	5(3%)	3(1.9%)	2(1.2%)
21	14(8.8%)	16(9.7%)	1(0.6%)	9(5.5%)	4(2.6%)	0 (0.0%)
24	9(5.6%)	12(7.3%)	0 (0.0%)	2(1.2%)	5(3.2%)	3(1.8%)
27	7(4.4%)	4(2.4%)	0 (0.0%)	1(0.6%)	4(2.6%)	2(1.2%)
30	4(2.5%)	4(2.4%)	0 (0.0%)	6(3.7%)	2(1.3%)	1(0.6%)
33	4(2.5%)	1(0.6%)	0 (0.0%)	6(3.7%)	1(0.6%)	0 (0.0%)
36	4(2.5%)	4(2.4%)	1(0.6%)	4(2.4%)	1(0.6%)	1(0.6%)
39	1(0.6%)	2(1.2%)	0 (0.0%)	1(0.6%)	1(0.6%)	0 (0.0%)

Source: Reviewer's analysis. Note subjects are counted more than once as they report IOP related AE on several occasions.

Based on the previous summaries, the two commonly reported adverse events were related to elevated IOP and cataract formation. The summary of subjects who reported at least one IOP related AE and one cataract related AE is presented in Table 27. Because some baseline Pseudophakic subjects also reported cataract related adverse events, the summary includes both baseline Phakic and Pseudophakic subjects. A total of 68/324 (21.0%) subjects in the DEX 700 arm reported at least one IOP and cataract related adverse events compared to only 4/328 (1.2%) in the Sham arm.

Table 27: Cross-tabulation of Cataract –related AE and IOP-related AE

IOP AE	Cataract AE: Yes			Cataract AE: No		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Yes	68 (21.0%)	53 (16.6%)	4 (1.2%)	52 (16.0%)	54 (16.9%)	14 (4.3%)
No	98 (30.2%)	96 (30.0%)	45 (13.7%)	106 (32.7%)	117 (36.6%)	265 (80.8%)

Source: Reviewer's analysis. Both baseline Phakic and Pseudophakic subjects are included in this summary

For baseline Pseudophakic subjects, the differences between the two DEX arms and the Sham arm in the proportion of subjects who reported at least one IOP related adverse event were slightly lower than the Phakic subjects. Note that, 6 baseline Pseudophakic subjects (2 in DEX 700, 0 in DEX 350 and 2 in Sham) reported at least one cataract related AE; and one baseline Pseudophakic subject from the Sham arm had cataract surgery (Table 28).

Table 28: Summary of Adverse Events (AE) (Pooled: Psuedophakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=81	DEX 350 N=84	Sham N=98	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	77(95.1%)	83(98.8%)	84(85.7%)	9.3%(1%,17.7%)	13.1%(5.8%,20.4%)
Any Ocular AE	59(72.8%)	70(83.3%)	60(61.2%)	11.6%(-2.1%,25.3%)	22.1%(9.6%,34.6%)
Any Serious AE	29(35.8%)	36(42.9%)	36(36.7%)	-0.9%(-15.1%,13.2%)	6.1%(-8.1%,20.4%)
Any Ocular Serious AE	2(2.5%)	0(0%)	0(0%)	2.5%(-0.9%,5.8%)	
Any Severe AE	35(43.2%)	40(47.6%)	37(37.8%)	5.5%(-9%,19.9%)	9.9%(-4.5%,24.2%)
Any Ocular Severe AE	10(12.3%)	15(17.9%)	8(8.2%)	4.2%(-4.8%,13.2%)	9.7%(-0.1%,19.5%)
Any IOP Related AE	25(30.9%)	29(34.5%)	9(9.2%)	21.7%(10.1%,33.3%)	25.3%(13.7%,37%)
≥10 mm Hg IOP Change	20(24.7%)	24(28.6%)	2(2%)	22.7%(12.9%,32.4%)	26.5%(16.5%,36.6%)

from Baseline at any visit					
≥25 mm Hg IOP at any visit	21(25.9%)	24(28.6%)	6(6.1%)	19.8%(9.1%,30.5%)	22.4%(11.7%,33.2%)
≥35 mm Hg IOP at any visit	6(7.4%)	4(4.8%)	1(1%)	6.4%(0.3%,12.4%)	3.7%(-1.2%,8.7%)
Glaucoma	1(1.2%)	1(1.2%)	0(0%)	1.2%(-1.2%,3.6%)	1.2%(-1.1%,3.5%)
Any Cataract Related AE	4(4.9%)	0(0%)	2(2%)	2.9%(-2.6%,8.4%)	
Cataract Surgery	0(0%)	0(0%)	1 (1.0%)		
IOP Lowering Procedures	1(1.2%)	0(0%)	0(0%)	1.2%(-1.2%,3.6%)	
Death	1(1.2%)	3(3.6%)	2(2%)	-0.8%(-4.5%,2.9%)	1.5%(-3.3%,6.4%)
Escape Therapy	7(8.6%)	9(10.7%)	12(12.2%)	-3.6%(-12.5%,5.3%)	-1.5%(-10.8%,7.7%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

The summary of the study duration by the number of injections received is provided in Table 40 and Figure 32 and Figure 33. From these summaries, subjects who received 3 or less injections left the study early. For example the median duration for subjects who received a single injection was 6 months, and was around 12 months for those who received 2 injections. Subjects in the Sham arm with fewer injections left earlier than their counterparts in the DEX arms. Of the 40 subjects in the DEX 700 arm who received a single injection, only 5(12.5%) subjects have completed the study. The remaining 35 (87.5%) have discontinued the study (9(22.5%) for lack of efficacy, 14 (35%) due to adverse event and the rest discontinued due to personal reason, lost-to-follow-up or other reasons (Table 41).

Summary of selected adverse events grouped by number of injections received is provided in Table 50-Table 53. Based on these summaries, it appears that IOP related AE was not substantially affected by the number of injections received which could be mainly because subjects received IOP lowering drugs after reported incidents. Cataract related AE and Cataract surgery however increased significantly with increased number of injections with the highest difference observed for those who received more than 5 injections. The summary of study duration by number of injections is presented in Table 56, and the summary of selected adverse events by the study duration is provided in Table 57. Because large proportion of subjects left the study early, the overall adverse event rate during the study duration might have been underestimated. However it is also important to note that subjects who left the study early had less number of injections. Consequently, the degree by which the event rate was underestimated might be minimal especially for IOP related AE.

Table 29: Summary of Adverse Events (AE) (Pooled: Phakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=243	DEX 350 N=236	Sham N=230	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	233(95.9%)	228(96.6%)	176(76.5%)	19.4%(13.3%,25.4%)	20.1%(14.1%,26%)
Any Ocular AE	215(88.5%)	212(89.8%)	130(56.5%)	32%(24.4%,39.5%)	33.3%(25.8%,40.8%)
Any Serious AE	81(33.3%)	77(32.6%)	43(18.7%)	14.6%(6.9%,22.4%)	13.9%(6.1%,21.8%)
Any Ocular Serious AE	22(9.1%)	14(5.9%)	4(1.7%)	7.3%(3.3%,11.3%)	4.2%(0.7%,7.6%)
Any Severe AE	116(47.7%)	109(46.2%)	63(27.4%)	20.3%(11.8%,28.9%)	18.8%(10.2%,27.4%)

Any Ocular Severe AE	81(33.3%)	56(23.7%)	26(11.3%)	22%(14.8%,29.2%)	12.4%(5.6%,19.2%)
Any IOP Related AE	95(39.1%)	78(33.1%)	9(3.9%)	35.2%(28.6%,41.8%)	29.1%(22.6%,35.6%)
≥10 mm Hg IOP Change from Baseline at any visit	71(29.2%)	55(23.3%)	11(4.8%)	24.4%(18.1%,30.8%)	18.5%(12.5%,24.6%)
≥25 mm Hg IOP at any visit	85(35%)	62(26.3%)	9(3.9%)	31.1%(24.6%,37.6%)	22.4%(16.2%,28.5%)
≥35 mm Hg IOP at any visit	14(5.8%)	12(5.1%)	2(0.9%)	4.9%(1.7%,8.1%)	4.2%(1.2%,7.3%)
Glaucoma	3(1.2%)	2(0.8%)	1(0.4%)	0.8%(-0.8%,2.4%)	0.4%(-1%,1.9%)
Any Cataract Related AE	166(68.3%)	149(63.1%)	49(21.3%)	47%(39.1%,54.9%)	41.8%(33.7%,49.9%)
Cataract Surgery	148(60.9%)	125(53%)	18(7.8%)	53.1%(46%,60.1%)	45.1%(37.9%,52.4%)
IOP Lowering Procedures	3(1.2%)	1(0.4%)	1(0.4%)	0.8%(-0.8%,2.4%)	0%(-1.2%,1.2%)
Death	8(3.3%)	11(4.7%)	3(1.3%)	2.0%(-0.7%, 4.7%)	3.4%(0.3%,6.4%)
Escape Therapy	24(9.9%)	29(12.3%)	51(22.2%)	-12.3%(-18.8%,-5.7%)	-9.9%(-16.7%,-3.1%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 30: Summary of time (Month) to first reported Cataract related AE, IOP and Surgery

Treatment	Time to first reported Cataract related AE					
	Study 206207-010		Study 206207-011		Pooled	
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
DEX 350	16.8(9.2)	18	13.8(8)	12	15.5(8.8)	15
DEX 700	16.4(9.4)	15	15.7(7.7)	15	16(8.5)	15
Sham	17.5(11.3)	21	12.3(10.5)	11	14.1(11)	11
	Time to first IOP related AE					
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
DEX 350	7.6(8.5)	6	6(6.6)	3	6.9(7.7)	3
DEX 700	6.4(6.6)	6	5.9(7.1)	2	6.1(6.8)	3
Sham	16.2(12.3)	15	9.5(9.8)	8	11.4(10.6)	8
	Time to Cataract Surgery					
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
DEX 350	21.4(7.9)	21	21.8(8.8)	24	21.6(8.2)	21
DEX 700	20.9(8.5)	21	21.5(7.1)	21	21.2(7.8)	21
Sham	26.1(9.5)	26	14(10)	15	19.3(11.3)	20

Source: Reviewer's Analysis.

3 Risk Benefit Analysis

The reviewer conducted two types of risk-benefit analyses: one at subject level and one at population level. Subjects who received one study treatment were included in these analyses and were analyzed according to the treatment to which they were randomized. These results demonstrated unfavorable risk-benefit profile for the test product.

3.1 Risk-benefit Analysis at Subject Level

For a given benefit and risk of interest, this analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in

each scenario for each treatment arm. The first scenario, referred to here as the best case scenario is the case in which a pre-specified level of BCVA improvement was observed without incurring an AE. The worst case scenario is incurring an AE without achieving a pre-specified level of improvement in BCVA from baseline at Month 36. The other two scenarios are having benefit with AE, and no benefit and no AE.

Compared to Sham, the two DEX arms had a higher proportion of subjects with the worst case scenario, and lower or only slightly higher proportion of subjects with the best case scenario for the majority of risks considered. Additionally, the two DEX arms also had a higher proportion of subjects who achieved improvement in BCVA but incurred an AE and lower proportion of subjects with no benefit and no AE compared to Sham (Table 31 and Table 59).

A higher proportion of subjects in the DEX 700 arm failed to achieve a 15 letter or more improvement in BCVA from baseline at Month 36 but reported at least one IOP related AE (Worst Case Scenario) compared to subjects in the Sham arm (98 (30.2%) vs. 17 (5.2%)). On the other hand, there were comparable proportion of subjects with the best case scenario i.e., ≥ 15 letters improvement without reporting any IOP related AE in the DEX 700 and Sham arm [35 (10.8%) vs. 33 (10.1%); Figure 8].

For baseline Phakic subjects, more subjects underwent cataract surgery but failed to achieve a 15 letter or more BCVA improvement from baseline at Month 36 (Worst Case Scenario) in the DEX 700 arm compared to Sham (121 (49.8%) vs. 15 (6.6%)). The proportion of baseline Phakic subjects with a 15 letter or more BCVA improvement from baseline at Month 36 without requiring cataract surgery (Best Case Scenario) however was 3.4% lower in the DEX 700 arm compared to Sham (13 (5.3%) vs. 20 (8.7%)) (Figure 8 and Table 31).

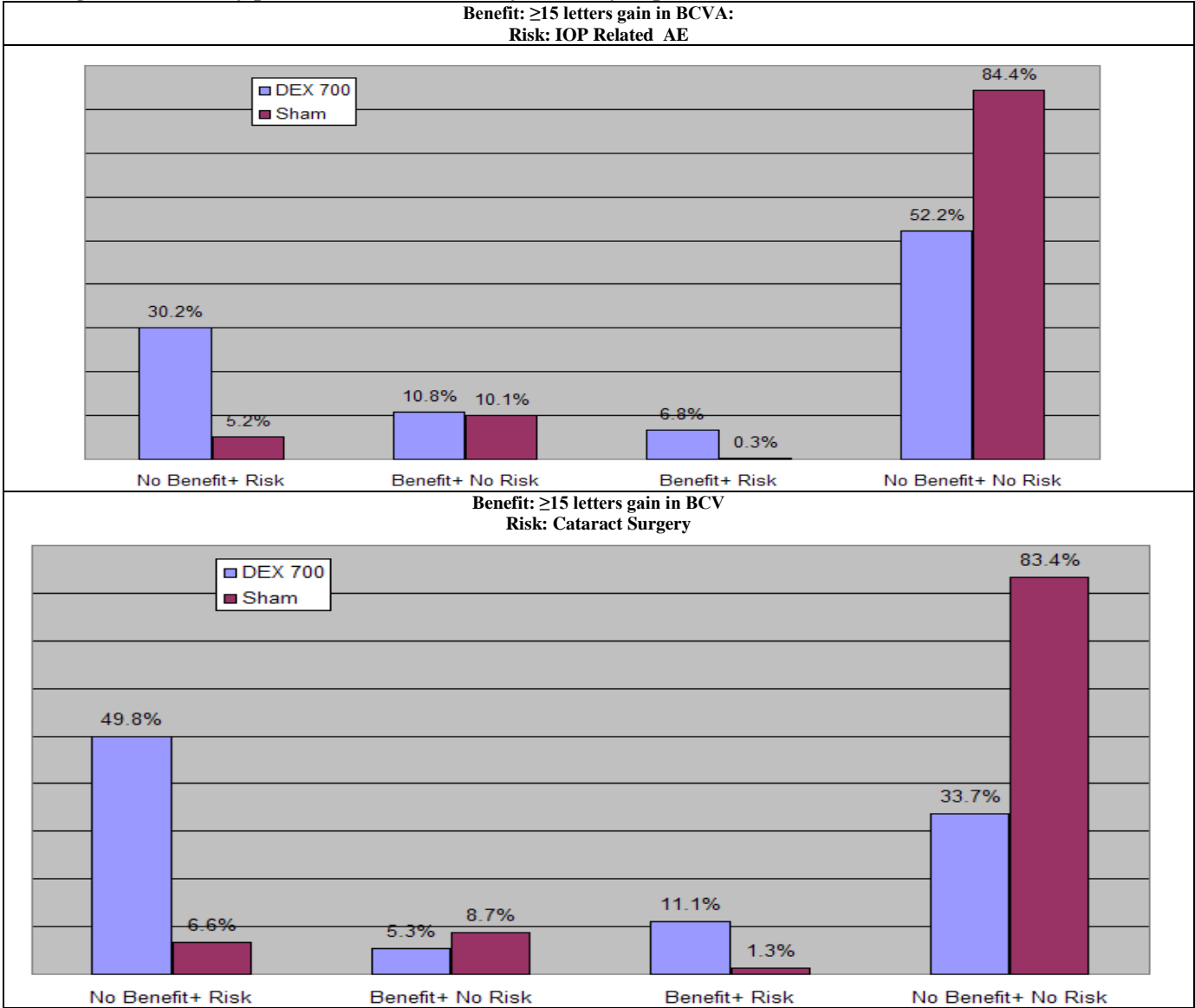
A similar risk-benefit analysis for baseline pseudophakic subjects was performed with IOP related AE as the assumed risk. Because of an improved treatment effect and slightly lower risk estimate, the risk-benefit profile for this subgroup of subjects appears to be slightly better than the whole population. For this subgroup of subjects, in the DEX 700 arm, 21/81 (25.9%) subjects failed to achieve a 15 letter or more improvement in BCVA from baseline at Month 36 but reported at least one IOP related AE (Worst Case Scenario) compared to 8/98 (8.20%) in the Sham arm. On the other hand, the proportion of subjects with the best case scenario i.e., ≥ 15 letters improvement without reporting any IOP related AE was 13/81 (16.0%) in the DEX 700 arm compared to 10/98 (11.2%) in the Sham arm (Table 32).

3.2 Risk-benefit Analysis at Population Level

For the majority of risks considered, the Benefit-to-Risk Ratios (BRR) were less than one or equivalently the NNT was larger than the NNH. This implies that fewer subjects were needed to be treated using DEX 700 to observe an AE compared to the number needed to be treated to observe one subject with a 15 letter or more BCVA improvement from baseline at 3 years. For example, the BRR values of 0.23 and 0.12 corresponding to Any IOP related AE and Cataract Surgery for Phakic subjects imply that for every subject with a 15 letter or more BCVA improvement due to DEX 700, 5 subjects had at least one IOP related AE and 9 Phakic subjects required cataract surgery, respectively. The IOP related AE adjusted number needed to treat was 45% higher than the unadjusted value, i.e., compared to Sham, more subjects need to be treated

using DEX 700 to observe a 15 letter or more improvement in BCVA without incurring an IOP related AE (Table 33).

Figure 8: Summary plot for Risk-Benefit Analysis (Safety Population)



Source: Reviewer’s Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Table 31: Summary of Risk-Benefit Analysis (Safety Population)

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 700 N=324	Sham N=327	DEX 700 N=324	Sham N=327	DEX 700 N=324	Sham N=327	DEX 700 N=324	Sham N=327
BCVA improvement of ≥ 15 letters	Any AE	2(0.6%)	0(0%)	255(78.7%)	225(68.8%)	55(17%)	34(10.4%)	12(3.7%)	68(20.8%)
	Any Ocular AE	11(3.4%)	11(3.4%)	228(70.4%)	166(50.8%)	46(14.2%)	23(7%)	39(12%)	127(38.8%)
	Any Serious AE	34(10.5%)	20(6.1%)	87(26.9%)	64(19.6%)	23(7.1%)	14(4.3%)	180(55.6%)	229(70%)
	Any Ocular Serious AE	53(16.4%)	33(10.1%)	20(6.2%)	2(0.6%)	4(1.2%)	1(0.3%)	247(76.2%)	291(89%)
	Any Severe AE	27(8.3%)	19(5.8%)	121(37.3%)	84(25.7%)	30(9.3%)	15(4.6%)	146(45.1%)	209(63.9%)
	Any Severe Ocular AE	40(12.3%)	33(10.1%)	74(22.8%)	32(9.8%)	17(5.2%)	1(0.3%)	193(59.6%)	261(79.8%)
	Any IOP Related AE	35(10.8%)	33(10.1%)	98(30.2%)	17(5.2%)	22(6.8%)	1(0.3%)	169(52.2%)	276(84.4%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	44(13.6%)	34(10.4%)	78(24.1%)	13(4%)	13(4%)	0(0%)	189(58.3%)	280(85.6%)
	≥ 25 mm Hg IOP at any visit	42(13%)	34(10.4%)	91(28.1%)	15(4.6%)	15(4.6%)	0(0%)	176(54.3%)	278(85%)
	≥ 35 mm Hg IOP at any visit	55(17%)	34(10.4%)	18(5.6%)	3(0.9%)	2(0.6%)	0(0%)	249(76.9%)	290(88.7%)
	Cataract Surgery in Phakic Subjects	13(5.3%)	20(8.7%)	121(49.8%)	15(6.6%)	27(11.1%)	3(1.3%)	82(33.7%)	191(83.4%)
BCVA improvement of ≥ 10 letters	Any AE	4(1.2%)	5(1.5%)	212(65.4%)	196(59.9%)	98(30.2%)	63(19.3%)	10(3.1%)	63(19.3%)
	Any Ocular AE	18(5.6%)	26(8%)	190(58.6%)	147(45%)	84(25.9%)	42(12.8%)	32(9.9%)	112(34.3%)
	Any Serious AE	61(18.8%)	49(15%)	69(21.3%)	59(18%)	41(12.7%)	19(5.8%)	153(47.2%)	200(61.2%)
	Any Ocular Serious AE	98(30.2%)	67(20.5%)	20(6.2%)	2(0.6%)	4(1.2%)	1(0.3%)	202(62.3%)	257(78.6%)
	Any Severe AE	55(17%)	47(14.4%)	104(32.1%)	78(23.9%)	47(14.5%)	21(6.4%)	118(36.4%)	181(55.4%)
	Any Severe Ocular AE	77(23.8%)	64(19.6%)	66(20.4%)	29(8.9%)	25(7.7%)	4(1.2%)	156(48.1%)	230(70.3%)
	Any IOP Related AE	62(19.1%)	63(19.3%)	80(24.7%)	13(4%)	40(12.3%)	5(1.5%)	142(43.8%)	246(75.2%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	74(22.8%)	66(20.2%)	63(19.4%)	11(3.4%)	28(8.6%)	2(0.6%)	159(49.1%)	248(75.8%)
	≥ 25 mm Hg IOP at any visit	70(21.6%)	66(20.2%)	74(22.8%)	13(4%)	32(9.9%)	2(0.6%)	148(45.7%)	246(75.2%)
	≥ 35 mm Hg IOP at any visit	95(29.3%)	68(20.8%)	13(4%)	3(0.9%)	7(2.2%)	0(0%)	209(64.5%)	256(78.3%)
	Cataract Surgery in Phakic Subjects	21(8.6%)	43(18.8%)	98(40.3%)	13(5.7%)	50(20.6%)	5(2.2%)	74(30.5%)	168(73.4%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Summary of Risk-Benefit Analysis (Continued)

Benefit	Risk	Differences: DEX 700- Sham (95% CI)			
		Benefit + No Risk (Best Case Scenario)	No Benefit + Risk (Worst Case Scenario)	Benefit + Risk	No Benefit + No Risk
BCVA improvement of ≥15 letters	Any AE	0.6%(-0.2%, 1.5%)	9.9%(3.2%, 16.6%)	6.6%(1.3%, 11.8%)	-17.1%(-21.9%, -12.2%)
	Any Ocular AE	0%(-2.7%, 2.8%)	19.6%(12.3%, 27%)	7.2%(2.5%, 11.9%)	-26.8%(-33.2%, -20.4%)
	Any Serious AE	4.4%(0.1%, 8.6%)	7.3%(0.8%, 13.7%)	2.8%(-0.7%, 6.4%)	-14.5%(-21.8%, -7.1%)
	Any Ocular Serious AE	6.3%(1.1%, 11.5%)	5.6%(2.8%, 8.3%)	0.9%(-0.4%, 2.3%)	-12.8%(-18.5%, -7%)
	Any Severe AE	2.5%(-1.4%, 6.5%)	11.7%(4.6%, 18.7%)	4.7%(0.8%, 8.6%)	-18.9%(-26.4%, -11.3%)
	Any Ocular Severe AE	2.3%(-2.6%, 7.1%)	13.1%(7.5%, 18.6%)	4.9%(2.4%, 7.4%)	-20.2%(-27.1%, -13.4%)
	Any IOP Related AE	0.7%(-4%, 5.4%)	25%(19.5%, 30.6%)	6.5%(3.7%, 9.3%)	-32.2%(-39%, -25.5%)
	≥10 mm Hg IOP Change from Baseline at any visit	3.2%(-1.8%, 8.2%)	20.1%(15%, 25.2%)	4%(1.9%, 6.1%)	-27.3%(-33.9%, -20.7%)
	≥25 mm Hg IOP at any visit	2.6%(-2.4%, 7.5%)	23.5%(18.1%, 28.9%)	4.6%(2.3%, 6.9%)	-30.7%(-37.4%, -24%)
	≥35 mm Hg IOP at any visit	6.6%(1.3%, 11.8%)	4.6%(1.9%, 7.3%)	0.6%(-0.2%, 1.5%)	-11.8%(-17.6%, -6.1%)
	Cataract Surgery in Phakic Subjects	-3.4%(-8%, 1.2%)	43.2%(36.2%, 50.3%)	9.8%(5.6%, 14%)	-49.7%(-57.3%, -42%)
BCVA improvement of ≥10 letters	Any AE	-0.3%(-2.1%, 1.5%)	5.5%(-1.9%, 12.9%)	11%(4.4%, 17.6%)	-16.2%(-20.9%, -11.5%)
	Any Ocular AE	-2.4%(-6.2%, 1.5%)	13.7%(6.1%, 21.3%)	13.1%(7.1%, 19.1%)	-24.4%(-30.5%, -18.3%)
	Any Ocular Serious AE	3.8%(-1.9%, 9.6%)	3.3%(-2.8%, 9.4%)	6.8%(2.4%, 11.3%)	-13.9%(-21.5%, -6.4%)
	Any Ocular Serious AE	9.8%(3.1%, 16.4%)	5.6%(2.8%, 8.3%)	0.9%(-0.4%, 2.3%)	-16.2%(-23.1%, -9.3%)
	Any Severe AE	2.6%(-3%, 8.2%)	8.2%(1.4%, 15.1%)	8.1%(3.4%, 12.7%)	-18.9%(-26.4%, -11.4%)
	Any Ocular Severe AE	4.2%(-2.1%, 10.5%)	11.5%(6.1%, 16.9%)	6.5%(3.4%, 9.6%)	-22.2%(-29.5%, -14.8%)
	Any IOP Related AE	-0.1%(-6.2%, 5.9%)	20.7%(15.6%, 25.9%)	10.8%(7%, 14.6%)	-31.4%(-38.5%, -24.3%)
	≥10 mm Hg IOP Change from Baseline at any visit	2.7%(-3.7%, 9%)	16.1%(11.3%, 20.8%)	8%(4.9%, 11.2%)	-26.8%(-33.9%, -19.6%)
	≥25 mm Hg IOP at any visit	1.4%(-4.8%, 7.7%)	18.9%(13.8%, 23.9%)	9.3%(5.9%, 12.6%)	-29.6%(-36.7%, -22.4%)
	≥35 mm Hg IOP at any visit	8.5%(1.9%, 15.2%)	3.1%(0.7%, 5.5%)	2.2%(0.6%, 3.7%)	-13.8%(-20.6%, -6.9%)
	Cataract Surgery in Phakic Subjects	-10.1%(-16.3%, -4%)	34.7%(27.8%, 41.5%)	18.4%(13%, 23.8%)	-42.9%(-51%, -34.8%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

Table 32: Summary of Risk-Benefit Analysis for Psuedophakic subjects

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 700 N=81	Sham N=98	DEX 700 N=81	Sham N=98	DEX 700 N=81	Sham N=98	DEX 700 N=81	Sham N=98
BCVA improvement of ≥ 15 letters	Any AE			60(74.1%)	73(74.5%)	17(21%)	11(11.2%)	4(4.9%)	14(14.3%)
	Any Ocular AE	4(4.9%)	3(3.1%)	46(56.8%)	52(53.1%)	13(16%)	8(8.2%)	18(22.2%)	35(35.7%)
	Any Serious AE	7(8.6%)	6(6.1%)	19(23.5%)	31(31.6%)	10(12.3%)	5(5.1%)	45(55.6%)	56(57.1%)
	Any Ocular Serious AE	17(21%)	11(11.2%)	2(2.5%)	0(0%)			62(76.5%)	87(88.8%)
	Any Severe AE	7(8.6%)	6(6.1%)	25(30.9%)	32(32.7%)	10(12.3%)	5(5.1%)	39(48.1%)	55(56.1%)
	Any Severe Ocular AE	14(17.3%)	11(11.2%)	7(8.6%)	8(8.2%)	3(3.7%)	0(0%)	57(70.4%)	79(80.6%)
	Any IOP Related AE	13(16%)	10(10.2%)	21(25.9%)	8(8.2%)	4(4.9%)	1(1%)	43(53.1%)	79(80.6%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	14(17.3%)	11(11.2%)	17(21%)	2(2%)	3(3.7%)	0(0%)	47(58%)	85(86.7%)
	≥ 25 mm Hg IOP at any visit	14(17.3%)	11(11.2%)	18(22.2%)	6(6.1%)	3(3.7%)	0(0%)	46(56.8%)	81(82.7%)
	≥ 35 mm Hg IOP at any visit	16(19.8%)	11(11.2%)	5(6.2%)	1(1%)	1(1.2%)	0(0%)	59(72.8%)	86(87.8%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

Table 33: Summary of Population level Risk-Benefit Measures (Safety Population)

Benefit	Risk	Estimates (95% CI)			
		NNT	NNTadj	NNH	BRR
BCVA improvement of ≥15 letters	Any AE	13.9(8,52.9)	16.6(10.2,59.8)	6.1(4.7,8.7)	0.44
	Any Ocular AE	13.9(8,52.9)	19(12,66.2)	3.7(3,5)	0.27
	Any Serious AE	13.9(8,52.9)	15.5(9.6,54.6)	9.9(5.9,31.5)	0.71
	Any Ocular Serious AE	13.9(8,52.9)	14.9(8.8,54.8)	15.4(10.5,28.9)	1.11
	Any Severe AE	13.9(8,52.9)	16.6(10.5,58.1)	6.1(4.2,11.2)	0.44
	Any Ocular Severe AE	13.9(8,52.9)	16.9(10.5,60.2)	5.6(4.2,8.3)	0.4
	Any IOP Related AE	13.9(8,52.9)	20.3(12.8,71.2)	3.2(2.7,3.9)	0.23
	≥10 mm Hg IOP Change from Baseline at any visit	13.9(8,52.9)	18.3(11.3,65.1)	4.1(3.4,5.3)	0.3
	≥25 mm Hg IOP at any visit	13.9(8,52.9)	19.3(12.1,68.3)	3.6(3,4.4)	0.26
	≥35 mm Hg IOP at any visit	13.9(8,52.9)	14.7(8.7,54.2)	19(12.4,41)	1.37
	Cataract Surgery in Phakic Subjects	15.6(8,291.4)	33.2(20.1,539.6)	1.9(1.7,2.2)	0.12
BCVA improvement of ≥10 letters	Any AE	9.4(5.8,25.1)	11.2(7.3,28.4)	6.1(4.7,8.7)	0.65
	Any Ocular AE	9.4(5.8,25.1)	12.8(8.6,31.4)	3.7(3,5)	0.4
	Any Ocular Serious AE	9.4(5.8,25.1)	10.4(6.9,25.9)	9.9(5.9,31.5)	1.06
	Any Ocular Serious AE	9.4(5.8,25.1)	10(6.4,26)	15.4(10.5,28.9)	1.65
	Any Severe AE	9.4(5.8,25.1)	11.2(7.5,27.6)	6.1(4.2,11.2)	0.65
	Any Ocular Severe AE	9.4(5.8,25.1)	11.4(7.6,28.6)	5.6(4.2,8.3)	0.59
	Any IOP Related AE	9.4(5.8,25.1)	13.7(9.2,33.8)	3.2(2.7,3.9)	0.34
	≥10 mm Hg IOP Change from Baseline at any visit	9.4(5.8,25.1)	12.3(8.2,30.9)	4.1(3.4,5.3)	0.44
	≥25 mm Hg IOP at any visit	9.4(5.8,25.1)	13(8.7,32.4)	3.6(3,4.4)	0.38
	≥35 mm Hg IOP at any visit	9.4(5.8,25.1)	9.9(6.3,25.7)	19(12.4,41)	2.03
	Cataract Surgery in Phakic Subjects	12.1(6.2,208.2)	25.8(15.6,385.6)	1.9(1.7,2.2)	0.16

Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. Let $P_{DEX\ 700}$ and P_{SHAM} be proportion of success and Q_{DEX} and Q_{SHAM} be proportion of subjects with adverse event in the DEX 700 and Sham arms respectively. BRR: Benefit-Risk Ratio= $(P_{DEX\ 700} - P_{SHAM}) / (Q_{DEX\ 700} - Q_{SHAM})$. NNT= $1 / (P_{DEX\ 700} - P_{SHAM})$: Number Need to be treated to observe one success. NNTadj= $1 / ((P_{DEX\ 700} - P_{SHAM}) * (1 - (Q_{DEX\ 700} - Q_{SHAM})))$: Number Need to be treated to observe one success without adverse event. NNH= $1 / (Q_{DEX\ 700} - Q_{SHAM})$: Number Needed Harm.

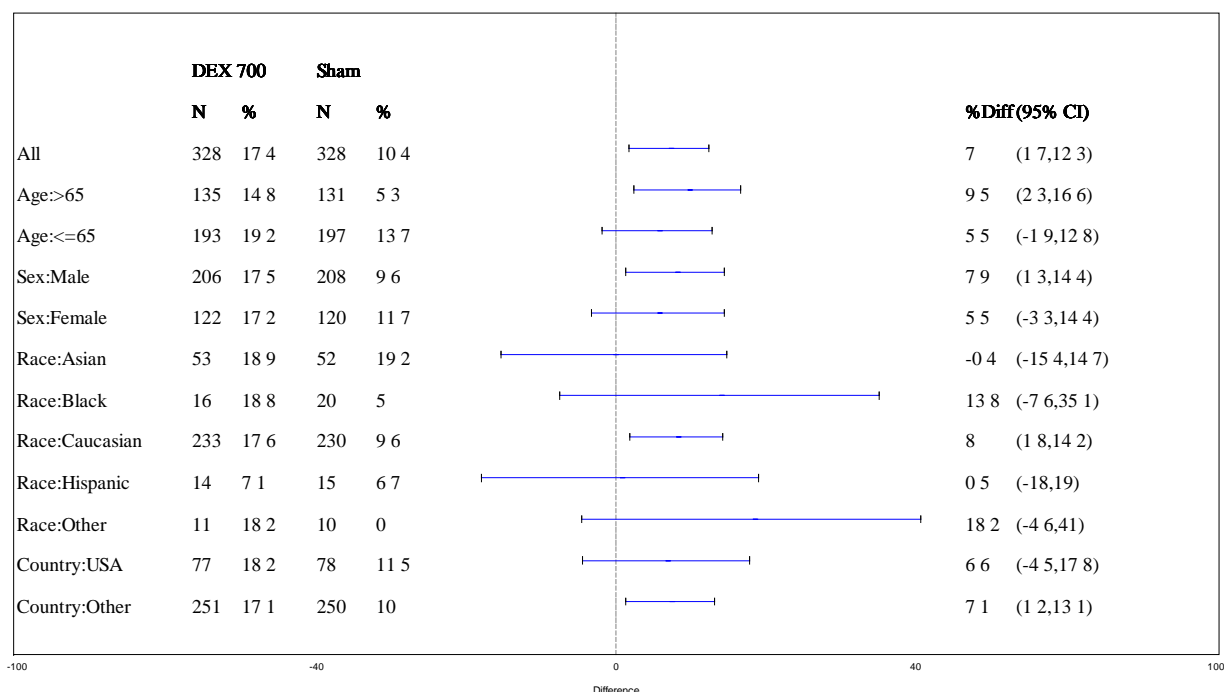
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The summary results for the comparison of the DEX arms and Sham with respect to the proportion of subjects with a 15 letter or more gain from baseline at Month 36 and the mean change from baseline BCVA for subgroup of subjects formed based on baseline demographics and disease characteristics are summarized below. The conclusions for the subgroup analyses are based on the pooled data from the two Phase 3 studies. The subgroup analysis results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Unless stated otherwise, all analyses are performed on the ITT population with LOCF used to impute missing data.

4.1 Age Gender Race and Country

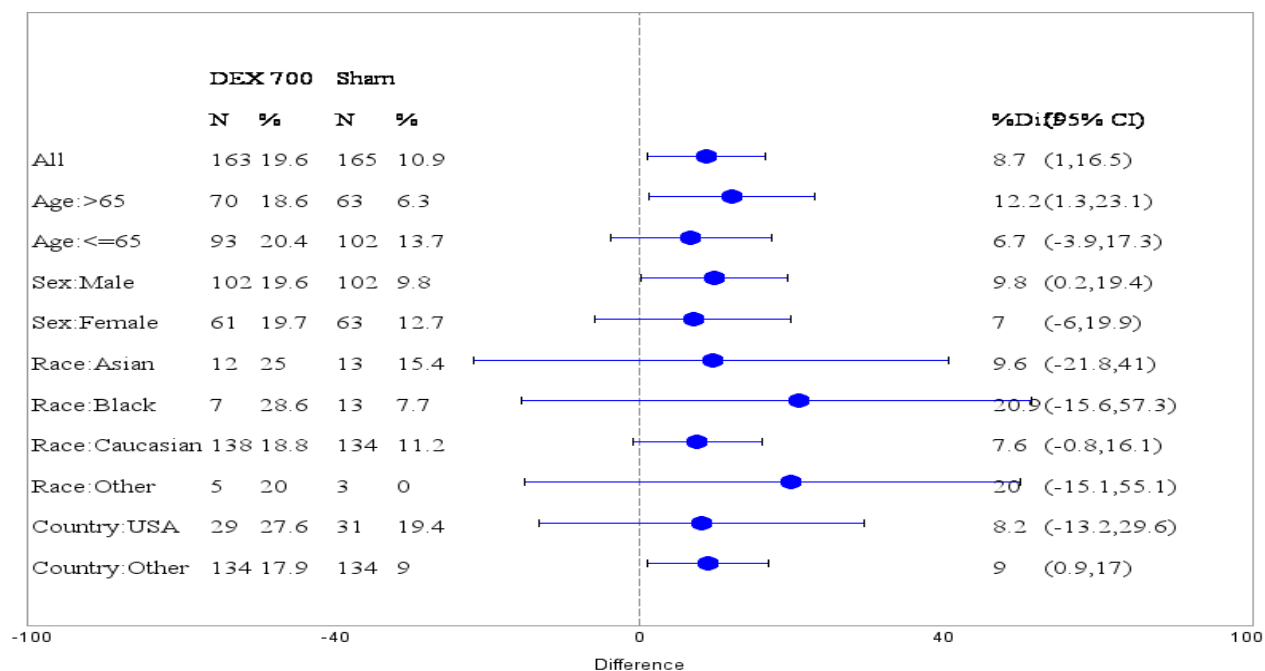
Overall, the subgroup analysis results based on baseline demographics were consistent with the primary efficacy analysis results.

Figure 9: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Pooled)



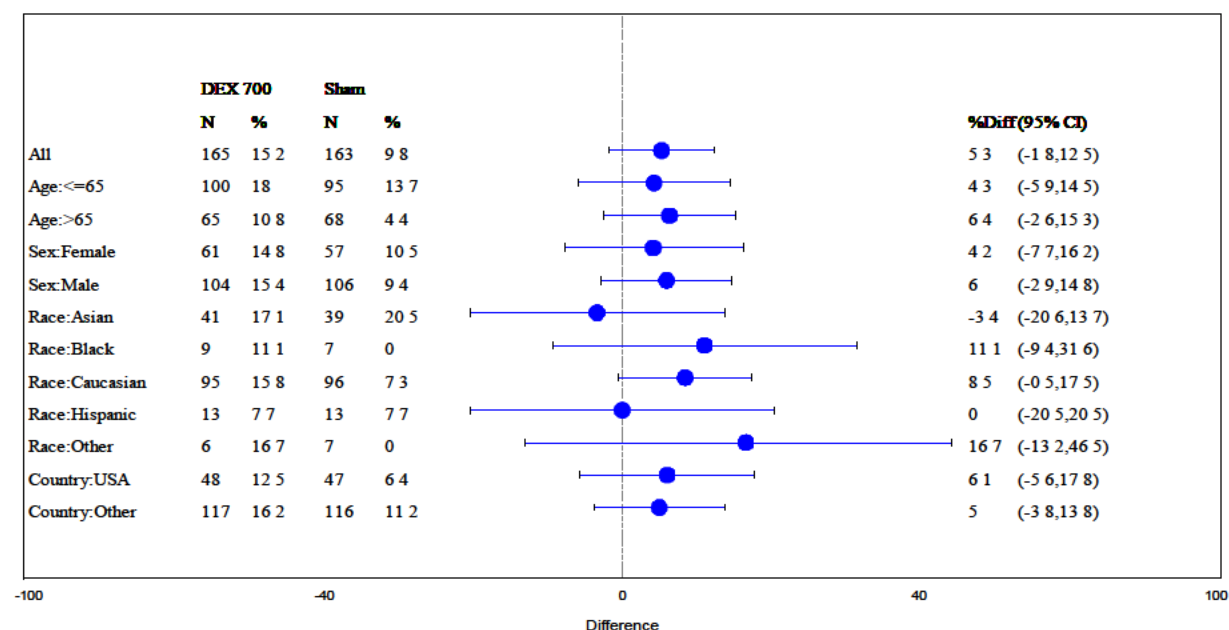
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 10: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 10)



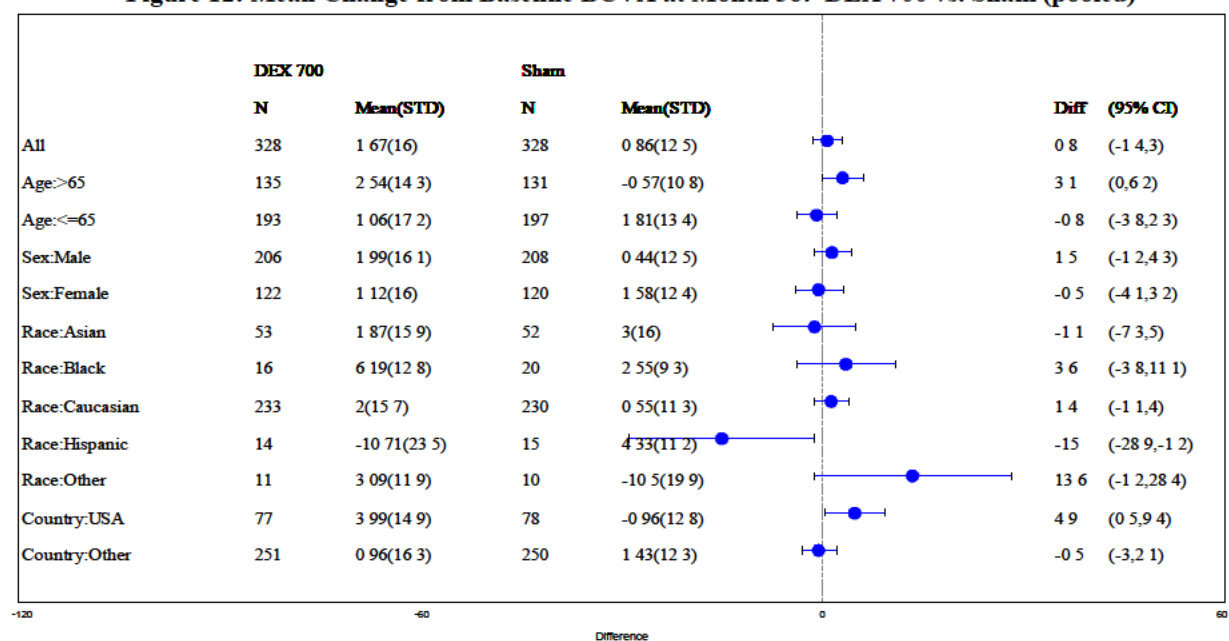
Source: Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

Figure 11: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 11)



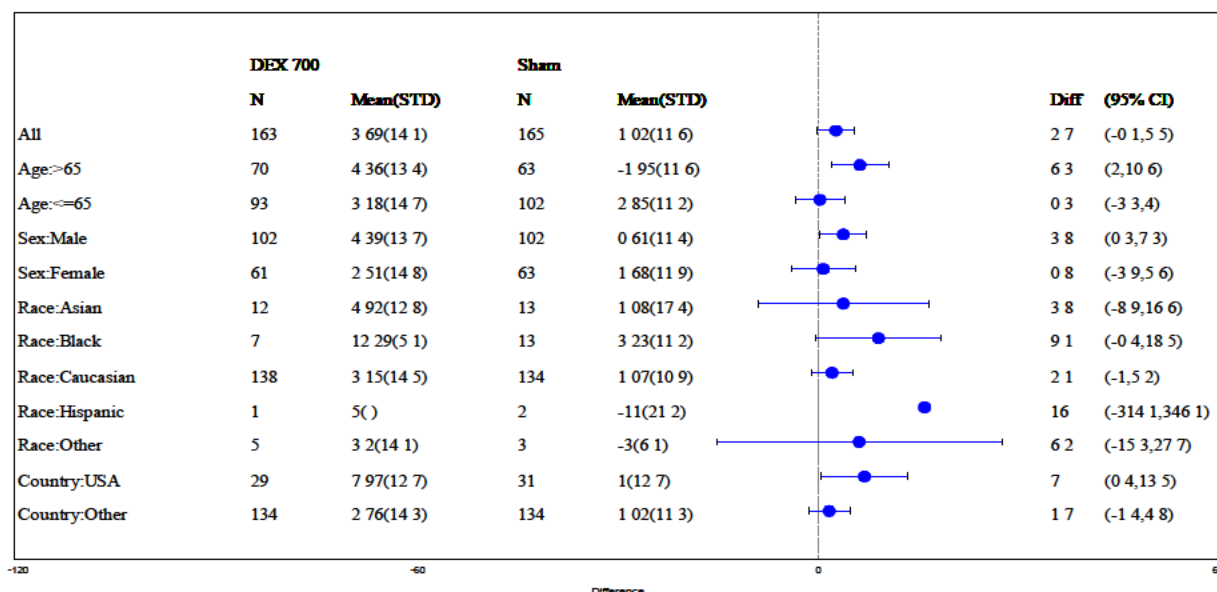
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 12: Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (pooled)



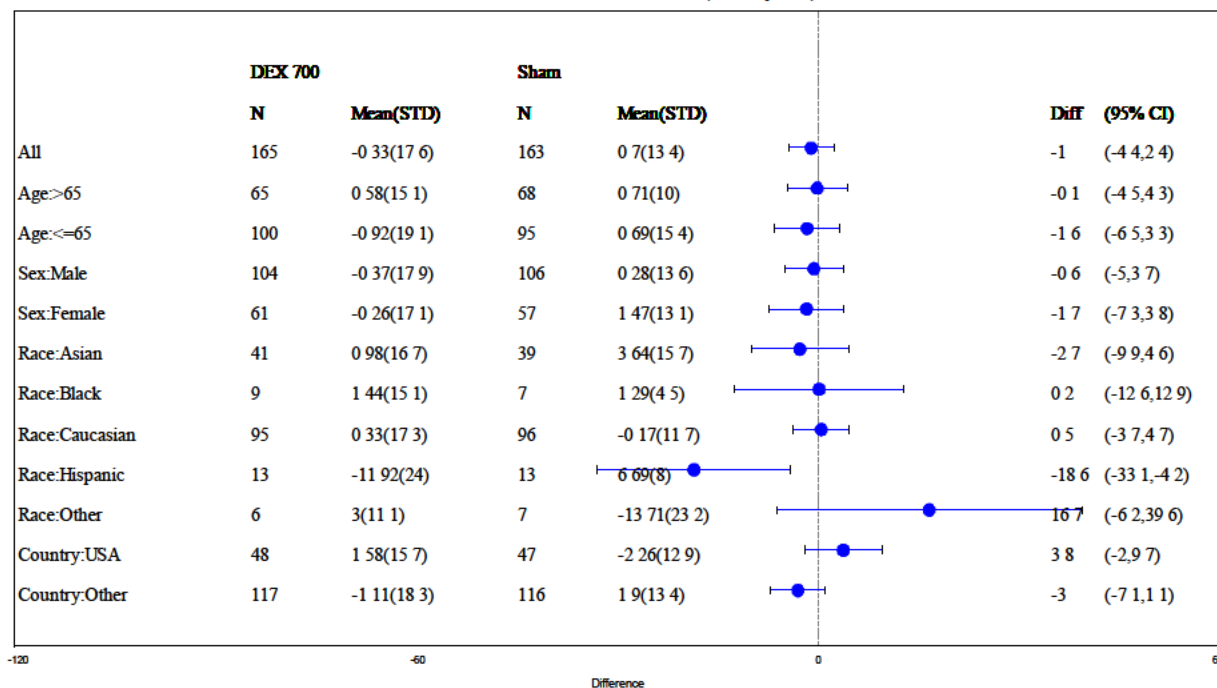
Source: Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

Figure 13: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Study 10)



Source: Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

Figure 14: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Study 11)



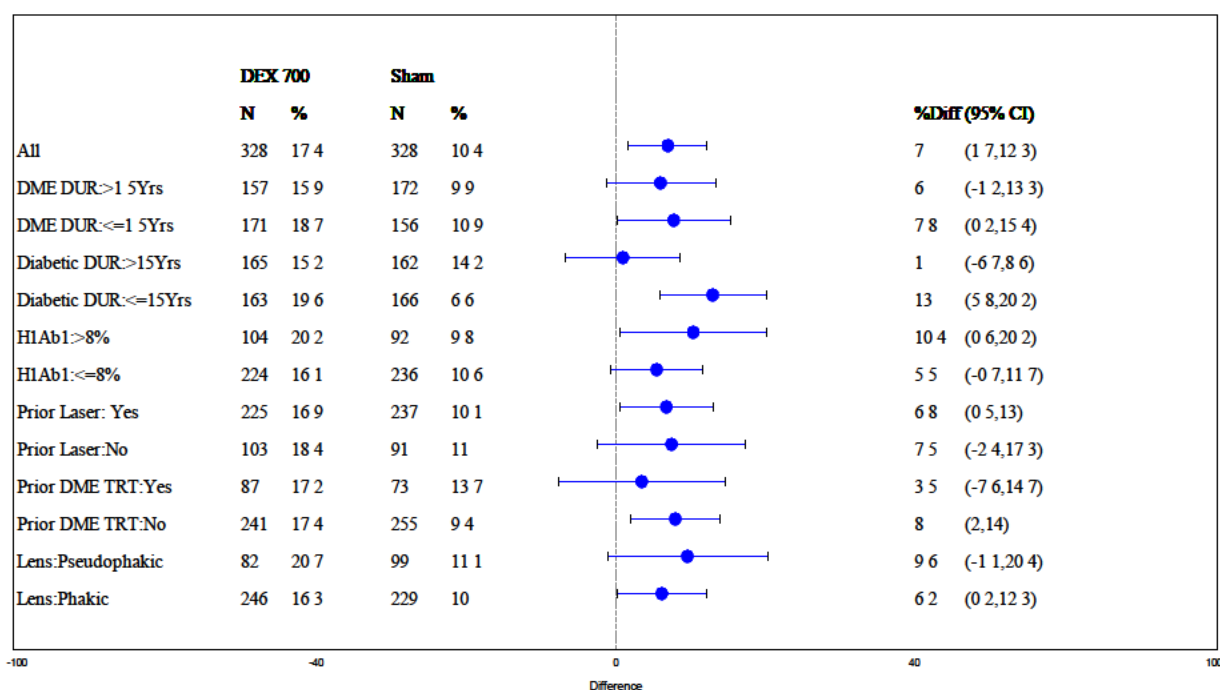
Source: Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

4.2 Other Special/Subgroup Populations

Additional subgroup analyses for subgroups formed based on duration of diabetes (≤ 15 years versus > 15 years), duration of DME (≤ 1.5 years versus > 1.5 years), baseline HbA1c ($\leq 8\%$ versus $> 8\%$), prior laser treatment (yes versus no), any prior treatment (yes versus no) and lens status at baseline (phakic study eye versus pseudophakic study eye) are summarized below.

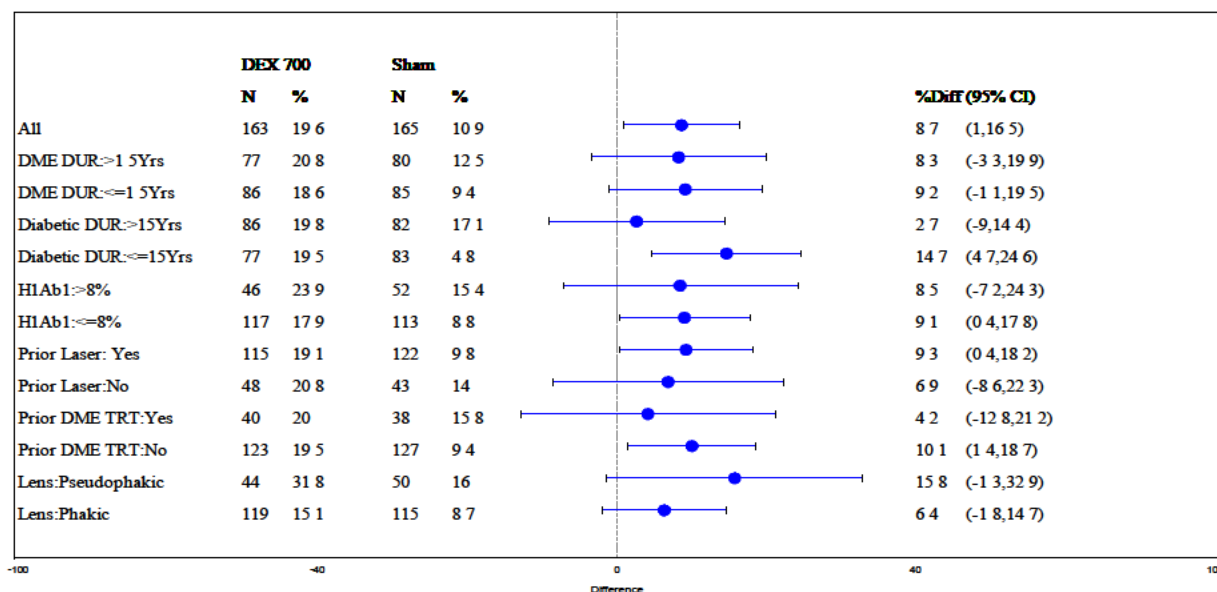
Here also, the subgroup analysis results were consistent with the primary efficacy analysis results. Note that the DME duration was calculated as a difference between dates of DME onset and randomization divided by 30 and rounded to the nearest integer. If both date and month were missing, June 30 was imputed; and if only date was missing 15 was imputed.

Figure 15: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Pooled)



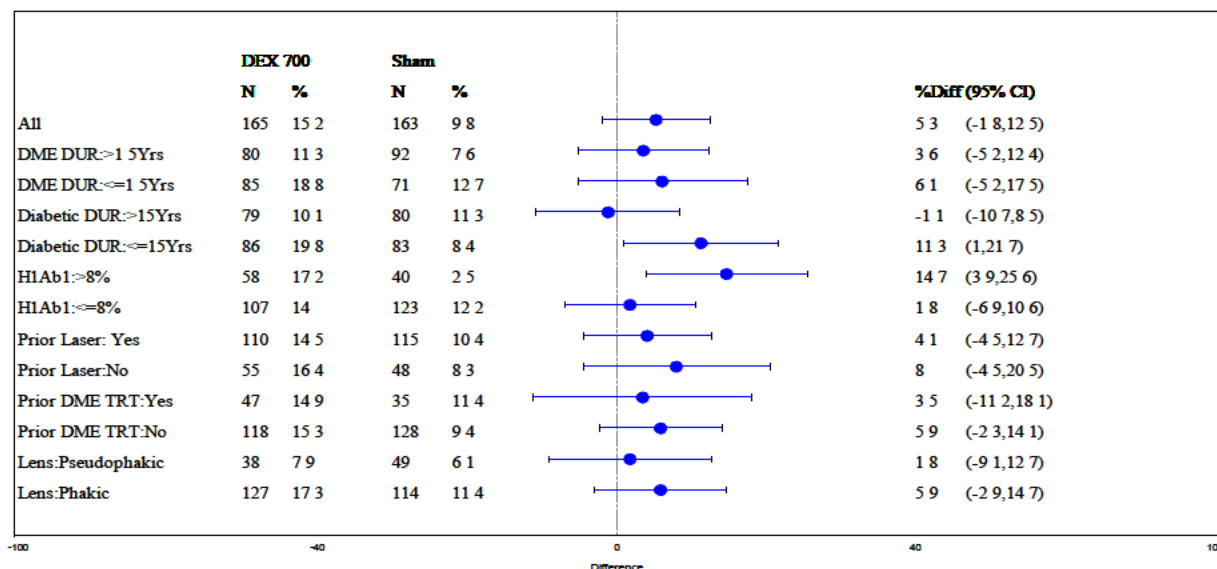
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 16: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 10)



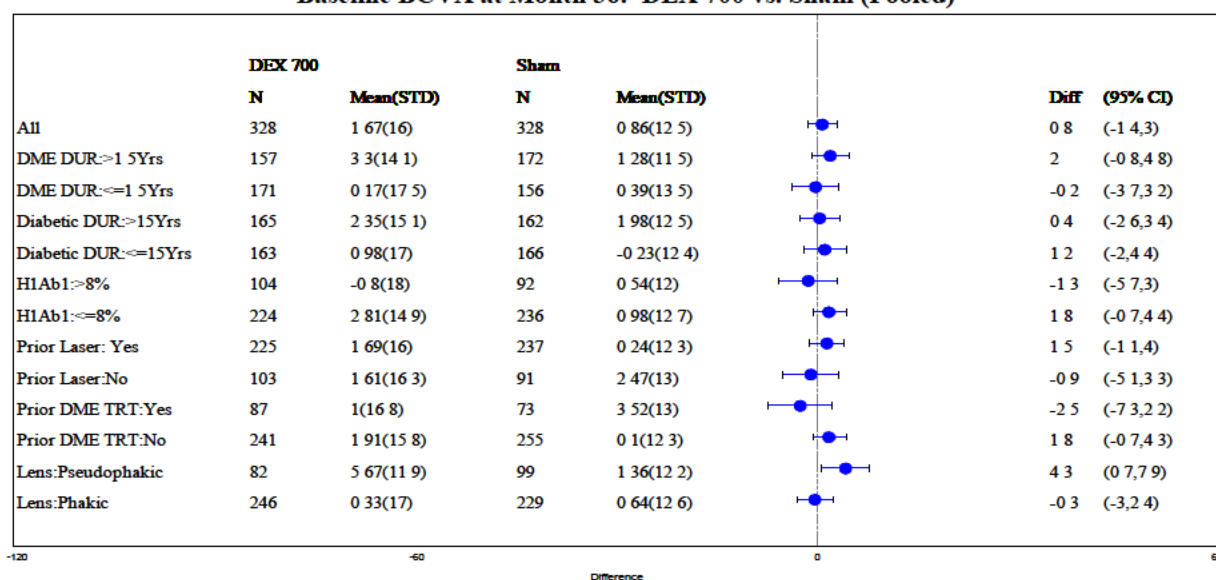
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 17: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 700 vs. Sham (Study 11)



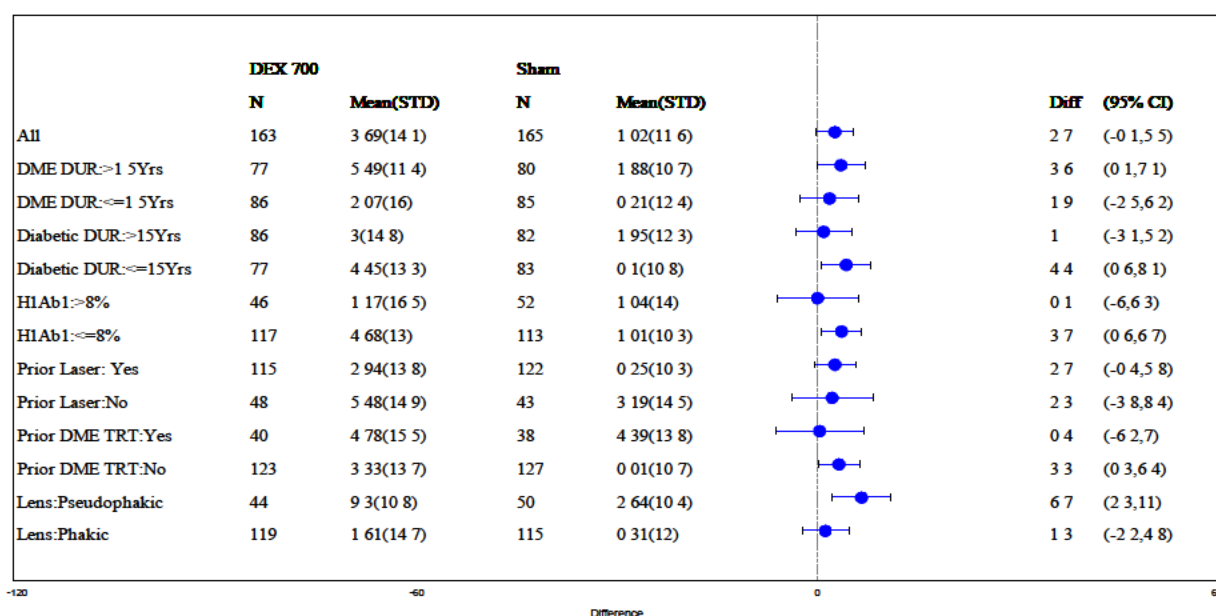
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 18: Additional Subgroup Analysis by Baseline Disease Characteristics for the Mean Change from Baseline BCVA at Month 36: DEX 700 vs. Sham (Pooled)



Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

Figure 19: Additional Subgroup Analysis by Baseline Disease Characteristics for the Mean Change from Baseline BCVA at 3 Years: DEX 700 vs. Sham (Study 10)



Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

	DEX 700		Sham			
	N	Mean(STD)	N	Mean(STD)		Diff (95% CI)
All	165	-0.33(17.6)	163	0.7(13.4)		-1 (-4.2, 4)
DME DUR:>1.5Yrs	80	1.19(16.1)	92	0.77(12.2)		0.4 (-3.8, 4.7)
DME DUR:<=1.5Yrs	85	-1.75(18.9)	71	0.61(14.9)		-2.4 (-7.8, 3.1)
Diabetic DUR:>15Yrs	79	1.65(15.4)	80	2.01(12.7)		-0.4 (-4.8, 4.1)
Diabetic DUR:<=15Yrs	86	-2.14(19.3)	83	-0.57(14)		-1.6 (-6.7, 3.6)
H1Ab1:>8%	58	-2.36(19.2)	40	-0.1(8.8)		-2.3 (-8.7, 4.2)
H1Ab1:<=8%	107	0.78(16.6)	123	0.96(14.6)		-0.2 (-4.2, 3.9)
Prior Laser: Yes	110	0.39(17.9)	115	0.23(14.1)		0.2 (-4.1, 4.4)
Prior Laser:No	55	-1.76(16.8)	48	1.83(11.6)		-3.6 (-9.3, 2.1)
Prior DME TRT:Yes	47	-2.21(17.3)	35	2.57(12.1)		-4.8 (-11.6, 2)
Prior DME TRT:No	118	0.42(17.7)	128	0.19(13.7)		0.2 (-3.7, 4.2)
Lens:Pseudophakic	38	1.47(11.9)	49	0.06(13.9)		1.4 (-4.2, 7)
Lens:Phakic	127	-0.87(18.9)	114	0.97(13.2)		-1.8 (-6.2, 3)

5 SUMMARY AND CONCLUSIONS

Besides the removal of the 68 subjects from site 2707 in Study 2062070-11, and the presence of substantial missing data in both studies, two major statistical issues were encountered in this review. The first was regarding subjects who received a rescue (escape) therapy. During the study period, a total of 132 subjects received escape therapy (Table 20). Among these 132 subjects, 12 subjects (6 in the DEX 700, 2 in DEX 350 and 4 in the Sham arm) were treated as treatment successes in the primary efficacy analysis in contradiction with section 5.2.2 of the study protocol. Section 5.2.2 of the study protocol clearly stated that subjects who received a rescue therapy would be treated as treatment failures.

Page 45 of 93

efficacy and *safety*. Additionally, at the Type C meeting in September 2011, the agency argued that, an earlier treatment success is not necessarily a good indicator of a later success. Consequently, the agency recommended that for indication of DME, the treatment effect of a test product be demonstrated at a time point of at least *36 month or later*. Thus, technically, the applicant's re-defined primary efficacy endpoint is in line with the agency's recommendation. However because of the aforementioned missing data problem and the concern with the timing of the amendment, in this review, efficacy results evaluated at both Month 36 and Month 39/final (Month 39-or-earlier) will be presented with slightly more emphasis given to the results at Month 36.

5.2 Collective Evidence

There were more subjects in the DEX 700 arm who gained at least 15 letters in BCVA from baseline at Month 36 compared to subjects in the Sham arm in study 2062070-10. However, there was no statistically significant difference between DEX 700 and Sham in the proportion of subjects who gained at least 15 letters in BCVA from baseline at Month 36 in study 2062070-11. In both studies, the proportion of subjects who gained at least 15 letters in BCVA from baseline at Month 39/final visit was higher in the DEX arm compared to the Sham arm. There was no statistically significant difference between DEX 700 and Sham in the mean change from baseline BCVA both at the Month 36 and Month 39/final visits. The estimated difference in fact was negative *favoring* the Sham arm.

Similar to the original review, the two studies highlighted the safety issues associated with the study treatments. Two of the prominent adverse events associated with the study treatment were cataract formation and IOP related adverse events. The IOP-related adverse events included elevated IOP, ocular hypertension and glaucoma. A substantially large proportion of subjects in the two study treatments had IOP-related adverse events and required cataract surgery compared to the subjects randomized to the Sham arm. There were also more deaths in the two DEX arms compared to the Sham arm, although the applicant reported the deaths as not related to study treatment. The risk-benefit analysis showed that the both DEX arms had a less than favorable safety profile.

5.3 Conclusions and Recommendations

Because the two studies showed a very modest treatment effect favoring the DEX 700 arm and that the risk of cataract surgery and IOP related adverse events was significantly higher in the DEX 700 arm, this reviewer does not recommend the approval of this drug for the (b) (4) treatment of Diabetic Macular Edema (DME). Limiting the indication to subjects who already had cataract surgery or are scheduled to have one might reduce the treatment induced risk of cataract formation leading to surgery. Therefore, from a safety perspective, the agency's proposed limited indication, the treatment of DME for subjects who are either Pseudophakic or Phakic subjects who are scheduled for cataract surgery, is acceptable. For baseline Pseudophakic subjects, there was no statistically significant difference between DEX 700 and Sham in the proportion of subjects with a 15 letter or more gain from baseline BCVA at 3 years. There was also no data in the submission to support the efficacy and safety of subjects who are *scheduled* to undergo cataract surgery. The subsequent recommendation for approval of the limited indication therefore should be done based on clinical grounds.

6 Appendix A: Efficacy and Safety Summary Excluding Site 2707

Table 34: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by study Visit (ITT LOCF)

Visit	DEX700 N=163	DEX350 N=166	Sham N=165	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207010					
Month 1.5	20(12.3%)	18(10.8%)	6(3.6%)	8.6%(2.8%,14.4%)	7.2%(1.7%,12.7%)
Month 3	23(14.1%)	23(13.9%)	10(6.1%)	8%(1.6%,14.5%)	7.8%(1.4%,14.2%)
Month 4.5	25(15.3%)	21(12.7%)	11(6.7%)	8.7%(2%,15.4%)	6%(-0.3%,12.3%)
Month 6	23(14.1%)	17(10.2%)	13(7.9%)	6.2%(-0.5%,13%)	2.4%(-3.8%,8.5%)
Month 7.5	26(16%)	26(15.7%)	11(6.7%)	9.3%(2.5%,16.1%)	9%(2.3%,15.7%)
Month 9	31(19%)	30(18.1%)	12(7.3%)	11.7%(4.5%,19%)	10.8%(3.7%,17.9%)
Month 10.5	26(16%)	29(17.5%)	11(6.7%)	9.3%(2.5%,16.1%)	10.8%(3.9%,17.7%)
Month 12	22(13.5%)	25(15.1%)	13(7.9%)	5.6%(-1%,12.3%)	7.2%(0.4%,14%)
Month 15	25(15.3%)	27(16.3%)	10(6.1%)	9.3%(2.7%,15.9%)	10.2%(3.5%,16.9%)
Month 18	27(16.6%)	16(9.6%)	15(9.1%)	7.5%(0.3%,14.7%)	0.5%(-5.7%,6.8%)
Month 21	25(15.3%)	25(15.1%)	12(7.3%)	8.1%(1.3%,14.9%)	7.8%(1.1%,14.5%)
Month 24	21(12.9%)	25(15.1%)	15(9.1%)	3.8%(-3%,10.6%)	6%(-1%,13%)
Month 27	31(19%)	32(19.3%)	18(10.9%)	8.1%(0.4%,15.8%)	8.4%(0.7%,16%)
Month 30	25(15.3%)	33(19.9%)	16(9.7%)	5.6%(-1.5%,12.8%)	10.2%(2.6%,17.7%)
Month 33	34(20.9%)	29(17.5%)	16(9.7%)	11.2%(3.5%,18.9%)	7.8%(0.4%,15.1%)
Month 36	32(19.6%)	33(19.9%)	18(10.9%)	8.7%(1%,16.5%)	9%(1.3%,16.7%)
Month 39	34(20.9%)	31(18.7%)	19(11.5%)	9.3%(1.4%,17.3%)	7.2%(-0.5%,14.8%)
Study 206207011					
	DEX700 N=165	DEX350 N=158	Sham N=163	DEX 700 vs. Sham	DEX 350 vs. Sham
Month 1.5	15(9.1%)	18(11.4%)	2(1.2%)	7.9%(3.2%,12.6%)	10.2%(4.9%,15.4%)
Month 3	18(10.9%)	21(13.3%)	5(3.1%)	7.8%(2.4%,13.3%)	10.2%(4.3%,16.1%)
Month 4.5	19(11.5%)	16(10.1%)	7(4.3%)	7.2%(1.4%,13%)	5.8%(0.2%,11.5%)
Month 6	14(8.5%)	8(5.1%)	6(3.7%)	4.8%(-0.3%,9.9%)	1.4%(-3.1%,5.9%)
Month 7.5	21(12.7%)	16(10.1%)	14(8.6%)	4.1%(-2.5%,10.8%)	1.5%(-4.8%,7.9%)
Month 9	22(13.3%)	19(12%)	12(7.4%)	6%(-0.6%,12.5%)	4.7%(-1.8%,11.1%)
Month 10.5	21(12.7%)	17(10.8%)	14(8.6%)	4.1%(-2.5%,10.8%)	2.2%(-4.3%,8.6%)
Month 12	19(11.5%)	15(9.5%)	16(9.8%)	1.7%(-5%,8.4%)	-0.3%(-6.8%,6.1%)
Month 15	18(10.9%)	20(12.7%)	15(9.2%)	1.7%(-4.8%,8.2%)	3.5%(-3.4%,10.3%)
Month 18	16(9.7%)	13(8.2%)	13(8%)	1.7%(-4.4%,7.9%)	0.3%(-5.7%,6.2%)
Month 21	21(12.7%)	11(7%)	15(9.2%)	3.5%(-3.2%,10.3%)	-2.2%(-8.2%,3.7%)
Month 24	27(16.4%)	13(8.2%)	15(9.2%)	7.2%(0%,14.3%)	-1%(-7.1%,5.2%)
Month 27	23(13.9%)	15(9.5%)	15(9.2%)	4.7%(-2.2%,11.6%)	0.3%(-6.1%,6.7%)
Month 30	27(16.4%)	14(8.9%)	15(9.2%)	7.2%(0%,14.3%)	-0.3%(-6.6%,5.9%)
Month 33	28(17%)	18(11.4%)	14(8.6%)	8.4%(1.2%,15.5%)	2.8%(-3.8%,9.4%)

Month 36	25(15.2%)	21(13.3%)	16(9.8%)	5.3%(-1.8%,12.5%)	3.5%(-3.5%,10.5%)
Month 39	30(18.2%)	24(15.2%)	16(9.8%)	8.4%(0.9%,15.8%)	5.4%(-1.8%,12.6%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

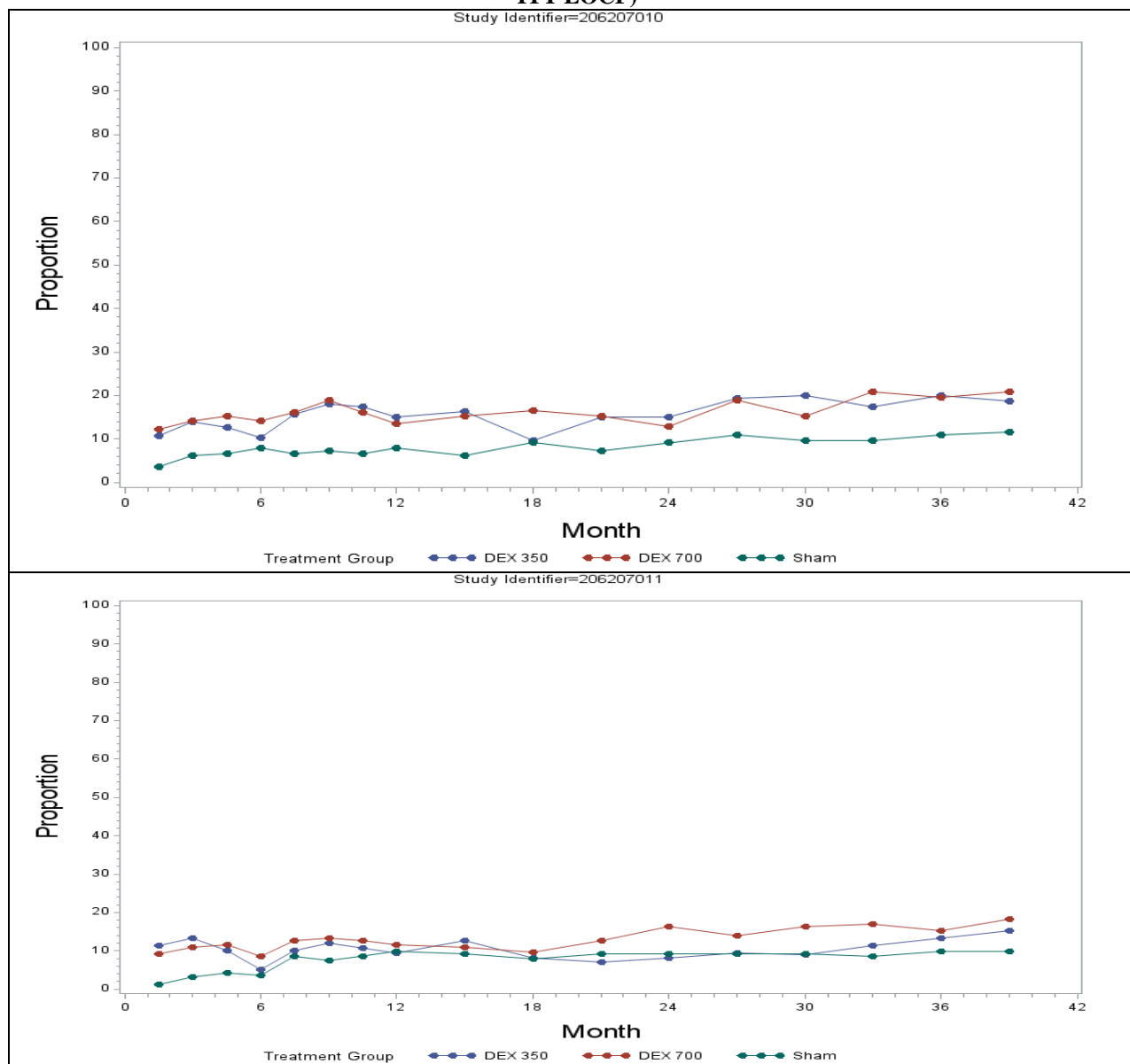
Table 35: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)

Visit	DEX700 N=163	DEX350 N=166	Sham N=165	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207010					
Month 1.5	5.9(7)	5.8(7.3)	2.8(6.5)	3.1(1.6,4.6)	3(1.5,4.5)
Month 3	5.9(7.7)	6(8.4)	2.4(8.5)	3.5(1.7,5.2)	3.5(1.7,5.3)
Month 4.5	4.5(9.8)	5.6(8.1)	2.4(8.5)	2.1(0.1,4.1)	3.2(1.4,5)
Month 6	4.6(9)	3.7(9.1)	2(9)	2.6(0.7,4.6)	1.8(-0.2,3.7)
Month 7.5	5.8(9)	6.2(9.4)	1.6(9.2)	4.2(2.2,6.1)	4.6(2.6,6.6)
Month 9	5.5(10)	6.2(9.8)	1.4(10.2)	4.1(1.9,6.3)	4.8(2.7,7)
Month 10.5	4.2(11.5)	5.2(10.1)	1.2(9.9)	2.9(0.6,5.3)	4(1.8,6.1)
Month 12	3.3(10.7)	3.7(10.4)	1.2(10.2)	2.1(-0.2,4.4)	2.5(0.3,4.8)
Month 15	4.6(10.8)	4.5(11.3)	0.8(10.5)	3.8(1.5,6.1)	3.7(1.4,6.1)
Month 18	2.3(12.4)	2.1(11.3)	1.1(10.9)	1.1(-1.4,3.7)	0.9(-1.5,3.3)
Month 21	4(11.7)	3.4(12.4)	1(10.7)	3(0.6,5.5)	2.4(-0.1,4.9)
Month 24	1.5(14.4)	2.3(14.7)	1.1(11.1)	0.5(-2.3,3.2)	1.2(-1.6,4.1)
Month 27	3.1(14.5)	2.9(14.3)	1.2(11.4)	1.9(-0.9,4.7)	1.7(-1.1,4.5)
Month 30	2.3(14.8)	2.3(15.2)	1.3(11.7)	1(-1.9,3.9)	1(-1.9,4)
Month 33	3.5(14.3)	4.2(13.4)	1(11.4)	2.5(-0.3,5.3)	3.1(0.4,5.8)
Month 36	3.7(14.1)	5.1(12.3)	1(11.6)	2.7(-0.1,5.5)	4.1(1.5,6.7)
Month 39	4.1(13.9)	5(12)	0.8(11.9)	3.3(0.5,6.1)	4.2(1.7,6.8)
Study 206207011					
	DEX700 N=165	DEX350 N=158	Sham N=163	DEX 700 vs. Sham	DEX 350 vs. Sham
Month 1.5	5.9(7.4)	5.7(8.3)	2.4(5.5)	3.6(2.2,5)	3.3(1.8,4.9)
Month 3	6.1(8.2)	6.5(8.5)	2.8(7.2)	3.2(1.6,4.9)	3.7(2,5.4)
Month 4.5	4.8(8.7)	4.3(8.8)	1.9(9.2)	2.9(1,4.9)	2.4(0.4,4.4)
Month 6	3.1(8.8)	1.5(10.9)	1.5(10.3)	1.6(-0.5,3.7)	0(-2.4,2.3)
Month 7.5	4.9(9.8)	3.8(11.9)	2(11)	2.9(0.6,5.2)	1.8(-0.7,4.3)
Month 9	3.9(11.2)	3.4(10.8)	1.5(11.6)	2.4(-0.1,4.8)	1.9(-0.6,4.3)
Month 10.5	1.6(12.3)	3.2(11.5)	1.6(12.3)	0(-2.7,2.7)	1.6(-1,4.2)
Month 12	1.1(12.8)	1.6(11.4)	1.2(12.6)	0(-2.8,2.7)	0.4(-2.2,3.1)
Month 15	1.2(12.8)	2.7(12.4)	1(12.8)	0.2(-2.5,3)	1.7(-1,4.5)
Month 18	-2(14.6)	-0.8(13.8)	0.4(13.2)	-2.4(-5.4,0.6)	-1.3(-4.2,1.7)
Month 21	-1.1(15.3)	0(13)	0.9(13.4)	-2(-5.1,1.1)	-1(-3.8,1.9)
Month 24	-2.1(17.5)	-2(14.3)	0.4(13.5)	-2.5(-5.9,0.9)	-2.4(-5.5,0.6)
Month 27	-0.9(16.4)	-0.5(14.3)	0.4(13.7)	-1.4(-4.7,1.9)	-1(-4,2.1)
Month 30	-1(17.3)	-0.9(14.5)	0.7(13.2)	-1.7(-5.1,1.6)	-1.6(-4.7,1.4)

Month 33	0(17)	-0.3(15.2)	0.5(13.3)	-0.5(-3.8,2.8)	-0.9(-4,2.3)
Month 36	-0.3(17.6)	0(15.7)	0.7(13.4)	-1(-4.4,2.4)	-0.7(-3.9,2.5)
Month 39	0.4(17.5)	1.1(15.2)	0.8(13.6)	-0.5(-3.9,2.9)	0.3(-2.9,3.4)

Source: Reviewer's Analysis. LOCF was used for imputing missing data

Figure 21: Plot of the proportion of subjects with a 15 letter or more gain from baseline (ITT LOCF)



Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

Table 36: Summary of Mean Change from baseline for sites with at least 10 subjects per arm

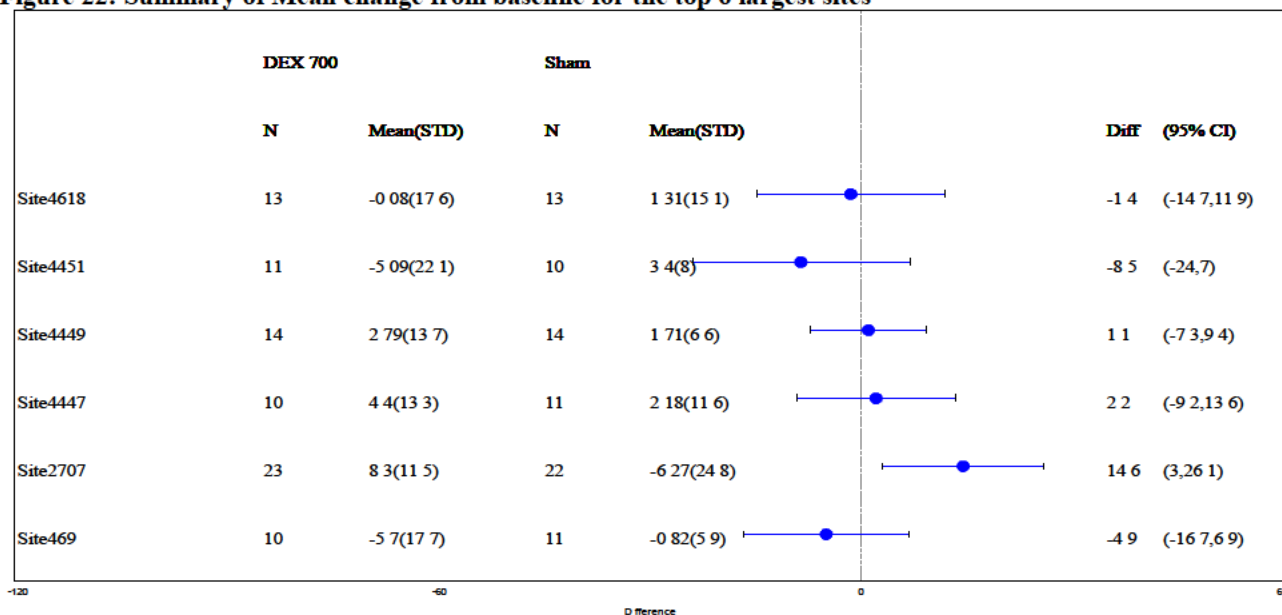
Study	INV	DEX 700 Mean (sd)	DEX 350 Mean (Std)	Sham Mean (Std)	DEX700 vs Sham	DEX350 vs Sham
010	4447	4.4(13.3)	7.6(8.9)	2.2(11.6)	2.2(-9.3,13.7)	5.4(-4,14.9)
010	4451	-5.1(22.1)	11.1(9.1)	3.4(8)	-8.5(-23.9,6.9)	7.7(-0.3,15.7)
010	4449	2.8(13.7)	6(13.1)	1.7(6.6)	1.1(-7.4,9.6)	4.3(-3.9,12.5)
011	469	-5.7(17.7)	1.6(10.7)	-0.8(5.9)	-4.9(-17.8,8.1)	2.5(-5.3,10.2)
011	4618	-0.1(17.6)	1.1(20.2)	1.3(15.1)	-1.4(-14.7,11.9)	-0.2(-14.7,14.3)
011	2707	8.3(11.5)	3.5(14.4)	-6.3(24.8)	14.6(2.7,26.5)	9.8(-2.6,22.1)

Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Table 37: Summary of proportion of subjects with a 15 letter or more improvement from baseline at Month 36 for sites with at least 10 subjects per arm

Study	INV	DEX700	DEX350	Sham	DEX700 vs Sham	DEX350 vs Sham
010	4447	2/10(20%)	1/10(10%)	1/11(9.1%)	10.9%(-19.1%, 41%)	0.9%(-24.3%, 26.1%)
010	4451	3/11(27.3%)	3/10(30%)	1/10(10%)	17.3%(-15%, 49.5%)	20%(-13.9%, 53.9%)
010	4449	2/14(14.3%)	3/14(21.4%)	0/14(0%)	14.3%(-4%, 32.6%)	21.4%(-0.1%, 42.9%)
011	469	1/10(10%)	1/11(9.1%)	0/11(0%)	10%(-8.6%, 28.6%)	9.1%(-7.9%, 26.1%)
011	4618	3/13(23.1%)	4/13(30.8%)	1/13(7.7%)	15.4%(-11.7%, 42.5%)	23.1%(-5.9%, 52%)
011	2707	8/23(34.8%)	7/23(30.4%)	3/22(13.6%)	21.1%(-3%, 45.3%)	16.8%(-6.9%, 40.4%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

Figure 22: Summary of Mean change from baseline for the top 6 largest sites

Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup. (site 2707 is the investigated site)

Table 38: Summary OCT at Baseline for sites with at least 10 subjects per arm

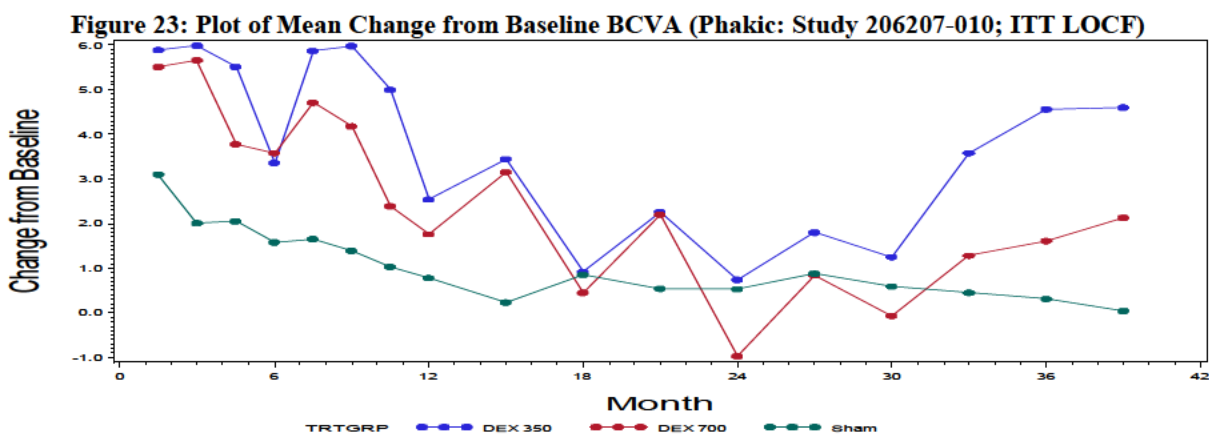
Study	Site	Treatment: Mean (std)			Diff (95% CI)	
		DEX700	DEX350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	4447	403.6(176.5)	513.1(131.4)	475.2(159.3)	-71.6(-226.1,83)	37.9(-95.1,170.9)
011	4449	502(168)	489.2(186.4)	466(119.6)	36(-81.3,153.3)	23.2(-99.5,145.9)
010	4451	422.4(133.2)	423.6(95)	507.2(96.2)	-84.8(-190.6,20.9)	-83.6(-173.4,6.2)
011	0469	456.6(130.1)	540.9(97.5)	365.7(54.4)	90.9(-5.8,187.5)	175.2(100.2,250.2)
011	2707	368.2(126.7)	357.8(128)	312.5(116.4)	55.7(-22.6,134.1)	45.3(-34.3,125)
011	4618	474.8(188.7)	407.4(124.5)	484.9(149.9)	-10.1(-150.7,130.6)	-77.5(-192.5,37.5)

Source: Reviewer's Analysis. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

Table 39: Summary of Mean OCT change from Baseline at Month 36 for sites with at least 10 subjects per arm

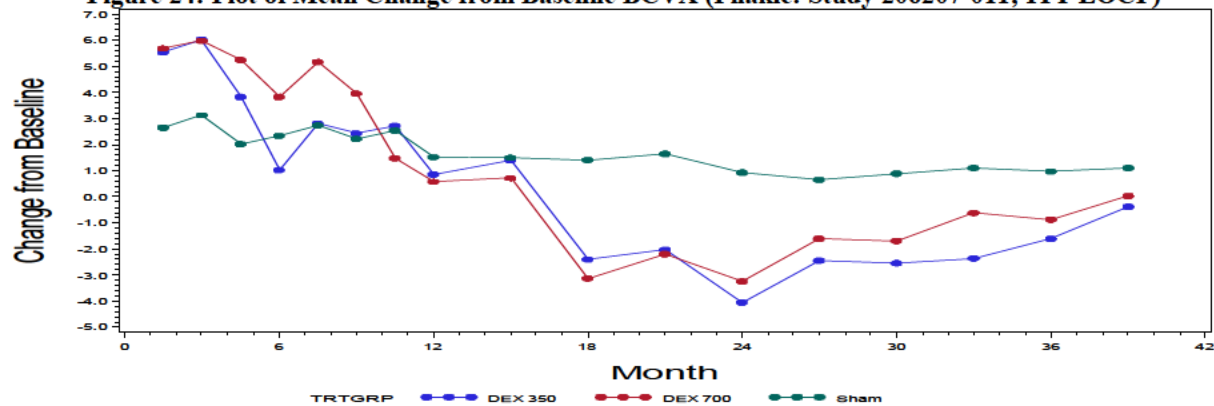
Study	Site	Treatment: Mean (std)			Diff (95% CI)	
		DEX700	DEX350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	4447	-44.7(256.9)	-260.7(164)	-64.7(122.8)	20(-173.4,213.5)	-196(-330.6,-61.3)
010	4449	-53.1(180.5)	-78.6(208.3)	-34.4(78.6)	-18.6(-133.6,96.3)	-44.2(-170.81.5)
010	4451	16.9(105.1)	-81.9(167.7)	-37.4(108.6)	54.3(-43.6,152.2)	-44.5(-178.8,89.8)
011	0469	-94.1(179.4)	-87.7(192.9)	14.7(169.9)	-108.8(-269.1,51.4)	-102.4(-269.7,64.9)
011	2707	-106.9(175.8)	-68.3(169.9)	-14.9(121.2)	-92(-187.1,3.2)	-53.4(-147.9,41.2)
011	4618	-63.5(340.5)	37.2(253.7)	-195.3(199.8)	131.8(-99.3,362.9)	232.6(44.1,421)

Source: Reviewer's Analysis. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.



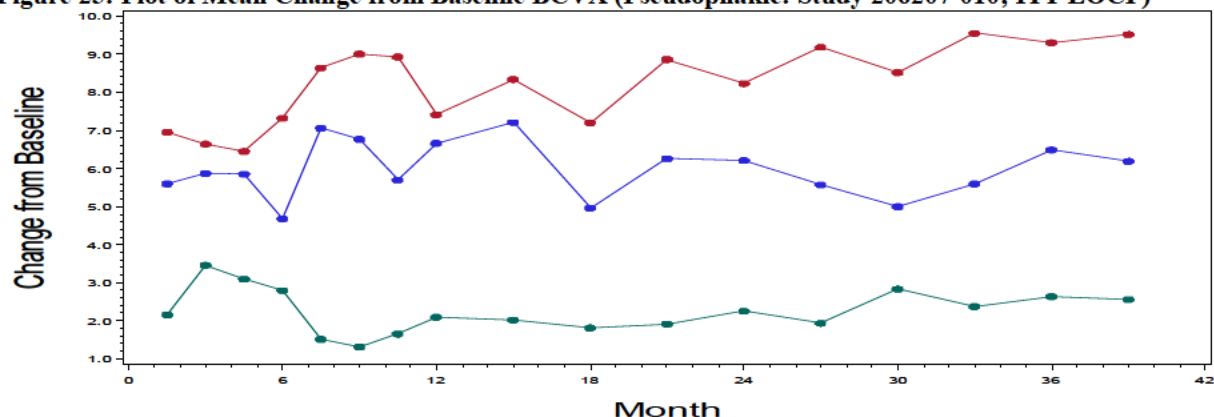
Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 24: Plot of Mean Change from Baseline BCVA (Phakic: Study 206207-011; ITT LOCF)



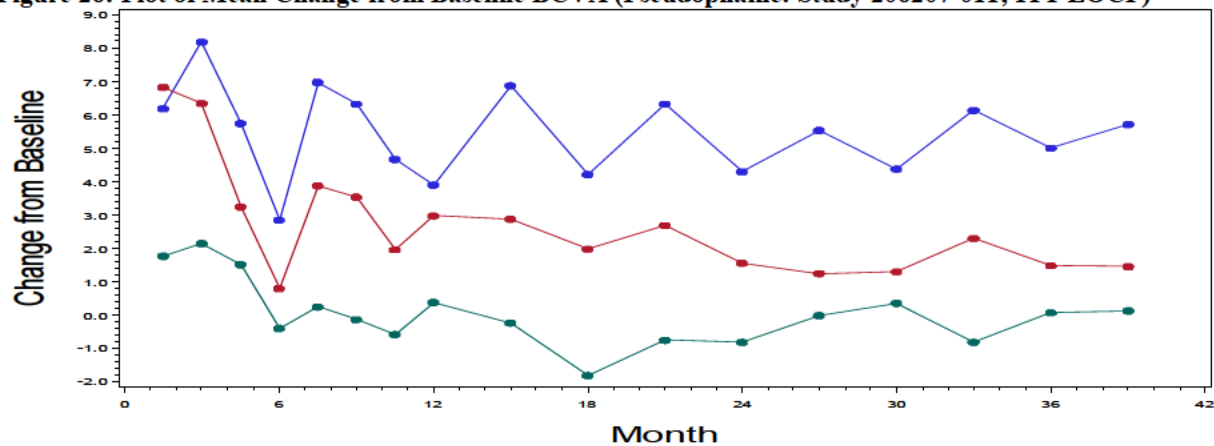
Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 25: Plot of Mean Change from Baseline BCVA (Pseudophakic: Study 206207-010; ITT LOCF)



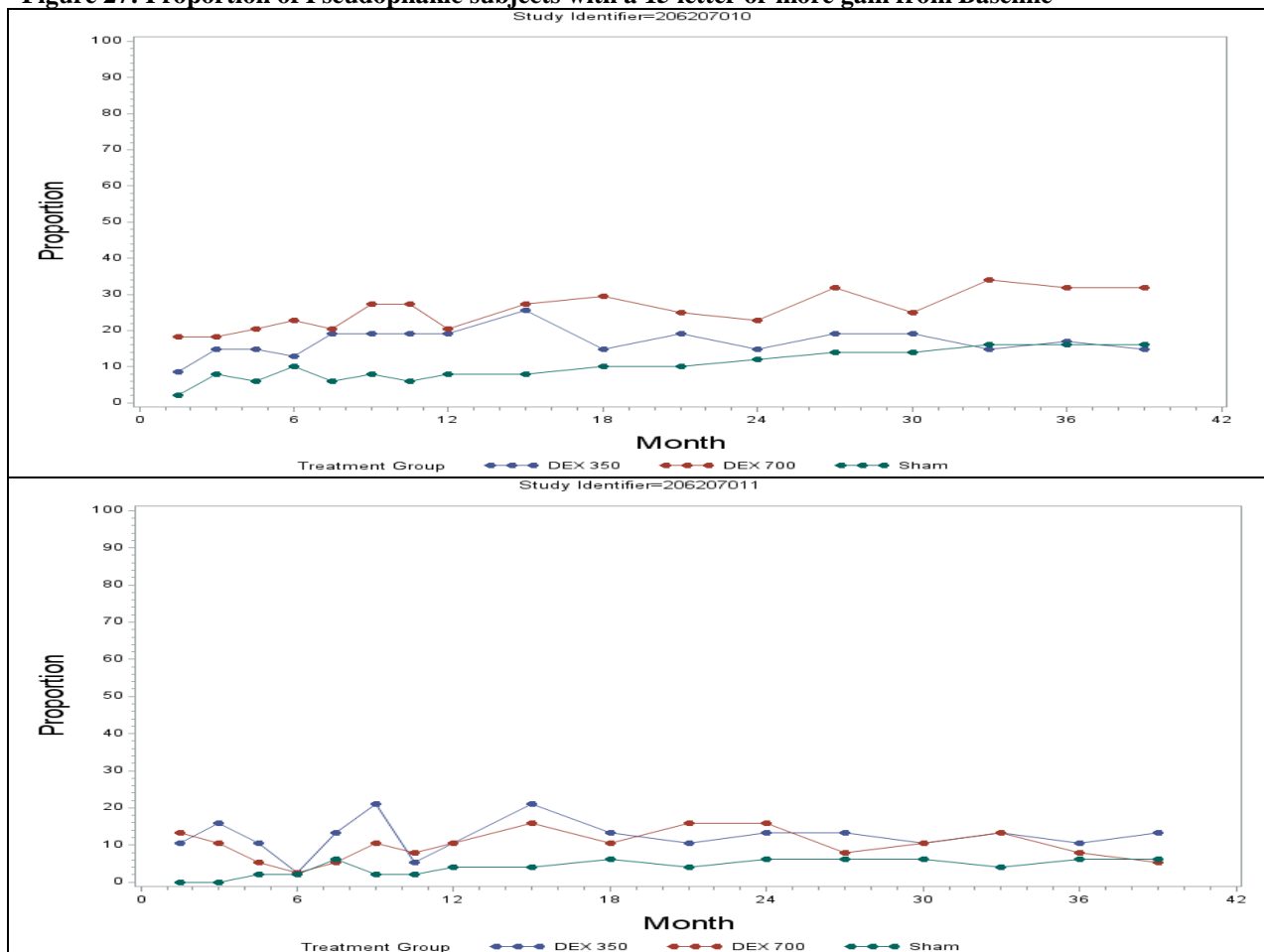
Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 26: Plot of Mean Change from Baseline BCVA (Pseudophakic: Study 206207-011; ITT LOCF)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 27: Proportion of Pseudophakic subjects with a 15 letter or more gain from Baseline



Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures

Table 40: Summary of Study duration by number of Injection by treatment arm (Month)

NUMINJ	DEX 700			DEX 350			Sham			Total		
	Mean (std)	Median	Min	Mean (std)	Median	Min	Mean (std)	Median	Min	Mean (std)	Median	Min
1	12(10.5)	7.5	1.5	15(15)	7.5	1	7.5(7.5)	6	1	10.5(10.5)	6	1
2	21(12)	15	6	21(10.5)	21	9	18(10.5)	12	6	21(10.5)	12	6
3	30(9)	36	12	27(9)	27	12	24(9)	21	15	27(9)	27	12
4	33(6)	36	21	30(6)	36	18	33(6)	36	18	30(6)	36	18
5	36(3)	36	24	33(3)	36	24	36(3)	36	27	36(3)	36	24
6	36(1.5)	36	30	36(1.5)	36	36	36(1.5)	36	36	36(1.5)	36	30
7	39(1)	39	39	39(1)	39	39	39(1)	39	36	39(1)	39	36

Source: Reviewer's Analysis.

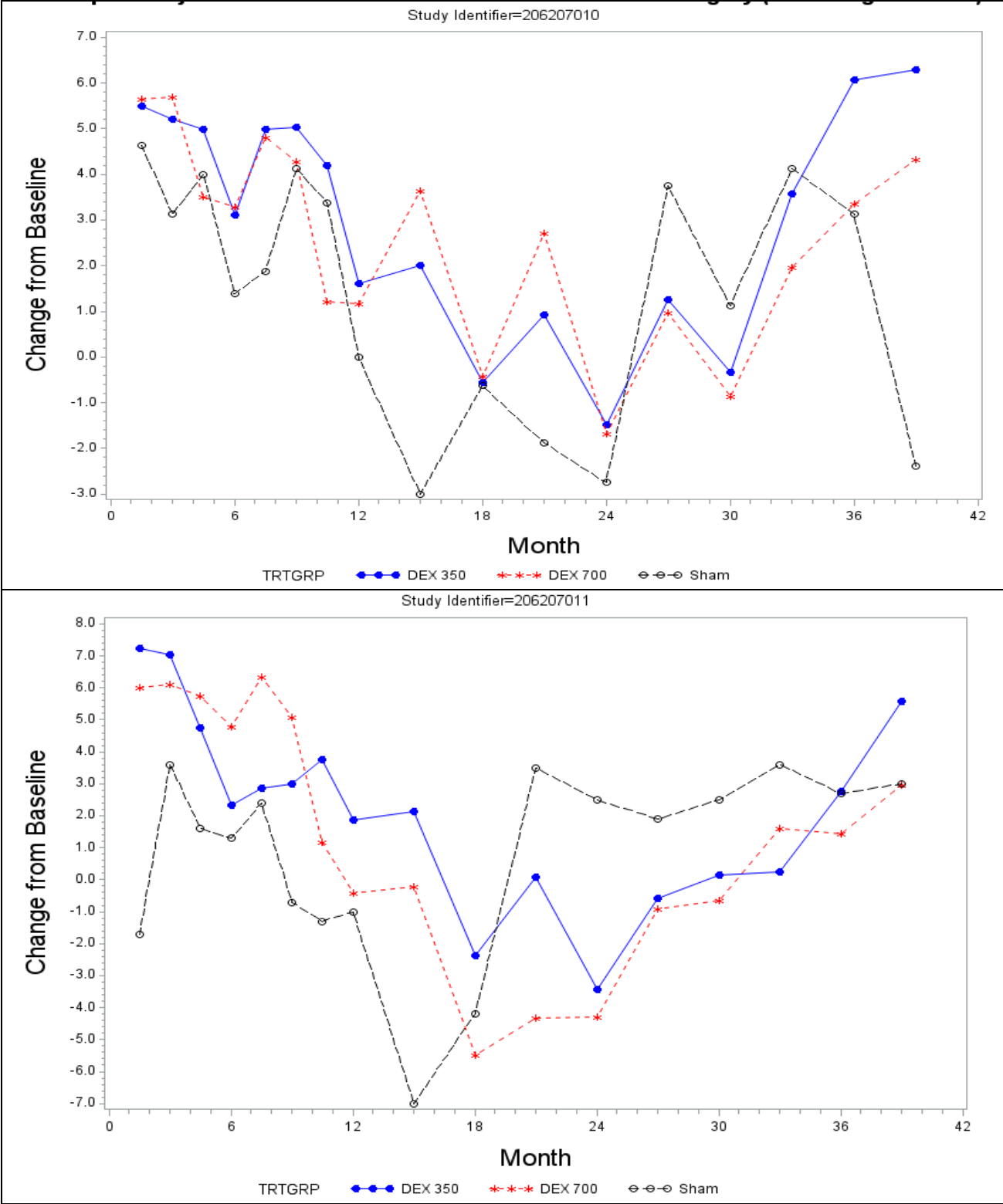
Table 41: Summary of reason for discontinuation by # of injections

NUMINJ	Reason for Discontinuation	DEX 700	DEX 700	Sham
1	Adverse Event	14(35)	12(34.3)	19(19)
	Lack of Efficacy	9(22.5)	4(11.4)	38(38)
	Lost to Follow-up	2(5)	2(5.7)	7(7)
	Other	7(17.5)	5(14.3)	12(12)

	Personal Reasons	2(5)	1(2.9)	18(18)
	Protocol Violation	1(2.5)	1(2.9)	1(1)
2	Adverse Event	15(29.4)	11(26.2)	9(17.6)
	Lack of Efficacy	7(13.7)	8(19)	17(33.3)
	Lost to Follow-up	5(9.8)	2(4.8)	2(3.9)
	Other	5(9.8)	7(16.7)	8(15.7)
	Personal Reasons	1(2)	4(9.5)	3(5.9)
	Protocol Violation	1(2)	0(0)	0(0)
2	Adverse Event	4(11.1)	10(27)	6(15)
	Lack of Efficacy	0(0)	8(21.6)	11(27.5)
	Lost to Follow-up	0(0)	0(0)	4(10)
	Other	4(11.1)	0(0)	3(7.5)
	Personal Reasons	4(11.1)	2(5.4)	3(7.5)
	Protocol Violation	0(0)	1(2.7)	0(0)
4	Adverse Event	7(18.9)	6(15.8)	3(13)
	Lack of Efficacy	4(10.8)	3(7.9)	4(17.4)
	Lost to Follow-up	0(0)	2(5.3)	1(4.3)
	Other	4(10.8)	4(10.5)	1(4.3)
	Personal Reasons	3(8.1)	1(2.6)	0(0)
	Protocol Violation	0(0)	1(2.6)	0(0)
6	Adverse Event	3(6.8)	6(16.2)	1(3.4)
	Lack of Efficacy	1(2.3)	1(2.7)	3(10.3)
	Lost to Follow-up	1(2.3)	3(8.1)	1(3.4)
	Other	1(2.3)	0(0)	1(3.4)
	Personal Reasons	2(4.5)	2(5.4)	1(3.4)
	Protocol Violation	0(0)	0(0)	0(0)
	Adverse Event	2(2.4)	2(2.1)	0(0)
	Lack of Efficacy	0(0)	0(0)	0(0)
	Lost to Follow-up	0(0)	0(0)	0(0)
	Other	2(2.4)	0(0)	0(0)
	Personal Reasons	1(1.2)	0(0)	1(2)
	Protocol Violation	0(0)	0(0)	0(0)
7	Adverse Event	0(0)	0(0)	1(2.9)
	Lack of Efficacy	0(0)	0(0)	0(0)
	Lost to Follow-up	0(0)	0(0)	2(5.7)
	Other	0(0)	0(0)	0(0)
	Personal Reasons	0(0)	0(0)	0(0)
	Protocol Violation	0(0)	0(0)	0(0)

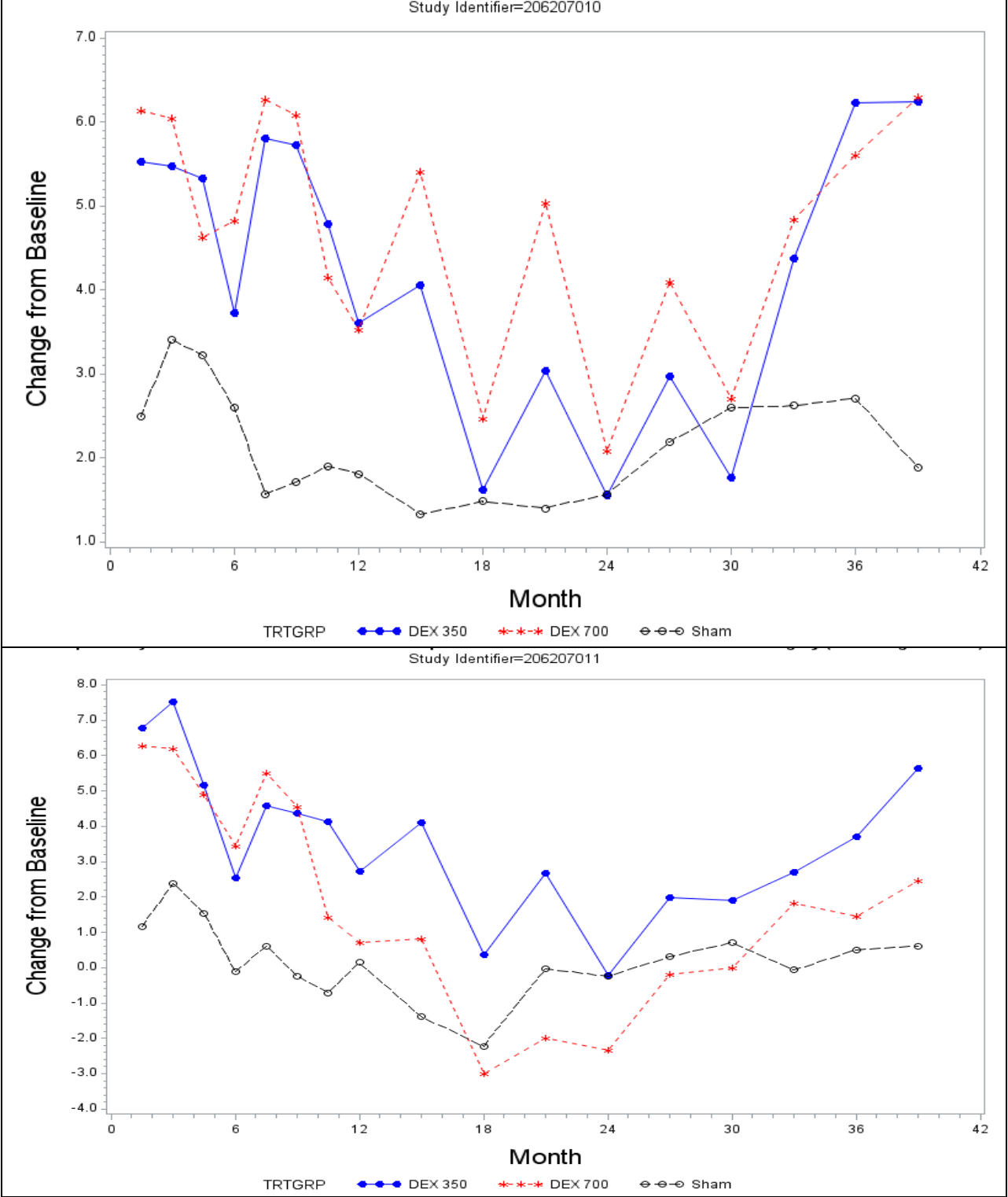
Source: Reviewer's Analysis

Figure 28: Mean BCVA plot for baseline Phakic Subjects Who Underwent Cataract Surgery



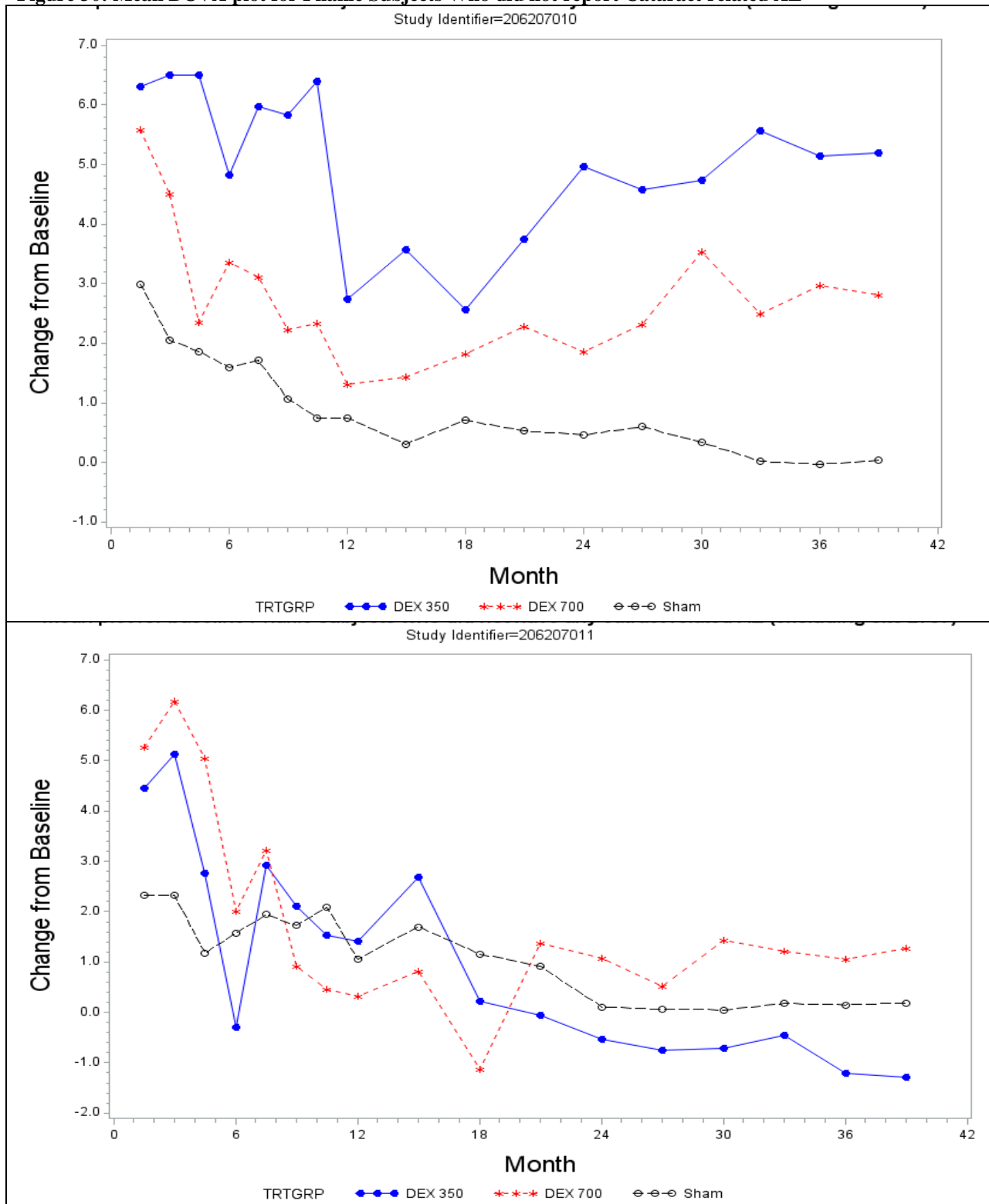
Source: Reviewer's Analysis

Figure 29: Mean BCVA plot for baseline Pseudophakic subjects and Phakic Subjects Who Underwent Cataract Surgery



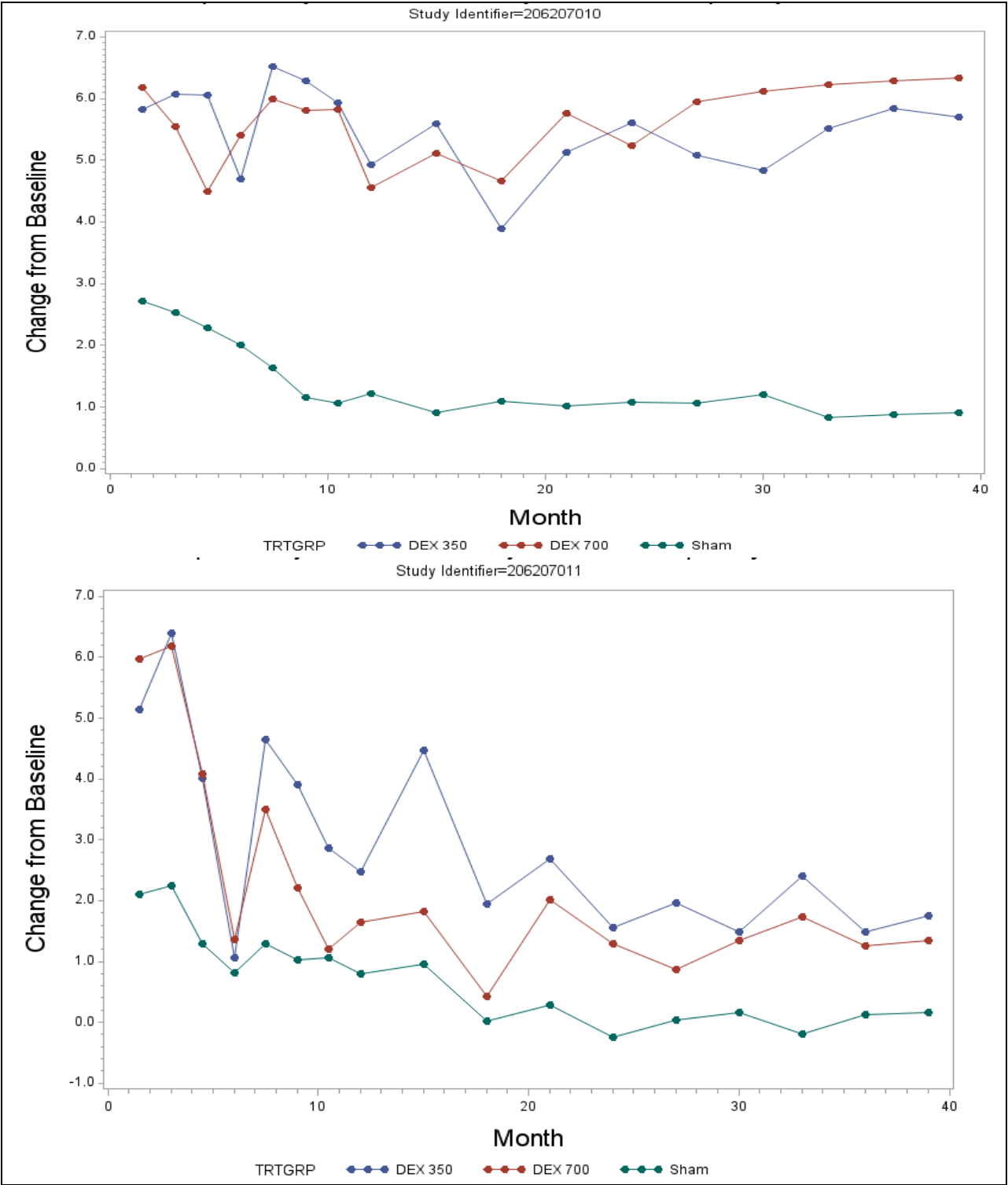
Source: Reviewer's Analysis

Figure 30: Mean BCVA plot for Phakic Subjects Who did not report Cataract related AE



Source: Reviewer's Analysis

Figure 31: Mean BCVA plot for baseline Pseudophakic subjects and Phakic Subjects Who did not report Cataract related AE



Source: Reviewer's Analysis

Table 42: Proportion of subjects with ≥ 15 letters from baseline at Month 39/final for subgroups based on lens status and cataract

Subgroup	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 010					
Pseudophakic (1)	14/44(31.8%)	7/47(14.9%)	8/50(16%)	15.8%(-1.3%,32.9%)	-1.1%(-15.5%,13.3%)
Phakic who had surgery (2)	15/72(20.8%)	15/72(20.8%)	2/8(25%)	-4.2%(-35.6%,27.3%)	-4.2%(-35.6%,27.3%)
(1)+ (2)	29/116(25%)	22/119(18.5%)	10/58(17.2%)	7.8%(-4.8%,20.3%)	1.2%(-10.7%,13.2%)
Phakic no cataract related AE (3)	6/39(15.4%)	8/37(21.6%)	8/98(8.2%)	7.2%(-5.3%,19.8%)	13.5%(-0.9%,27.8%)
(1)+ (3)	20/83(24.1%)	15/84(17.9%)	16/148(10.8%)	13.3%(2.8%,23.8%)	7%(-2.6%,16.6%)
Study 011					
Pseudophakic (1)	2/38(5.3%)	5/38(13.2%)	3/49(6.1%)	-0.9%(-10.6%,8.9%)	7%(-5.6%,19.7%)
Phakic who had surgery (2)	20/76(26.3%)	15/53(28.3%)	1/10(10%)	16.3%(-4.7%,37.4%)	18.3%(-3.9%,40.5%)
(1)+ (2)	22/114(19.3%)	20/91(22%)	4/59(6.8%)	12.5%(2.8%,22.2%)	15.2%(4.5%,25.9%)
no cataract related AE (3)	9/41(22%)	4/52(7.7%)	9/83(10.8%)	11.1%(-3.2%,25.4%)	-3.2%(-13%,6.7%)
1+3	11/79(13.9%)	9/90(10%)	12/132(9.1%)	4.8%(-4.2%,13.9%)	0.9%(-7%,8.8%)
Pooled					
Pseudophakic (1)	16/82(19.5%)	12/85(14.1%)	11/99(11.1%)	8.4%(-2.2%,19%)	3%(-6.6%,12.7%)
Phakic who had surgery (2)	35/148(23.6%)	30/125(24%)	3/18(16.7%)	7%(-11.5%,25.5%)	7.3%(-11.4%,26.1%)
(1)+ (2)	51/230(22.2%)	42/210(20%)	14/117(12%)	10.2%(2.2%,18.2%)	8%(0%,16%)
Phakic no cataract related AE (3)	15/80(18.8%)	12/89(13.5%)	17/181(9.4%)	9.4%(-0.2%,18.9%)	4.1%(-4.2%,12.4%)
(1)+ (3)	31/162(19.1%)	24/174(13.8%)	28/280(10%)	9.1%(2.1%,16.1%)	3.8%(-2.4%,10%)

Source: Reviewer's Analysis

Table 43: Mean change from baseline at baseline at Month 39/final for subgroups based on lens status and cataract

Subgroup	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 010					
Pseudophakic (1)	9.5(10.5)	6.2(10.3)	2.6(10.4)	7(2.7,11.2)	3.6(-0.6,7.8)
Phakic who had surgery (2)	4.3(14.3)	6.3(11.4)	-2.4(21)	6.7(-10.9,24.4)	8.7(-9,26.3)
(1)+ (2)	6.3(13.2)	6.2(11)	1.9(12.3)	4.4(0.4,8.4)	4.4(0.6,8.1)
Phakic No cataract AE (3)	2.7(12.2)	5.1(11.5)	0(12)	2.6(-2,7.3)	5(0.5,9.6)
(1)+ (3)	6.3(11.7)	5.7(10.8)	0.9(11.5)	5.4(2.3,8.6)	4.8(1.8,7.8)
Study 011					
Pseudophakic (1)	1.4(11.5)	5.7(10.9)	0.1(14)	1.3(-4.1,6.8)	5.6(0.3,10.9)
Phakic who had surgery (2)	2.9(17.3)	5.6(13.7)	3(12)	-0.1(-9.2,9.1)	2.6(-6.5,11.7)
(1)+ (2)	2.4(15.6)	5.6(12.5)	0.6(13.6)	1.8(-2.7,6.4)	5(0.7,9.4)

No cataract AE (3)	1.2(16.3)	-1.3(15.7)	0.2(14.4)	1(-5.2,7.3)	-1.4(-6.9,4)
1+3	1.3(14)	1.8(14.2)	0.2(14.2)	1.2(-2.9,5.2)	1.6(-2.3,5.5)
Pooled					
Pseudophakic (1)	5.8(11.6)	6(10.6)	1.4(12.3)	4.4(0.9,7.9)	4.6(1.3,7.9)
Phakic who had surgery (2)	3.6(15.9)	6(12.4)	0.6(16.3)	3(-5.4,11.4)	5.4(-3,13.7)
(1)+(2)	4.4(14.5)	6(11.6)	1.2(12.9)	3.2(0.1,6.2)	4.7(1.9,7.6)
Phakic with no cataract related AE (3)	1.9(14.3)	1.4(14.3)	0.1(13.1)	1.8(-2,5.6)	1.3(-2.3,4.9)
(1)+(3)	3.9(13.1)	3.7(12.8)	0.6(12.8)	3.4(0.8,5.9)	3.1(0.7,5.6)

Source: Reviewer's analysis

Table 44: Proportion of Phakic Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at Month 36 grouped by Cataract Surgery and AE status

Studies	Population	Treatment: N (%)			%Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	Phakic	18/119(15.1%)	25/119(21%)	10/115(8.7%)	6.4%(-1.8%, 14.7%)	12.3% (3.4%, 21.3%)
	<i>Surgery: Yes</i>	13/72(18.1%)	16(22.2%)	2/8(25%)	-6.9%(-38.2%,24.3%)	-2.8%(-34.3%,28.7%)
	<i>Surgery: No</i>	5/47(10.6%)	9/47(19.1%)	8/107(7.5%)	3.2%(-7%,13.3%)	11.7%(-0.6%,24%)
	<i>Cat AE: Yes</i>	12/80(15%)	17/82(20.7%)	3/17 (17.6%)	-2.6%(-22.4%,17.1%)	3.1%(-17%,23.2%)
	<i>Cat AE: No</i>	6/39(15.4%)	8/37(21.6%)	7/98(7.1%)	8.2%(-4.2%,20.7%)	14.5%(0.3%,28.7%)
011	Phakic	22/127(17.3%)	17/120(14.2%)	13/114(11.4%)	5.9%(-2.9%, 14.7%)	2.8% (-5.8%, 11.3%)
	<i>Surgery: Yes</i>	14/76(18.4%)	13/53(24.5%)	1/10(10%)	8.4%(-12.1%,29%)	14.5%(-7.4%, 36.4%)
	<i>Surgery: No</i>	8/51(15.7%)	4/67(6%)	12/104(11.5%)	4.1%(-7.6%, 15.9%)	-5.6%(-13.9%, 2.8%)
	<i>Cat AE: Yes</i>	14/86(16.3%)	13/68(19.1%)	3/31(9.7%)	6.6%(-6.4%,19.6%)	9.4%(-4.5%,23.4%)
	<i>Cat AE: No</i>	8/41(19.5%)	4/52(7.7%)	10/83(12%)	7.5%(-6.5%,21.5%)	-4.4%(-14.4%,5.7%)
Pooled	Phakic	40/246(16.3%)	42/239(17.6%)	23/229(10%)	6.2% (0.2%, 12.3%)	7.5% (1.3%,13.7%)
	<i>Surgery: Yes</i>	27/148(18.2%)	29/125(23.2%)	3/18(16.7%)	1.6%(-16.7%,19.9%)	6.5%(-12.2%,25.3%)
	<i>Surgery: No</i>	13/98(13.3%)	13/114(11.4%)	20/211(9.5%)	3.8%(-4%,11.6%)	1.9%(-5.1%,9%)
	<i>Cat AE: Yes</i>	26/166(15.7%)	30/150(20%)	6/48(12.5%)	3.2%(-7.7%,14%)	7.5%(-3.8%,18.8%)
	<i>Cat AE: No</i>	14/80(17.5%)	12/89(13.5%)	17/181(9.4%)	8.1%(-1.2%,17.5%)	4.1%(-4.2%,12.4%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

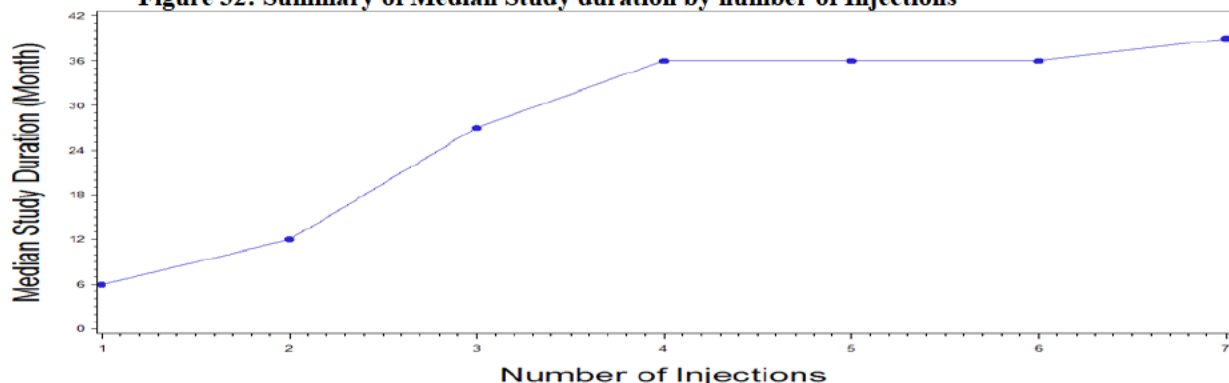
Table 45: Mean Change from baseline BCVA at Month 36 for Phakic subjects by cataract surgery and AE status

Studies	Population	Treatment: Mean std)			Mean Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	Phakic	1.6(14.7)	4.6(13)	0.3(12)	1.3(-2.1,4.8)	4.2(1,7.5)
	<i>Surgery: Yes</i>	3.4(14.7)	6.1(12.5)	3.1(16.8)	0.2(-13.9,14.4)	2.9(-11.2,17)
	<i>Surgery: No</i>	-1.1(14.4)	2.3(13.6)	0.1(11.7)	-1.2(-5.9,3.6)	2.2(-2.4,6.7)
	<i>Cat AE: Yes</i>	1(15.8)	4.4(13.4)	2.1(12.3)	-1(-7.7,5.7)	2.3(-4.2,8.8)
	<i>Cat AE: No</i>	2.8(12.1)	5(12)	0(12)	2.8(-1.8,7.5)	5(0.3,9.7)
011	Phakic	-0.9(18.9)	-1.6(16.8)	1(13.2)	-1.8(-6,2.3)	-2.6(-6.5,1.3)
	<i>Surgery: Yes</i>	1.4(17.6)	2.8(16.3)	2.7(12.1)	-1.3(-10.5,8)	0.1(-9.4,9.5)
	<i>Surgery: No</i>	-4.3(20.5)	-5.1(16.4)	0.8(13.3)	-5.1(-11.4,1.2)	-5.9(-10.6,-1.1)
	<i>Cat AE: Yes</i>	-1.7(20)	-1.9(17.7)	2.8(10.4)	-4.5(-10,1)	-4.7(-10.2,0.7)
	<i>Cat AE: No</i>	1(16.3)	-1.2(15.6)	0.2(14.3)	0.9(-5.3,7)	-1.4(-6.8,4.1)
Pooled	Phakic	0.3(17)	1.5(15.3)	0.6(12.6)	-0.3(-3,2.4)	0.8(-1.7,3.4)
	<i>Surgery: Yes</i>	2.4(16.2)	4.7(14.2)	2.9(13.9)	-0.5(-7.8,6.8)	1.8(-5.5,9.1)
	<i>Surgery: No</i>	-2.8(17.8)	-2(15.7)	0.5(12.5)	-3.2(-7.1,0.7)	-2.5(-5.9,0.9)
	<i>Cat AE: Yes</i>	-0.4(18.1)	1.5(15.8)	2.6(11)	-2.9(-7,1.1)	-1.1(-4.9,2.8)

	Cat AE: No	1.9(14.3)	1.4(14.5)	0.1(13)	1.9(-1.9,5.7)	1.3(-2.3,5)
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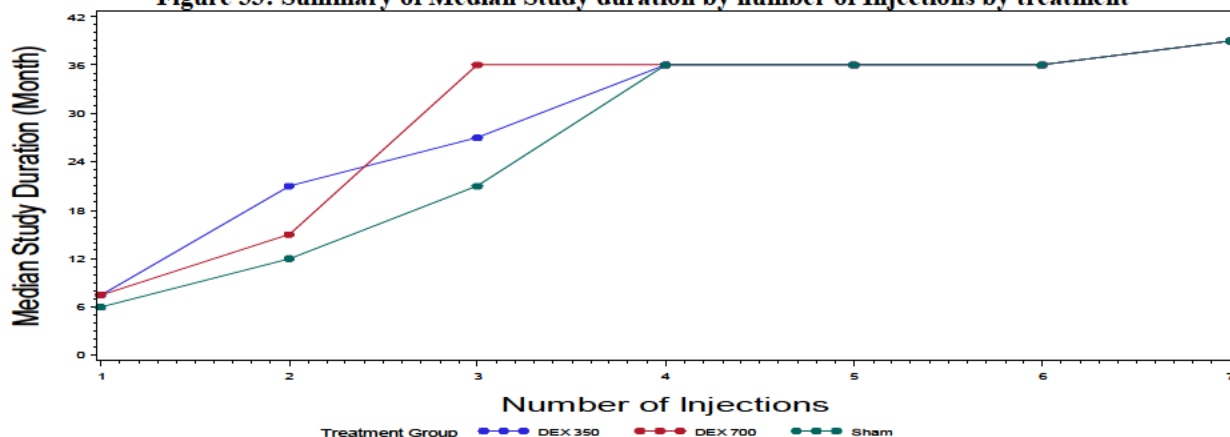
Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

Figure 32: Summary of Median Study duration by number of Injections



Source: Reviewer's Analysis.

Figure 33: Summary of Median Study duration by number of Injections by treatment



Source: Reviewer's Analysis.

Table 46: Summary of proportion of subjects with a ≥ 15 letter gain from baseline at Month 36 by number of injection (by study)

STUDY	NUMINJ	Treatment: N (%)			Diff (95% CI)	
		DEX700	DEX350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
206207010	1	3/20(15%)	1/11(9.1%)	3/52(5.8%)	9.2%(-7.7%,26.1%)	3.3%(-14.8%,21.5%)
	2	6/27(22.2%)	3/17(17.6%)	3/31(9.7%)	12.5%(-6.3%,31.4%)	8%(-12.9%,28.9%)
	3	6/17(35.3%)	2/20(10%)	1/17(5.9%)	29.4%(4.1%,54.7%)	4.1%(-13.1%,21.4%)
	4	3/15(20%)	3/20(15%)	1/11(9.1%)	10.9%(-15.5%,37.3%)	5.9%(-17.2%,29%)
	5	2/22(9.1%)	6/27(22.2%)	3/14(21.4%)	-12.3%(-37%,12.3%)	0.8%(-25.8%,27.4%)
	6	10/44(22.7%)	11/48(22.9%)	4/22(18.2%)	4.5%(-15.8%,24.9%)	4.7%(-15.3%,24.8%)
	7	2/15(13.3%)	7/22(31.8%)	3/17(17.6%)	-4.3%(-29.3%,20.7%)	14.2%(-12.4%,40.8%)
206207011	1	2/20(10%)	2/24(8.3%)	0/48(0%)	10%(-3.1%,23.1%)	8.3%(-2.7%,19.4%)
	2	3/24(12.5%)	2/25(8%)	4/20(20%)	-7.5%(-29.5%,14.5%)	-12%(-32.5%,8.5%)
	3	3/19(15.8%)	1/17(5.9%)	2/23(8.7%)	7.1%(-12.9%,27.1%)	-2.8%(-18.9%,13.2%)
	4	4/22(18.2%)	5/18(27.8%)	2/12(16.7%)	1.5%(-25%,28.1%)	11.1%(-18.4%,40.7%)

	5	3/22(13.6%)	2/10(20%)	2/15(13.3%)	0.3%(-22.1%,22.7%)	6.7%(-23.5%,36.8%)
	6	6/41(14.6%)	8/47(17%)	2/27(7.4%)	7.2%(-7.4%,21.9%)	9.6%(-5%,24.2%)
	7	4/16(25%)	1/18(6.7%)	4/15(22.2%)	2.8%(-25.8%,31.4%)	-15.6%(-38.5%,7.4%)
Pooled	1	5/40(12.5%)	3/35(8.6%)	3/100(3%)	9.5%(-1.3%,20.3%)	5.6%(-4.3%,15.4%)
	2	9/51(17.6%)	5/42(11.9%)	7/51(13.7%)	3.9%(-10.2%,18%)	-1.8%(-15.4%,11.8%)
	3	9/36(25%)	3/37(8.1%)	3/40(7.5%)	17.5%(1.2%,33.8%)	0.6%(-11.4%,12.6%)
	4	7/37(18.9%)	8/38(21.1%)	3/23(13%)	5.9%(-12.8%,24.5%)	8%(-10.9%,26.9%)
	5	5/44(11.4%)	8/37(21.6%)	5/29(17.2%)	-5.9%(-22.5%,10.8%)	4.4%(-14.7%,23.5%)
	6	16/85(18.8%)	19/95(20%)	6/49(12.2%)	6.6%(-5.8%,19%)	7.8%(-4.4%,20%)
	7	6/31(19.4%)	8/37(21.6%)	7/35(20%)	-0.6%(-19.9%,18.6%)	1.6%(-17.1%,20.4%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

Table 47: Summary of Adverse Events (AE) (Study 10: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=160	DEX 350 N=165	Sham N=164	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	153(95.6%)	162(98.2%)	124(75.6%)	20%(12.7%,27.3%)	22.6%(15.7%,29.5%)
Any Ocular AE	139(86.9%)	147(89.1%)	85(51.8%)	35%(25.8%,44.3%)	37.3%(28.3%,46.3%)
Any Serious AE	52(32.5%)	52(31.5%)	34(20.7%)	11.8%(2.2%,21.3%)	10.8%(1.4%,20.2%)
Any Ocular Serious AE	9(5.6%)	7(4.2%)	2(1.2%)	4.4%(0.5%,8.4%)	3%(-0.5%,6.5%)
Any Severe AE	71(44.4%)	77(46.7%)	42(25.6%)	18.8%(8.6%,29%)	21.1%(10.9%,31.2%)
Any Ocular Severe AE	45(28.1%)	38(23%)	17(10.4%)	17.8%(9.4%,26.1%)	12.7%(4.7%,20.6%)
Any IOP Related AE	65(40.6%)	60(36.4%)	5(3%)	37.6%(29.5%,45.6%)	33.3%(25.5%,41.1%)
≥10 mm Hg IOP Change from Baseline at any visit	51(31.9%)	46(27.9%)	4(2.4%)	29.4%(21.8%,37%)	25.4%(18.2%,32.7%)
≥25 mm Hg IOP at any visit	62(38.8%)	55(33.3%)	5(3%)	35.7%(27.7%,43.7%)	30.3%(22.6%,37.9%)
≥35 mm Hg IOP at any visit	14(8.8%)	12(7.3%)	1(0.6%)	8.1%(3.6%,12.7%)	6.7%(2.5%,10.8%)
Glaucoma	3(1.9%)	2(1.2%)	1(0.6%)	1.3%(-1.2%,3.7%)	0.6%(-1.4%,2.7%)
IOP Lowering Procedures	3(1.9%)	1(0.6%)	1(0.6%)	1.3%(-1.2%,3.7%)	0%(-1.7%,1.7%)
Any Cataract Related AE	80(68.3%)	82(69.5%)	17(14.8%)	53.5%(41.9%,63.5%)	54.7%(43.1%,64.5%)
Baseline Phakic Subjects					
Cataract Surgery in Baseline Phakic Subjects	72(61.5%)	72(61%)	8(7%)	54.6%(44.6%,64.5%)	54.1%(44.1%,64%)
≥15 Letters Loss from Baseline	15(9.4%)	9(5.5%)	17(10.4%)	-1%(-7.5%,5.5%)	-4.9%(-10.7%,0.9%)
Death	4(2.5%)	5(3%)	3(1.8%)	0.7%(-2.5%,3.8%)	1.2%(-2.1%,4.5%)
Escape Therapy	10(6.3%)	17(10.3%)	23(14%)	-7.8%(-14.3%,-1.3%)	-3.7%(-10.8%,3.3%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 48: Summary of Adverse Events (AE) (Study 11: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=164	DEX 350 N=155	Sham N=164	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	157(95.7%)	149(96.1%)	136(82.9%)	12.8%(6.3%,19.3%)	13.2%(6.7%,19.7%)
Any Ocular AE	135(82.3%)	135(87.1%)	105(64%)	18.3%(8.9%,27.7%)	23.1%(14%,32.1%)
Any Serious AE	58(35.4%)	61(39.4%)	45(27.4%)	7.9%(-2.1%,17.9%)	11.9%(1.6%,22.2%)
Any Ocular Serious AE	15(9.1%)	7(4.5%)	2(1.2%)	7.9%(3.2%,12.6%)	3.3%(-0.4%,7%)
Any Severe AE	80(48.8%)	72(46.5%)	58(35.4%)	13.4%(2.8%,24%)	11.1%(0.4%,21.8%)
Any Ocular Severe AE	46(28%)	33(21.3%)	17(10.4%)	17.7%(9.4%,26%)	10.9%(3%,18.9%)
Any IOP Related AE	55(33.5%)	47(30.3%)	13(7.9%)	25.6%(17.3%,33.9%)	22.4%(14.1%,30.7%)
≥10 mm Hg IOP Change from Baseline at any visit	40(24.4%)	33(21.3%)	9(5.5%)	18.9%(11.5%,26.3%)	15.8%(8.5%,23.1%)
≥25 mm Hg IOP at any visit	44(26.8%)	31(20%)	10(6.1%)	20.7%(13%,28.4%)	13.9%(6.6%,21.2%)
≥35 mm Hg IOP at any visit	6(3.7%)	4(2.6%)	2(1.2%)	2.4%(-0.9%,5.8%)	1.4%(-1.6%,4.4%)
Glaucoma	1(0.6%)	1(0.6%)	0(0%)	0.6%(-0.6%,1.8%)	0.6%(-0.6%,1.9%)
IOP Lowering Procedures	1(0.6%)		0(0%)	0.6%(-0.6%,1.8%)	0%(-1.7%,1.7%)
Any Cataract Related AE Baseline Phakic Subjects	86(68.2%)	67(56.8%)	32(27.8%)	40.4%(27.7%,51%)	29.0%(14.9%,39.5%)
Cataract Surgery in Baseline Phakic Subjects	76(60.3%)	53(44.9%)	10(8.7%)	51.6%(41.6%,61.6%)	36.2%(25.9%,46.6%)
≥15 Letters Loss from Baseline	32(19.5%)	25(16.1%)	18(11%)	8.5%(0.8%,16.3%)	5.2%(-2.4%,12.7%)
Death	5(3%)	9(5.8%)	2(1.2%)	1.8%(-1.3%,5%)	4.6%(0.5%,8.6%)
Escape Therapy	21(12.8%)	21(13.5%)	40(24.4%)	-11.6%(-19.9%,-3.3%)	-10.8%(-19.3%,-2.3%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 49: Summary of selected adverse events by number of Injections

NUMINJ	IOP Related AE			Cataract Surgery			Serious Ocular AE		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
1	13/40(32.5)	10/34(29.4)	2/101(2)	2/28(7.1)	0/26(0)	3/74(4.1)	0/40(0)	0/34(0)	1/101(1)
2	19/51(37.3)	11/42(26.2)	3/51(5.9)	10/34(29.4)	5/32(15.6)	1/38(2.6)	7/51(13.7)	2/42(4.8)	0/51(0)
3	12/36(33.3)	9/37(24.3)	3/40(7.5)	9/22(40.9)	7/24(29.2)	1/23(4.3)	3/36(8.3)	0/37(0)	0/40(0)
4	12/37(32.4)	16/38(42.1)	3/23(13)	18/27(66.7)	16/27(59.3)	1/16(6.3)	5/37(13.5)	1/38(2.6)	1/23(4.3)
5	16/44(36.4)	12/37(32.4)	2/29(6.9)	31/40(77.5)	22/29(75.9)	3/24(12.5)	2/44(4.5)	3/37(8.1)	1/29(3.4)
6	35/85(41.2)	39/95(41.1)	3/49(6.1)	55/66(83.3)	54/71(76.1)	3/31(9.7)	4/85(4.7)	7/95(7.4)	0/49(0)
7	13/31(41.9)	10/37(27)	2/35(5.7)	23/26(88.5)	21/27(77.8)	6/24(25)	3/31(9.7)	1/37(2.7)	1/35(2.9)

Source: Reviewer's Analysis.

Table 50: Summary of Adverse Events (AE) (for subjects with only one Injection)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=40	DEX 350 N=34	Sham N=101	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	35(87.5%)	31(91.2%)	62(61.4%)	26.1%(12.1%,40.1%)	29.8%(16.3%,43.2%)
Any Ocular AE	27(67.5%)	25(73.5%)	46(45.5%)	22%(4.5%,39.4%)	28%(10.3%,45.7%)
Any Serious AE	5(12.5%)	13(38.2%)	9(8.9%)	3.6%(-8.1%,15.2%)	29.3%(12.1%,46.6%)
Any Ocular Serious AE	0(0%)	0(0%)	1(1%)		-1%(-2.9%,0.9%)

Any Severe AE	13(32.5%)	13(38.2%)	20(19.8%)	12.7%(-3.8%,29.2%)	18.4%(0.3%,36.5%)
Any Ocular Severe AE	6(15%)	4(11.8%)	11(10.9%)	4.1%(-8.5%,16.7%)	0.9%(-11.5%,13.3%)
Any IOP Related AE	13(32.5%)	10(29.4%)	2(2%)	30.5%(15.8%,45.3%)	27.4%(11.9%,43%)
≥10 mm Hg IOP Change from Baseline at any visit	10(25%)	4(11.8%)	2(2%)	23%(9.3%,36.7%)	9.8%(-1.4%,20.9%)
≥25 mm Hg IOP at any visit	10(25%)	5(14.7%)	3(3%)	22%(8.2%,35.9%)	11.7%(-0.6%,24.1%)
≥35 mm Hg IOP at any visit	3(7.5%)		0(0%)	7.5%(-0.7%,15.7%)	
Any Cataract Related AE	7(25%)	5(19.2%)	7(9.5%)	15.5%(-1.8%,32.9%)	9.8%(-6.8%,26.3%)
Cataract Surgery in Baseline Phakic Subjects	2(7.1%)	0(0%)	3(4.1%)	3.1%(-7.5%,13.6%)	-4.1%(-8.5%,0.4%)
≥15 Letters Loss from Baseline	5(12.5%)	4(11.8%)	10(9.9%)	2.6%(-9.2%,14.4%)	1.9%(-10.4%,14.2%)
Death	2(5%)	3(8.8%)	0(0%)	5%(-1.8%,11.8%)	8.8%(-0.7%,18.4%)
Escape Therapy	7(17.5%)	4(11.8%)	21(20.8%)	-3.3%(-17.5%,10.9%)	-9%(-22.4%,4.4%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 51: Summary of Adverse Events (AE) (One or two injections)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=91	DEX 350 N=76	Sham N=152	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	84(92.3%)	70(92.1%)	100(65.8%)	26.5%(17.2%,35.8%)	26.3%(16.6%,36%)
Any Ocular AE	68(74.7%)	58(76.3%)	72(47.4%)	27.4%(15.4%,39.3%)	28.9%(16.5%,41.4%)
Any Serious AE	27(29.7%)	32(42.1%)	19(12.5%)	17.2%(6.4%,27.9%)	29.6%(17.3%,41.9%)
Any Ocular Serious AE	7(7.7%)	2(2.6%)	1(0.7%)	7%(1.4%,12.7%)	2%(-1.8%,5.8%)
Any Severe AE	37(40.7%)	32(42.1%)	35(23%)	17.6%(5.5%,29.7%)	19.1%(6.1%,32%)
Any Ocular Severe AE	20(22%)	12(15.8%)	14(9.2%)	12.8%(3.1%,22.4%)	6.6%(-2.8%,16%)
Any IOP Related AE	32(35.2%)	21(27.6%)	5(3.3%)	31.9%(21.7%,42.1%)	24.3%(13.9%,34.8%)
≥10 mm Hg IOP Change from Baseline at any visit	25(27.5%)	12(15.8%)	6(3.9%)	23.5%(13.8%,33.2%)	11.8%(3.1%,20.6%)
≥25 mm Hg IOP at any visit	26(28.6%)	11(14.5%)	7(4.6%)	24%(14.1%,33.8%)	9.9%(1.3%,18.5%)
≥35 mm Hg IOP at any visit	7(7.7%)	1(1.3%)	2(1.3%)	6.4%(0.6%,12.1%)	0%(-3.1%,3.1%)
Glaucoma					
IOP Lowering Procedures					
Any Cataract Related AE	20(32.3%)	15(25.9%)	10(8.9%)	23.3%(10.6%,36.1%)	16.9%(4.5%,29.4%)
Cataract Surgery in Baseline Phakic Subjects	12(19.4%)	5(8.6%)	4(3.6%)	15.8%(5.4%,26.2%)	5%(-2.9%,13%)
≥15 Letters Loss from Baseline	16(17.6%)	10(13.2%)	18(11.8%)	5.7%(-3.6%,15.1%)	1.3%(-7.9%,10.5%)
Death	5(5.5%)	8(10.5%)	1(0.7%)	4.8%(0%,9.7%)	9.9%(2.9%,16.9%)
Escape Therapy	11(12.1%)	12(15.8%)	33(21.7%)	-9.6%(-19%, -0.3%)	-5.9%(-16.4%,4.6%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 52: Summary of Adverse Events (AE) (3-4 injections)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=73	DEX 350 N=75	Sham N=63	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	69(94.5%)	74(98.7%)	57(90.5%)	4%(-4.9%,13%)	8.2%(0.5%,15.9%)
Any Ocular AE	61(83.6%)	65(86.7%)	39(61.9%)	21.7%(7%,36.4%)	24.8%(10.5%,39%)
Any Serious AE	34(46.6%)	22(29.3%)	21(33.3%)	13.2%(-3.1%,29.6%)	-4%(-19.5%,11.5%)
Any Ocular Serious AE	8(11%)	1(1.3%)	1(1.6%)	9.4%(1.6%,17.2%)	-0.3%(-4.3%,3.8%)
Any Severe AE	39(53.4%)	31(41.3%)	26(41.3%)	12.2%(-4.5%,28.9%)	0.1%(-16.4%,16.6%)
Any Ocular Severe AE	20(27.4%)	15(20%)	8(12.7%)	14.7%(1.6%,27.8%)	7.3%(-4.9%,19.5%)
Any IOP Related AE	24(32.9%)	25(33.3%)	6(9.5%)	23.4%(10.4%,36.3%)	23.8%(10.9%,36.7%)
≥10 mm Hg IOP Change from Baseline at any visit	15(20.5%)	18(24%)	2(3.2%)	17.4%(7.1%,27.6%)	20.8%(10.2%,31.4%)
≥25 mm Hg IOP at any visit	17(23.3%)	22(29.3%)	3(4.8%)	18.5%(7.5%,29.6%)	24.6%(13%,36.1%)
≥35 mm Hg IOP at any visit	1(1.4%)	4(5.3%)	0(0%)	1.4%(-1.3%,4%)	5.3%(0.2%,10.4%)
Glaucoma	4(5.5%)		0(0%)	5.5%(0.3%,10.7%)	
IOP Lowering Procedures	4(5.5%)		0(0%)	5.5%(0.3%,10.7%)	
Any Cataract Related AE	36(73.5%)	30(58.8%)	11(28.2%)	45.3%(26.5%,64%)	30.6%(11.1%,50.2%)
Cataract Surgery in Baseline Phakic Subjects	27(55.1%)	23(45.1%)	2(5.1%)	50%(34.4%,65.5%)	40%(24.7%,55.3%)
≥15 Letters Loss from Baseline	12(16.4%)	13(17.3%)	9(14.3%)	2.2%(-10%,14.3%)	3%(-9.1%,15.2%)
Death	3(4.1%)	2(2.7%)	4(6.3%)	-2.2%(-9.8%,5.3%)	-3.7%(-10.7%,3.4%)
Escape Therapy	8(11%)	13(17.3%)	11(17.5%)	-6.5%(-18.3%,5.3%)	-0.1%(-12.8%,12.6%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 53: Summary of Adverse Events (AE) (Five or more injections)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=160	DEX 350 N=169	Sham N=113	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	157(98.1%)	167(98.8%)	103(91.2%)	7%(1.3%,12.6%)	7.7%(2.2%,13.2%)
Any Ocular AE	145(90.6%)	159(94.1%)	79(69.9%)	20.7%(11.1%,30.3%)	24.2%(15%,33.3%)
Any Serious AE	49(30.6%)	59(34.9%)	39(34.5%)	-3.9%(-15.2%,7.4%)	0.4%(-10.9%,11.7%)
Any Ocular Serious AE	9(5.6%)	11(6.5%)	2(1.8%)	3.9%(-0.5%,8.2%)	4.7%(0.3%,9.2%)
Any Severe AE	75(46.9%)	86(50.9%)	39(34.5%)	12.4%(0.7%,24.1%)	16.4%(4.8%,27.9%)
Any Ocular Severe AE	51(31.9%)	44(26%)	12(10.6%)	21.3%(12.1%,30.4%)	15.4%(6.7%,24.1%)
Any IOP Related AE	64(40%)	61(36.1%)	7(6.2%)	33.8%(25%,42.6%)	29.9%(21.4%,38.4%)
≥10 mm Hg IOP Change from Baseline at any visit	51(31.9%)	49(29%)	5(4.4%)	27.5%(19.3%,35.6%)	24.6%(16.7%,32.4%)
≥25 mm Hg IOP at any visit	63(39.4%)	53(31.4%)	5(4.4%)	35%(26.5%,43.4%)	26.9%(19%,34.9%)
≥35 mm Hg IOP at any visit	12(7.5%)	11(6.5%)	1(0.9%)	6.6%(2.2%,11%)	5.6%(1.5%,9.7%)
Glaucoma	0(0%)	3(1.8%)	1(0.9%)	-0.9%(-2.6%,0.8%)	0.9%(-1.7%,3.5%)
IOP Lowering Procedures	0(0%)	1(0.6%)	1(0.9%)	-0.9%(-2.6%,0.8%)	-0.3%(-2.4%,1.8%)
Any Cataract Related AE	114(86.4%)	107(84.3%)	34(43%)	43.3%(30.9%,55.7%)	41.2%(28.6%,53.8%)
Cataract Surgery in Baseline Phakic Subjects	109(82.6%)	97(76.4%)	12(15.2%)	67.4%(57.2%,77.6%)	61.2%(50.4%,72%)
≥15 Letters Loss from Baseline	19(11.9%)	11(6.5%)	8(7.1%)	4.8%(-2.1%,11.7%)	-0.6%(-6.6%,5.4%)

Death	1(0.6%)	4(2.4%)	0(0%)	0.6%(-0.6%,1.8%)	2.4%(0.1%,4.7%)
Escape Therapy	12(7.5%)	13(7.7%)	19(16.8%)	-9.3%(-17.3%,-1.3%)	-9.1%(-17.1%,-1.1%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 54: Summary of Adverse Events (AE) (Subjects who lost 15 letters or more at Month 36

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=47	DEX 350 N=34	Sham N=35	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	45(95.7%)	33(97.1%)	26(74.3%)	21.5%(5.9%,37%)	22.8%(7.2%,38.3%)
Any Ocular AE	42(89.4%)	29(85.3%)	22(62.9%)	26.5%(8.2%,44.8%)	22.4%(2.5%,42.4%)
Any Serious AE	15(31.9%)	12(35.3%)	7(20%)	11.9%(-6.9%,30.7%)	15.3%(-5.5%,36.1%)
Any Ocular Serious AE	5(10.6%)	3(8.8%)	0(0%)	10.6%(1.8%,19.5%)	8.8%(-0.7%,18.4%)
Any Severe AE	21(44.7%)	20(58.8%)	11(31.4%)	13.3%(-7.7%,34.2%)	27.4%(4.8%,50%)
Any Ocular Severe AE	18(38.3%)	15(44.1%)	4(11.4%)	26.9%(9.4%,44.3%)	32.7%(12.9%,52.4%)
Any IOP Related AE	15(31.9%)	12(35.3%)	0(0%)	31.9%(18.6%,45.2%)	35.3%(19.2%,51.4%)
≥10 mm Hg IOP Change from Baseline at any visit	13(27.7%)	9(26.5%)	2(5.7%)	21.9%(7%,36.9%)	20.8%(4.1%,37.5%)
≥25 mm Hg IOP at any visit	12(25.5%)	13(38.2%)	1(2.9%)	22.7%(9%,36.3%)	35.4%(18.1%,52.6%)
≥35 mm Hg IOP at any visit	1(2.1%)	3(8.8%)	0(0%)	2.1%(-2%,6.3%)	8.8%(-0.7%,18.4%)
Glaucoma	2(4.3%)		0(0%)	4.3%(-1.5%,10%)	8.8%(-0.7%,18.4%)
IOP Lowering Procedures	2(4.3%)		0(0%)	4.3%(-1.5%,10%)	-11.1%(-28.7%,6.5%)
Any Cataract related AE in Baseline Phakic Subjects	30/42 (71.4%)	19/30 (63.3%)	4/28 (14.3%)	57.1%(38.3%,76%)	49%(27.5%,70.6%)
Cataract Surgery in Baseline Phakic Subjects	20/42 (47.6%)	11/30 (36.7%)	3/28 (10.7%)	36.9%(17.9%,55.9%)	26%(5.2%,46.7%)
Death	2(4.3%)	1(2.9%)	0(0%)	4.3%(-1.5%,10%)	2.9%(-2.7%,8.6%)
Escape Therapy	10(21.3%)	4(11.8%)	8(22.9%)	-1.6%(-19.8%,16.6%)	-11.1%(-28.7%,6.5%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 55: Summary of Adverse Events (AE) (Subjects who lost 15 letters or more at Month 36 by # of injections)

NUMINJ	IOP			Cataract Surgery			Serious Ocular AE		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
1	2/5(40)	1/4(25)	0/10(0)	0/4(0)	0/3(0)	0/8(0)	0/5(0)	0/4(0)	0/10(0)
2	3/11(27.3)	1/6(16.7)	0/8(0)	4/9(44.4)	2/6(33.3)	0/8(0)	2/11(18.2)	1/6(16.7)	0/8(0)
3	0/3(0)	2/8(25)	0/6(0)	1/3(33.3)	1/6(16.7)	1/5(20)	0/3(0)	0/8(0)	0/6(0)
4	2/9(22.2)	1/5(20)	0/3(0)	5/8(62.5)	2/5(40)	0/1(0)	3/9(33.3)	0/5(0)	0/3(0)
5	3/10(30)	3/4(75)	0/5(0)	5/10(50)	2/4(50)	0/3(0)	0/10(0)	1/4(25)	0/5(0)
6	5/8(62.5)	3/6(50)	0/2(0)	4/7(57.1)	4/5(80)	1/2(50)	0/8(0)	1/6(16.7)	0/2(0)
7				1/1(100)	0/1(0)	1/1(100)	0/1(0)	0/1(0)	0/1(0)

Source: Reviewer's Analysis.

Table 56: Summary of Cross tabulation of Number of Injections and study duration

Study Duration	Number of Injections							
	DEX 700							
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	Total
<=6 Month	17(89.5)	1(5.3)	0(0)	0(0)	0(0)	1(5.3)	0(0)	19
(6 to 12 Month]	14(40)	19(54.3)	2(5.7)	0(0)	0(0)	0(0)	0(0)	35
(12 to 18Month]	3(14.3)	12(57.1)	6(28.6)	0(0)	0(0)	0(0)	0(0)	21
(18 to 24Month]	0(0)	0(0)	3(20)	11(73.3)	1(6.7)	0(0)	0(0)	15
>24 Month	6(2.6)	19(8.1)	25(10.7)	26(11.1)	43(18.4)	84(35.9)	31(13.2)	234
	DEX 350							
Study Duration	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	Total
<=6 Month	14(93.3)	0(0)	0(0)	1(6.7)	0(0)	0(0)	0(0)	15
(6 to 12 Month]	8(28.6)	19(67.9)	1(3.6)	0(0)	0(0)	0(0)	0(0)	28
(12 to 18Month]	1(5.9)	2(11.8)	12(70.6)	2(11.8)	0(0)	0(0)	0(0)	17
(18 to 24Month]	1(4)	8(32)	5(20)	10(40)	1(4)	0(0)	0(0)	25
>24 Month	10(4.3)	13(5.5)	19(8.1)	25(10.6)	36(15.3)	95(40.4)	37(15.7)	235
	Sham							
Study Duration	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	Total
<=6 Month	72(94.7)	4(5.3)	0(0)	0(0)	0(0)	0(0)	0(0)	76
(6 to 12 Month]	17(37)	29(63)	0(0)	0(0)	0(0)	0(0)	0(0)	46
(12 to 18Month]	4(14.3)	4(14.3)	18(64.3)	2(7.1)	0(0)	0(0)	0(0)	28
(18 to 24Month]	3(21.4)	1(7.1)	7(50)	3(21.4)	0(0)	0(0)	0(0)	33
>24 Month	5(3)	13(7.9)	15(9.1)	18(11)	29(17.7)	49(29.9)	35(21.3)	29

Source: Reviewer's analysis.

Table 57: Summary of Adverse Events (AE) by study duration

Study Duration	Adverse Event	Treatment: N (%)			% Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs Sham	DEX 350 vs. Sham
<=6 Month	SAE	0/19(0%)	0/15(0%)	0/76(0%)		
	IOP	2/19(10.5%)	1/15(6.7%)	1/76(1.3%)	9.2%(-4.8%, 23.2%)	5.4%(-7.5%, 18.2%)
	Cataract related AE	2/10(20%)	1/11(9.1%)	0/53(0%)	20%(-4.8%, 44.8%)	9.1%(-7.9%, 26.1%)
	Cataract Surgery	1/10(10%)	0/11(0%)	0/53(0%)	10%(-8.6%, 28.6%)	
(6 to 12 Month]	SAE	3/35(8.6%)	0/28(0%)	0/46(0%)	8.6%(-0.7%,17.8%)	
	IOP	16/35(45.7%)	9/28(32.1%)	2/46(4.3%)	41.4%(23.8%,58.9%)	27.8%(9.5%,46.1%)
	Cataract related AE	7/28(25%)	5/23(21.7%)	5/39(12.8%)	12.2%(-7%,31.3%)	8.9%(-10.9%,28.8%)
	Cataract Surgery	3/28(10.7%)	2/23(8.7%)	2/39(5.1%)	5.6%(-7.8%,19%)	3.6%(-9.9%,17%)
(12 to 18	SAE	4/21(19%)	0/17(0%)	1/28(3.6%)	15.5%(-2.7%,33.6%)	-3.6%(-10.4%,3.3%)
	IOP	7/21(33.3%)	2/17(11.8%)	1/28(3.6%)	29.8%(8.5%,51.1%)	8.2%(-8.6%,25%)

Month]	Cataract related AE	5/11(45.5%)	5/13(38.5%)	4/16(25%)	20.5%(-15.8%,56.7%)	13.5%(-20.4%,47.4%)
	Cataract Surgery	5/11(45.5%)	2/13(15.4%)	1/16(6.3%)	39.2%(7.5%,70.9%)	9.1%(-13.8%,32.1%)
(18 to 24 Month]	SAE	3/15(20%)	3/25(12%)	0/14(0%)	20%(-0.2%,40.2%)	12%(-0.7%,24.7%)
	IOP	6/15(40%)	6/25(24%)	0/14(0%)	40%(15.2%,64.8%)	24%(7.3%,40.7%)
	Cataract related AE	6/9(66.7%)	14/21(66.7%)	1/12(8.3%)	58.3%(23.8%,92.9%)	58.3%(32.8%,83.8%)
	Cataract Surgery	4/9(44.4%)	10/21(47.6%)	1/12(8.3%)	36.1%(0.1%,72.1%)	39.3%(12.8%,65.8%)
>24 Month	SAE	14/234(6%)	11/235(4.7%)	3/164(1.8%)	4.2%(0.5%,7.8%)	2.9%(-0.5%,6.2%)
	IOP	89/234(38%)	89/235(37.9%)	14/164(8.5%)	29.5%(21.9%,37%)	29.3%(21.8%,36.9%)
	Cataract related AE	150/185(81.1%)	127/168(75.6%)	45/110(40.9%)	40.2%(29.4%,51%)	34.7%(23.4%,45.9%)
	Cataract Surgery	135/185(73%)	111/168(66.1%)	14/110(12.7%)	60.2%(51.3%,69.2%)	53.3%(43.9%,62.8%)

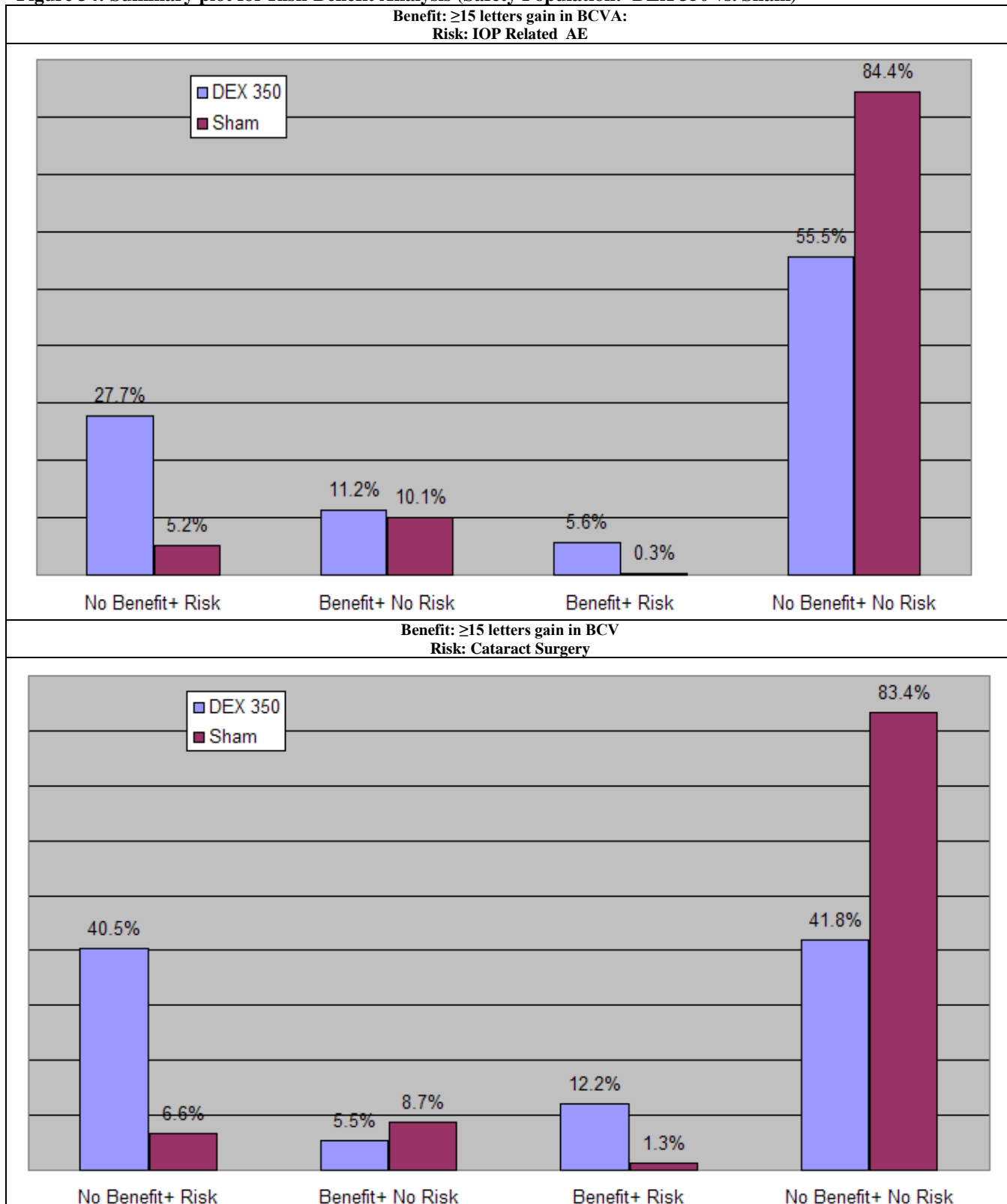
Source: Reviewer's Analysis. The denominator in this table is the number of subjects who had remained in the study for the duration indicated in the study duration column.

Table 58: Summary of disposition for subjects with 15 letters or more worsening

Status	DEX 700 N=47	DEX 350 N=34	Sham N=35
Completed	19(40.4)	14(41.2)	6(17.1)
Adverse Event	15(31.9)	13(38.2)	9(25.7)
Lack of Efficacy	5(10.6)	4(11.8)	10(28.6)
Lost to Follow-up	1(2.1)	1(2.9)	3(8.6)
Other	4(8.5)	1(2.9)	4(11.4)
Personal Reasons	2(4.3)	0(0)	3(8.6)
Protocol Violation	1(2.1)	1(2.9)	0(0)

Source: Reviewer's Analysis.

Figure 34: Summary plot for Risk-Benefit Analysis (Safety Population: DEX 350 vs. Sham)



Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Table 59: Summary of Risk-Benefit Analysis (Safety Population: DEX 350 vs. Sham)

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 350 N=321	Sham N=327	DEX 350 N=321	Sham N=327	DEX 350 N=321	Sham N=327	DEX 350 N=321	Sham N=327
BCVA improvement of ≥ 15 letters	Any AE	1(0.3%)	0(0%)	259(80.7%)	225(68.8%)	53(16.5%)	34(10.4%)	8(2.5%)	68(20.8%)
	Any Ocular AE	6(1.9%)	11(3.4%)	235(73.2%)	166(50.8%)	48(15%)	23(7%)	32(10%)	127(38.8%)
	Any Serious AE	39(12.1%)	20(6.1%)	99(30.8%)	64(19.6%)	15(4.7%)	14(4.3%)	168(52.3%)	229(70%)
	Any Ocular Serious AE	51(15.9%)	33(10.1%)	12(3.7%)	2(0.6%)	3(0.9%)	1(0.3%)	255(79.4%)	291(89%)
	Any Severe AE	34(10.6%)	19(5.8%)	130(40.5%)	84(25.7%)	20(6.2%)	15(4.6%)	137(42.7%)	209(63.9%)
	Any Severe Ocular AE	45(14%)	33(10.1%)	63(19.6%)	32(9.8%)	9(2.8%)	1(0.3%)	204(63.6%)	261(79.8%)
	Any IOP Related AE	36(11.2%)	33(10.1%)	89(27.7%)	17(5.2%)	18(5.6%)	1(0.3%)	178(55.5%)	276(84.4%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	38(11.8%)	34(10.4%)	63(19.6%)	13(4%)	16(5%)	0(0%)	204(63.6%)	280(85.6%)
	≥ 25 mm Hg IOP at any visit	41(12.8%)	34(10.4%)	73(22.7%)	15(4.6%)	13(4%)	0(0%)	194(60.4%)	278(85%)
	≥ 35 mm Hg IOP at any visit	52(16.2%)	34(10.4%)	14(4.4%)	3(0.9%)	2(0.6%)	0(0%)	253(78.8%)	290(88.7%)
	Cataract Surgery in Phakic Subjects	13(5.5%)	20(8.7%)	96(40.5%)	15(6.6%)	29(12.2%)	3(1.3%)	99(41.8%)	191(83.4%)
BCVA improvement of ≥ 10 letters	Any AE	2(0.6%)	5(1.5%)	224(69.8%)	196(59.9%)	88(27.4%)	63(19.3%)	7(2.2%)	63(19.3%)
	Any Ocular AE	11(3.4%)	26(8%)	204(63.6%)	147(45%)	79(24.6%)	42(12.8%)	27(8.4%)	112(34.3%)
	Any Serious AE	61(19%)	49(15%)	85(26.5%)	59(18%)	29(9%)	19(5.8%)	146(45.5%)	200(61.2%)
	Any Ocular Serious AE	87(27.1%)	67(20.5%)	12(3.7%)	2(0.6%)	3(0.9%)	1(0.3%)	219(68.2%)	257(78.6%)
	Any Severe AE	58(18.1%)	47(14.4%)	118(36.8%)	78(23.9%)	32(10%)	21(6.4%)	113(35.2%)	181(55.4%)
	Any Severe Ocular AE	76(23.7%)	64(19.6%)	58(18.1%)	29(8.9%)	14(4.4%)	4(1.2%)	173(53.9%)	230(70.3%)
	Any IOP Related AE	56(17.4%)	63(19.3%)	73(22.7%)	13(4%)	34(10.6%)	5(1.5%)	158(49.2%)	246(75.2%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	62(19.3%)	66(20.2%)	51(15.9%)	11(3.4%)	28(8.7%)	2(0.6%)	180(56.1%)	248(75.8%)
	≥ 25 mm Hg IOP at any visit	65(20.2%)	66(20.2%)	61(19%)	13(4%)	25(7.8%)	2(0.6%)	170(53%)	246(75.2%)
	≥ 35 mm Hg IOP at any visit	85(26.5%)	68(20.8%)	11(3.4%)	3(0.9%)	5(1.6%)	0(0%)	220(68.5%)	256(78.3%)
	Cataract Surgery in Phakic Subjects	21(8.9%)	43(18.8%)	88(37.1%)	13(5.7%)	37(15.6%)	5(2.2%)	91(38.4%)	168(73.4%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Summary of Risk-Benefit Analysis (Continued)

Benefit	Risk	Differences: DEX 350 Sham (95% CI)			
		Benefit + No Risk (Best Case Scenario)	No Benefit + Risk (Worst Case Scenario)	Benefit + Risk	No Benefit + No Risk
BCVA improvement of ≥15 letters	Any AE	0.3% (-0.3%, 0.9%)	11.9% (5.3%, 18.5%)	6.1% (0.9%, 11.4%)	-18.3% (-23%, -13.6%)
	Any Ocular AE	-1.5% (-3.9%, 1%)	22.4% (15.2%, 29.7%)	7.9% (3.1%, 12.7%)	-28.9% (-35.1%, -22.7%)
	Any Serious AE	6% (1.6%, 10.5%)	11.3% (4.6%, 17.9%)	0.4% (-2.8%, 3.6%)	-17.7% (-25.1%, -10.3%)
	Any Ocular Serious AE	5.8% (0.6%, 11%)	3.1% (0.9%, 5.4%)	0.6% (-0.6%, 1.8%)	-9.6% (-15.1%, -4%)
	Any Severe AE	4.8% (0.6%, 9%)	14.8% (7.7%, 22%)	1.6% (-1.8%, 5.1%)	-21.2% (-28.7%, -13.7%)
	Any Ocular Severe AE	3.9% (-1.1%, 8.9%)	9.8% (4.4%, 15.2%)	2.5% (0.6%, 4.4%)	-16.3% (-23.1%, -9.4%)
	Any IOP Related AE	1.1% (-3.6%, 5.9%)	22.5% (17.1%, 28%)	5.3% (2.7%, 7.9%)	-29% (-35.7%, -22.2%)
	≥10 mm Hg IOP Change from Baseline at any visit	1.4% (-3.4%, 6.3%)	15.7% (10.8%, 20.5%)	5% (2.6%, 7.4%)	-22.1% (-28.6%, -15.6%)
	≥25 mm Hg IOP at any visit	2.4% (-2.6%, 7.3%)	18.2% (13%, 23.3%)	4% (1.9%, 6.2%)	-24.6% (-31.2%, -18%)
	≥35 mm Hg IOP at any visit	5.8% (0.6%, 11%)	3.4% (1%, 5.9%)	0.6% (-0.2%, 1.5%)	-9.9% (-15.5%, -4.2%)
	Cataract Surgery in Phakic Subjects	-3.2% (-7.9%, 1.4%)	34% (26.9%, 41%)	10.9% (6.5%, 15.4%)	-41.6% (-49.5%, -33.7%)
BCVA improvement of ≥10 letters	Any AE	-0.9% (-2.5%, 0.7%)	9.8% (2.5%, 17.2%)	8.1% (1.7%, 14.6%)	-17.1% (-21.6%, -12.5%)
	Any Ocular AE	-4.5% (-8.1%, -1%)	18.6% (11.1%, 26.1%)	11.8% (5.8%, 17.7%)	-25.8% (-31.8%, -19.9%)
	Any Ocular Serious AE	4% (-1.8%, 9.8%)	8.4% (2.1%, 14.8%)	3.2% (-0.8%, 7.3%)	-15.7% (-23.3%, -8.1%)
	Any Ocular Serious AE	6.6% (0.1%, 13.2%)	3.1% (0.9%, 5.4%)	0.6% (-0.6%, 1.8%)	-10.4% (-17.1%, -3.6%)
	Any Severe AE	3.7% (-2%, 9.4%)	12.9% (5.9%, 19.9%)	3.5% (-0.7%, 7.8%)	-20.1% (-27.7%, -12.6%)
	Any Ocular Severe AE	4.1% (-2.2%, 10.4%)	9.2% (4%, 14.4%)	3.1% (0.6%, 5.7%)	-16.4% (-23.8%, -9.1%)
	Any IOP Related AE	-1.8% (-7.8%, 4.1%)	18.8% (13.7%, 23.8%)	9.1% (5.4%, 12.7%)	-26% (-33.2%, -18.8%)
	≥10 mm Hg IOP Change from Baseline at any visit	-0.9% (-7%, 5.3%)	12.5% (8.1%, 17%)	8.1% (4.9%, 11.3%)	-19.8% (-26.9%, -12.6%)
	≥25 mm Hg IOP at any visit	0.1% (-6.1%, 6.3%)	15% (10.2%, 19.8%)	7.2% (4.1%, 10.2%)	-22.3% (-29.5%, -15.1%)
	≥35 mm Hg IOP at any visit	5.7% (-0.8%, 12.2%)	2.5% (0.3%, 4.8%)	1.6% (0.2%, 2.9%)	-9.8% (-16.5%, -3%)
	Cataract Surgery in Phakic Subjects	-9.9% (-16.1%, -3.7%)	31.5% (24.6%, 38.3%)	13.4% (8.4%, 18.4%)	-35% (-43.4%, -26.5%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

Table 60: Summary of Risk-Benefit Analysis for Psuedophakic subjects (DEX 350 vs. Sham)

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 700 N=81	Sham N=98	DEX 700 N=81	Sham N=98	DEX 700 N=81	Sham N=98	DEX 700 N=81	Sham N=98
BCVA improvement of ≥ 15 letters	Any AE			71(84.5%)	73(74.5%)	12(14.3%)	11(11.2%)	1(1.2%)	14(14.3%)
	Any Ocular AE	1(1.2%)	3(3.1%)	59(70.2%)	52(53.1%)	11(13.1%)	8(8.2%)	13(15.5%)	35(35.7%)
	Any Serious AE	7(8.3%)	6(6.1%)	31(36.9%)	31(31.6%)	5(6%)	5(5.1%)	41(48.8%)	56(57.1%)
	Any Ocular Serious AE	12(14.3%)	11(11.2%)					72(85.7%)	87(88.8%)
	Any Severe AE	5(6%)	6(6.1%)	33(39.3%)	32(32.7%)	7(8.3%)	5(5.1%)	39(46.4%)	55(56.1%)
	Any Severe Ocular AE	10(11.9%)	11(11.2%)	13(15.5%)	8(8.2%)	2(2.4%)	0(0%)	59(70.2%)	79(80.6%)
	Any IOP Related AE	8(9.5%)	10(10.2%)	25(29.8%)	8(8.2%)	4(4.8%)	1(1%)	47(56%)	79(80.6%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	8(9.5%)	11(11.2%)	20(23.8%)	2(2%)	4(4.8%)	0(0%)	52(61.9%)	85(86.7%)
	≥ 25 mm Hg IOP at any visit	10(11.9%)	11(11.2%)	22(26.2%)	6(6.1%)	2(2.4%)	0(0%)	50(59.5%)	81(82.7%)
	≥ 35 mm Hg IOP at any visit	11(13.1%)	11(11.2%)	3(3.6%)	1(1%)	1(1.2%)	0(0%)	69(82.1%)	86(87.8%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

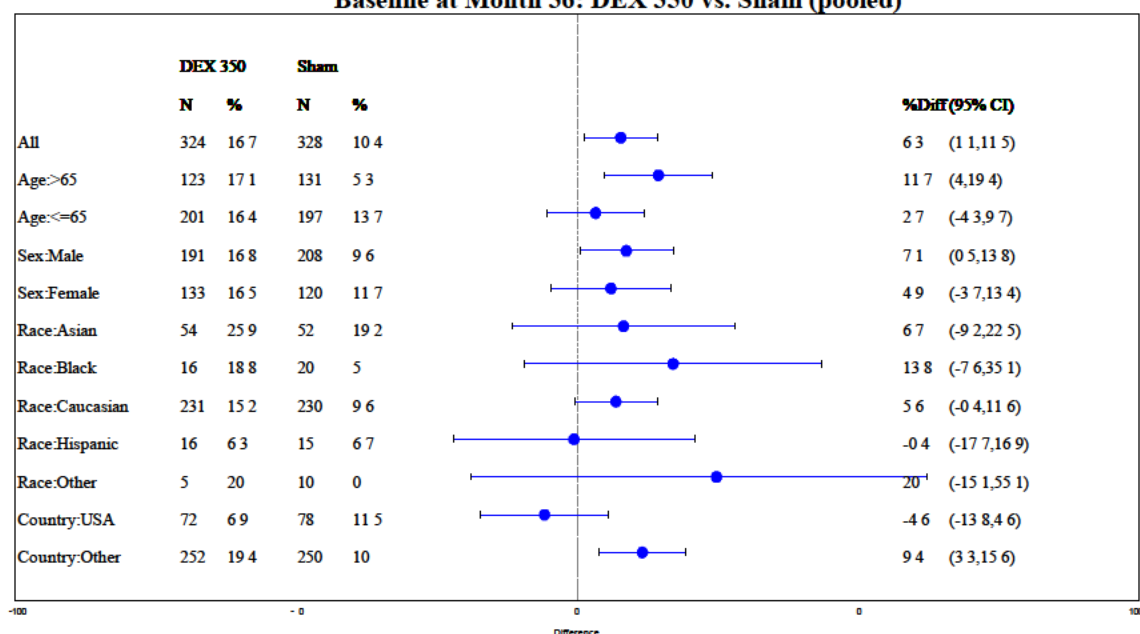
Table 61: Summary of Population level Risk-Benefit Measures (Safety Population: DEX 350 vs. Sham)

Benefit	Risk	Estimates (95% CI)			
		NNT	NNTadj	NNH	BRR
BCVA improvement of ≥ 15 letters	Any AE	15.6(8.6,86)	19(11.1,99.1)	5.6(4.4,7.6)	0.36
	Any Ocular AE	15.6(8.6,86)	22.4(13.5,113.1)	3.3(2.7,4.2)	0.21
	Any Serious AE	15.6(8.6,86)	17.6(10.5,90.2)	8.6(5.4,21.4)	0.55
	Any Ocular Serious AE	15.6(8.6,86)	16.2(9.1,87.1)	26.6(15.9,81.6)	1.71
	Any Severe AE	15.6(8.6,86)	18.6(11.2,94.6)	6.1(4.2,11)	0.39
	Any Ocular Severe AE	15.6(8.6,86)	17.8(10.4,92.2)	8.1(5.6,14.9)	0.52
	Any IOP Related AE	15.6(8.6,86)	21.6(12.9,110.4)	3.6(3.4,5)	0.23
	≥ 10 mm Hg IOP Change from Baseline at any visit	15.6(8.6,86)	19.6(11.5,101.7)	4.8(3.9,6.5)	0.31
	≥ 25 mm Hg IOP at any visit	15.6(8.6,86)	20(11.8,103.4)	4.5(3.6,5.9)	0.29
	≥ 35 mm Hg IOP at any visit	15.6(8.6,86)	16.2(9.2,87.3)	24.6(15,67.9)	1.58
	Cataract Surgery in Phakic Subjects	13(7.2,69)	23.6(15,110.6)	2.2(1.9,2.7)	0.17
BCVA improvement of ≥ 10 letters	Any AE	13.8(7.2,154.5)	16.8(9.4,178.1)	5.6(4.4,7.6)	0.4
	Any Ocular AE	13.8(7.2,154.5)	19.8(11.4,203.2)	3.3(2.7,4.2)	0.24
	Any Ocular Serious AE	13.8(7.2,154.5)	15.6(8.9,162.1)	8.6(5.4,21.4)	0.62
	Any Ocular Serious AE	13.8(7.2,154.5)	14.3(7.7,156.4)	26.6(15.9,81.6)	1.93
	Any Severe AE	13.8(7.2,154.5)	16.5(9.5,169.9)	6.1(4.2,11)	0.44
	Any Ocular Severe AE	13.8(7.2,154.5)	15.8(8.8,165.6)	8.1(5.6,14.9)	0.59
	Any IOP Related AE	13.8(7.2,154.5)	19.1(10.9,198.4)	3.6(3.4,5)	0.26
	≥ 10 mm Hg IOP Change from Baseline at any visit	13.8(7.2,154.5)	17.4(9.7,182.8)	4.8(3.9,6.5)	0.35
	≥ 25 mm Hg IOP at any visit	13.8(7.2,154.5)	17.7(10,185.8)	4.5(3.6,5.9)	0.33
	≥ 35 mm Hg IOP at any visit	13.8(7.2,154.5)	14.4(7.7,156.8)	24.6(15,67.9)	1.78
	Cataract Surgery in Phakic Subjects	28.5	51.7	2.2(1.9,2.7)	0.08

Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

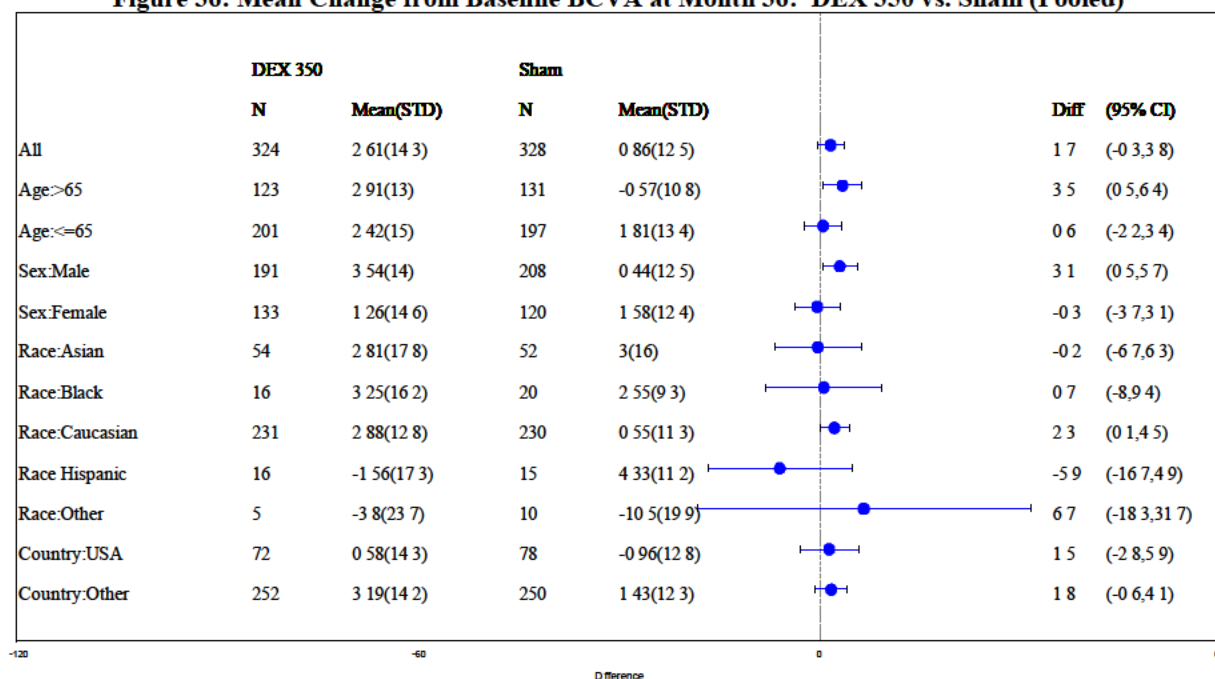
Let $P_{\text{DEX 700}}$ and P_{SHAM} be proportion of success and Q_{DEX} and Q_{SHAM} be proportion of subjects with adverse event in the DEX 700 and Sham arms respectively. BRR: Benefit-Risk Ratio= $(P_{\text{DEX 700}} - P_{\text{SHAM}}) / (Q_{\text{DEX 700}} - Q_{\text{SHAM}})$. NNT= $1 / (P_{\text{DEX 700}} - P_{\text{SHAM}})$: Number Need to be treated to observe one success. NNTadj= $1 / ((P_{\text{DEX 700}} - P_{\text{SHAM}}) * (1 - (Q_{\text{DEX 700}} - Q_{\text{SHAM}})))$: Number Need to be treated to observe one success without adverse event. NNH= $1 / (Q_{\text{DEX 700}} - Q_{\text{SHAM}})$: Number Needed Harm.

Figure 35: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 350 vs. Sham (pooled)



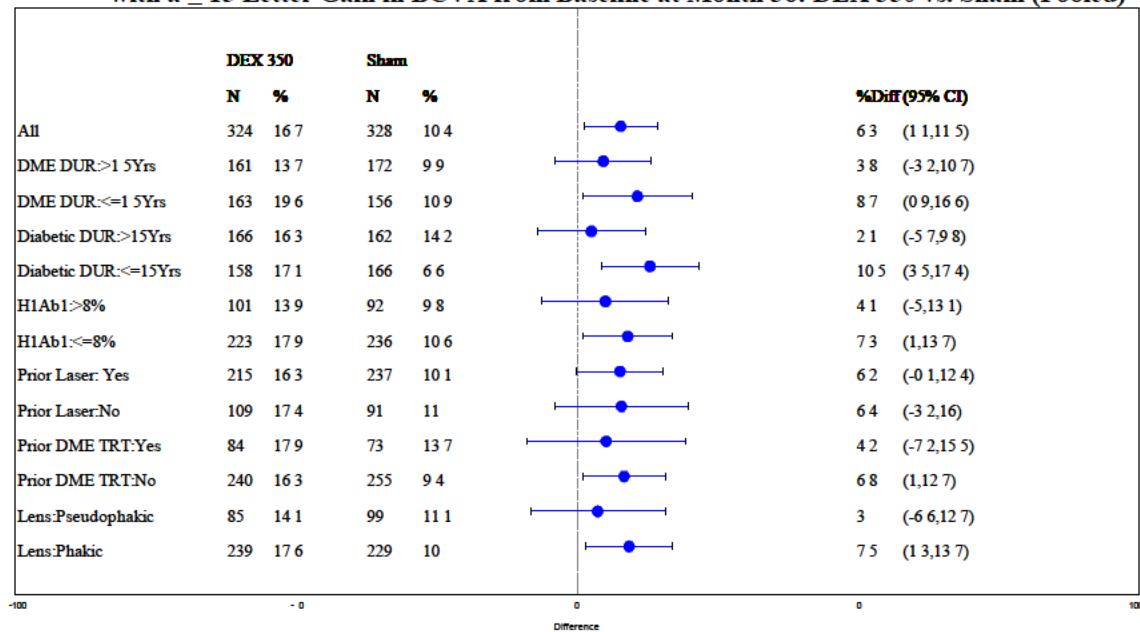
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 36: Mean Change from Baseline BCVA at Month 36: DEX 350 vs. Sham (Pooled)



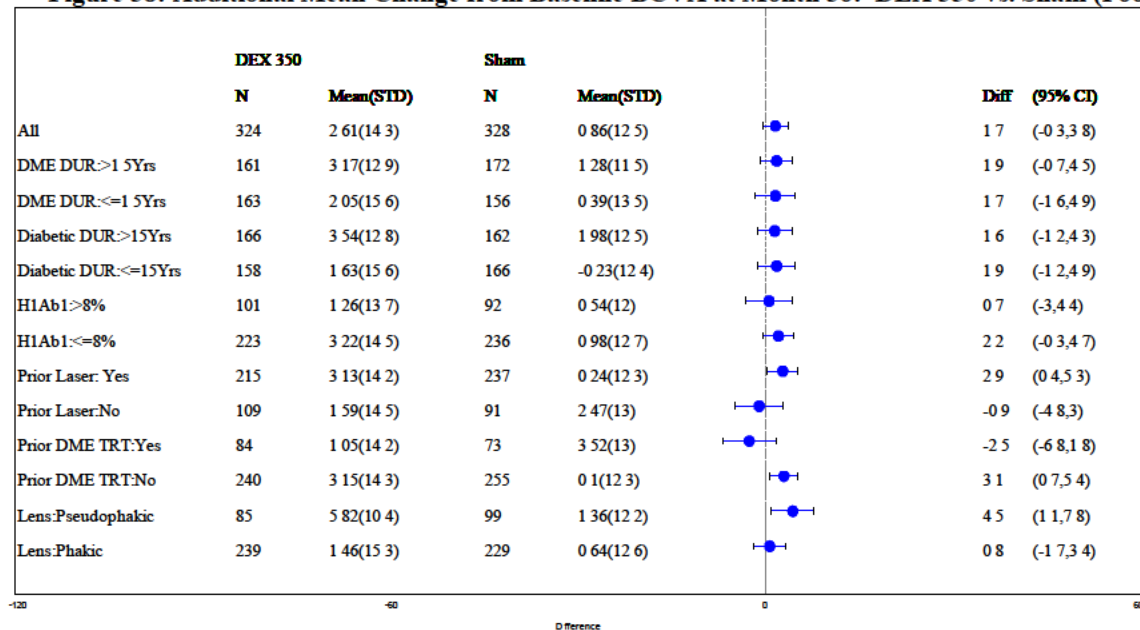
Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

Figure 37: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at Month 36: DEX 350 vs. Sham (Pooled)



Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at Month 36 in the subgroup.

Figure 38: Additional Mean Change from Baseline BCVA at Month 36: DEX 350 vs. Sham (Pooled)



Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at Month 36 in the subgroup.

Table 62: The 22 subjects with BCVA at Month 39 without re-treatment at Month 36

USUBJID	TRTGRP	BASELENS	Change from baseline BCVA			Cataract surgery (1=Yes)	Cataract AE (1=Yes)	Month of surgery	IOP (1=Yes)
			Month 33	Month 36	Month 39				
206207010-3084-5018	DEX 350	Phakic	9*	9	13*	1	1	10.5	0
206207010-3193-5266	DEX 350	Phakic	-26*	-29*	-22*	0	0		0
206207010-4258-4008	DEX 350	Phakic	6*	-12*	-18*	0	1		1
206207010-4447-4315	DEX 350	Pseudophakic	6*	6	8*	0	0		1
206207010-4539-4385	DEX 350	Phakic	-4*	1*	-1*	1	1	24	1
206207010-6415-4483	DEX 350	Phakic	30*	30	23*	1	1	15	1
206207011-4220-7780	DEX 350	Phakic	-39*	-39	5*	1	1	36	1
206207011-4292-7080	DEX 350	Phakic	-17*	-17	-20*	0	0		1
206207011-4533-7311	DEX 350	Phakic	-44*	-44	0*	1	1	33	1
206207011-5255-8392	DEX 350	Phakic	7*	7	14*	1	1	21	1
206207010-4396-4585	DEX 700	Phakic	7*	13*	13*	1	1	27	1
206207011-4220-7728	DEX 700	Pseudophakic	15*	15	2*	0	0		1
206207011-4220-7838	DEX 700	Phakic	-40*	-40	8*	1	1	36	1
206207011-4408-7497	DEX 700	Pseudophakic	-5*	-17*	-6*	0	0		1
206207011-4498-7512	DEX 700	Phakic	9	9	15*	1	0	18	0
206207011-4498-7986	DEX 700	Phakic	-2*	-2	2*	1	1	18	0
206207010-4396-4580	Sham	Phakic	-10	-17*	-9	0	0		0
206207010-4396-4584	Sham	Phakic	9*	14*	15*	0	0		0
206207010-4452-4338	Sham	Pseudophakic	6*	6*	0*	0	0		0
206207011-4044-7475	Sham	Pseudophakic	5	5	2*	0	0		0
206207011-4234-7190	Sham	Pseudophakic	2*	2	-1*	0	0		0

Source: Reviewer's Analysis. * Observed BCVA.

Table 63: Number of subjects with a BCVA measurement by Visit

Visit	Study 206207-010			Study 206207-011			Pooled		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
	N=163	N=166	N=165	N=165	N=158	N=163	N=328	N=324	N=328
1.5	156(95.7%)	160(96.4%)	155(93.9%)	162(98.2%)	153(96.8%)	151(92.6%)	318(97%)	313(96.6%)	306(93.3%)
3.0	156(95.7%)	161(97%)	147(89.1%)	159(96.4%)	150(94.9%)	153(93.9%)	315(96%)	311(96%)	300(91.5%)
4.5	151(92.6%)	154(92.8%)	139(84.2%)	153(92.7%)	144(91.1%)	139(85.3%)	304(92.7%)	298(92%)	278(84.8%)
6.0	143(87.7%)	154(92.8%)	126(76.4%)	150(90.9%)	143(90.5%)	132(81%)	293(89.3%)	297(91.7%)	258(78.7%)
7.5	137(84%)	145(87.3%)	111(67.3%)	145(87.9%)	133(84.2%)	115(70.6%)	282(86%)	278(85.8%)	226(68.9%)
9.0	138(84.7%)	152(91.6%)	102(61.8%)	139(84.2%)	135(85.4%)	110(67.5%)	277(84.5%)	287(88.6%)	212(64.6%)

10.5	133(81.6%)	139(83.7%)	102(61.8%)	138(83.6%)	130(82.3%)	98(60.1%)	271(82.6%)	269(83%)	200(61%)
12.0	137(84%)	151(91%)	103(62.4%)	140(84.8%)	126(79.7%)	99(60.7%)	277(84.5%)	277(85.5%)	202(61.6%)
15.0	129(79.1%)	141(84.9%)	90(54.5%)	132(80%)	113(71.5%)	96(58.9%)	261(79.6%)	254(78.4%)	186(56.7%)
18.0	124(76.1%)	136(81.9%)	81(49.1%)	127(77%)	122(77.2%)	89(54.6%)	251(76.5%)	258(79.6%)	170(51.8%)
21.0	114(69.9%)	133(80.1%)	79(47.9%)	116(70.3%)	103(65.2%)	79(48.5%)	230(70.1%)	236(72.8%)	158(48.2%)
24.0	116(71.2%)	125(75.3%)	75(45.5%)	113(68.5%)	98(62%)	73(44.8%)	229(69.8%)	223(68.8%)	148(45.1%)
27.0	107(65.6%)	122(73.5%)	69(41.8%)	106(64.2%)	95(60.1%)	70(42.9%)	213(64.9%)	217(67%)	139(42.4%)
30.0	102(62.6%)	110(66.3%)	65(39.4%)	99(60%)	92(58.2%)	64(39.3%)	201(61.3%)	202(62.3%)	129(39.3%)
33.0	102(62.6%)	112(67.5%)	61(37%)	96(58.2%)	91(57.6%)	62(38%)	198(60.4%)	203(62.7%)	123(37.5%)
36.0	104(63.8%)	107(64.5%)	63(38.2%)	95(57.6%)	84(53.2%)	64(39.3%)	199(60.7%)	191(59%)	127(38.7%)
39.0	30(18.4%)	38(22.9%)	18(10.9%)	25(15.2%)	25(15.8%)	22(13.5%)	55(16.8%)	63(19.4%)	40(12.2%)

Source: Reviewer's Analysis

Table 64: Number of who remained in the study by Visit

Visit	Study 206207-010			Study 206207-011			Pooled		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163	DEX 700 N=328	DEX 350 N=324	Sham N=328
1.0	163(100%)	166(100%)	165(100%)	165(100%)	158(100%)	163(100%)	328(100%)	324(100%)	328(100%)
1.5	160(98.2%)	164(98.8%)	160(97%)	164(99.4%)	156(98.7%)	160(98.2%)	324(98.8%)	320(98.8%)	320(97.6%)
3.0	160(98.2%)	164(98.8%)	154(93.3%)	162(98.2%)	156(98.7%)	157(96.3%)	322(98.2%)	320(98.8%)	311(94.8%)
4.5	158(96.9%)	163(98.2%)	148(89.7%)	161(97.6%)	154(97.5%)	153(93.9%)	319(97.3%)	317(97.8%)	301(91.8%)
6.0	156(95.7%)	162(97.6%)	137(83%)	161(97.6%)	153(96.8%)	149(91.4%)	317(96.6%)	315(97.2%)	286(87.2%)
7.5	151(92.6%)	159(95.8%)	122(73.9%)	155(93.9%)	148(93.7%)	129(79.1%)	306(93.3%)	307(94.8%)	251(76.5%)
9.0	147(90.2%)	158(95.2%)	118(71.5%)	151(91.5%)	145(91.8%)	124(76.1%)	298(90.9%)	303(93.5%)	242(73.8%)
10.5	145(89%)	157(94.6%)	115(69.7%)	146(88.5%)	142(89.9%)	118(72.4%)	291(88.7%)	299(92.3%)	233(71%)
12.0	144(88.3%)	156(94%)	112(67.9%)	144(87.3%)	138(87.3%)	114(69.9%)	288(87.8%)	294(90.7%)	226(68.9%)
15.0	134(82.2%)	148(89.2%)	100(60.6%)	137(83%)	131(82.9%)	105(64.4%)	271(82.6%)	279(86.1%)	205(62.5%)
18.0	128(78.5%)	146(88%)	93(56.4%)	135(81.8%)	129(81.6%)	100(61.3%)	263(80.2%)	275(84.9%)	193(58.8%)
21.0	123(75.5%)	142(85.5%)	86(52.1%)	127(77%)	119(75.3%)	92(56.4%)	250(76.2%)	261(80.6%)	178(54.3%)
24.0	122(74.8%)	137(82.5%)	82(49.7%)	124(75.2%)	113(71.5%)	87(53.4%)	246(75%)	250(77.2%)	169(51.5%)
27.0	119(73%)	131(78.9%)	79(47.9%)	116(70.3%)	105(66.5%)	85(52.1%)	235(71.6%)	236(72.8%)	164(50%)
30.0	114(69.9%)	127(76.5%)	76(46.1%)	113(68.5%)	104(65.8%)	80(49.1%)	227(69.2%)	231(71.3%)	156(47.6%)
33.0	111(68.1%)	123(74.1%)	74(44.8%)	109(66.1%)	100(63.3%)	80(49.1%)	220(67.1%)	223(68.8%)	154(47%)
36.0	110(67.5%)	120(72.3%)	73(44.2%)	106(64.2%)	96(60.8%)	79(48.5%)	216(65.9%)	216(66.7%)	152(46.3%)
39.0	30(18.4%)	41(24.7%)	22(13.3%)	27(16.4%)	26(16.5%)	26(16%)	57(17.4%)	67(20.7%)	48(14.6%)

Table 65: Number of Subjects who remained in the study and with BCVA outcomes by Visit (Site 2707)

Visit	Remained in the Study			BCVA outcome		
	DEX 700 N=23	DEX 350 N=23	Sham N=22	DEX 700 N=23	DEX 350 N=23	Sham N=22
1	23(100%)	23(100%)	22(100%)	NA	NA	NA
1.5	23(100%)	23(100%)	22(100%)	21(91.3%)	23(100%)	21(95.5%)
3.0	23(100%)	23(100%)	22(100%)	23(100%)	23(100%)	22(100%)
4.5	22(95.7%)	23(100%)	22(100%)	22(95.7%)	22(95.7%)	20(90.9%)
6.0	21(91.3%)	23(100%)	20(90.9%)	20(87%)	21(91.3%)	16(72.7%)
7.5	21(91.3%)	23(100%)	18(81.8%)	19(82.6%)	19(82.6%)	15(68.2%)
9.0	20(87%)	23(100%)	18(81.8%)	18(78.3%)	21(91.3%)	16(72.7%)
10.5	19(82.6%)	23(100%)	17(77.3%)	17(73.9%)	21(91.3%)	16(72.7%)
12.0	19(82.6%)	23(100%)	16(72.7%)	17(73.9%)	22(95.7%)	14(63.6%)
15.0	18(78.3%)	22(95.7%)	11(50%)	16(69.6%)	22(95.7%)	10(45.5%)
18.0	17(73.9%)	20(87%)	10(45.5%)	15(65.2%)	19(82.6%)	9(40.9%)
21.0	17(73.9%)	19(82.6%)	9(40.9%)	16(69.6%)	19(82.6%)	7(31.8%)
24.0	17(73.9%)	19(82.6%)	8(36.4%)	15(65.2%)	19(82.6%)	6(27.3%)
27.0	15(65.2%)	18(78.3%)	7(31.8%)	14(60.9%)	18(78.3%)	3(13.6%)
30.0	14(60.9%)	18(78.3%)	6(27.3%)	13(56.5%)	17(73.9%)	4(18.2%)
33.0	14(60.9%)	18(78.3%)	6(27.3%)	12(52.2%)	18(78.3%)	4(18.2%)
36.0	13(56.5%)	18(78.3%)	6(27.3%)	12(52.2%)	17(73.9%)	4(18.2%)
39.0	0(0%)	3(13%)	0(0%)	0(0%)	3(13%)	0(0%)

Source: Reviewer's Analysis

Table 66: Definition of visit Window

Visit	Target Number of Days from Day 0 (Randomization)	Window (Study Days)
Year 1		
Month 1.5	45	29-67
Month 3	90	68-112
Month 4.5	135	113-157
Month 6	180	158-202

Month 7.5	225	203-247
Month 9	270	248-292
Month 10.5	315	293-337
Month 12	360	338-404
Year 2		
Month 15	450	405-494
Month 18	540	495-584
Month 21	630	585-674
Month 24	720	675-764
Year 3		
Month 27	810	765-854
Month 30	900	855-944
Month 33	990	945-1034
Month 36	1080	1035- 1124
Month 39	1170	1125- 1215

7 Appendix B: Efficacy and Safety Summary Without Excluding Site 2707

• Efficacy Results

Table B1: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at Month 36

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
011	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2% (-1.6%, 12%)
Pooled	65 (18.5%)	61 (17.6%)	37 (10.6%)	7.9% (2.8%, 13.1%)	7.0% (1.9%, 12.1%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

Table B2: Sensitivity Analysis for the Primary Efficacy Endpoint

Studies	Methods	Treatment: N (%)			%Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
206207-010	Multiple Imputation	34/163 (20.8%)	39/166 (23.4%)	25/165 (15.1%)	5.7% (-5.6%, 16.7%)	8.4% (-5.2%, 22.0%)
	Per-Protocol	31/144 (21.5%)	31/155 (20.0%)	18/143 (12.6%)	8.9% (0.3%, 17.6%)	7.4% (-0.9%, 15.7%)
	Complete Case	25/104 (24.0%)	29/107 (27.1%)	13/63 (20.6%)	3.4% (-9.5%, 16.3%)	6.5% (-6.6%, 19.5%)
206207-011	Multiple Imputation	35/188 (18.6%)	35/181 (19.3%)	19/185 (10.5%)	8.1% (0.8%, 16.4%)	9.0% (-0.01%, 18.1%)
	Per-Protocol	31/170 (18.2%)	27/159 (17.0%)	19 /162 (11.7%)	6.5% (-1.0%, 14.1%)	5.2% (-2.4%, 12.9%)
	Complete Case	27/107 (25.2%)	25/101 (24.7%)	16/68 (23.5%)	1.7% (-11.3%, 14.7%)	1.2% (-11.9%, 14.4%)

Source: Reviewer's Analysis. For per-protocol analysis, LOCF was used to impute missing data for all subjects with missing data except for non-protocol violators. The complete case analysis is based on subjects who had a BCVA measurement at Month 36. For all analyses, subjects who received escape therapy prior to Month 36 were set as treatment failures.

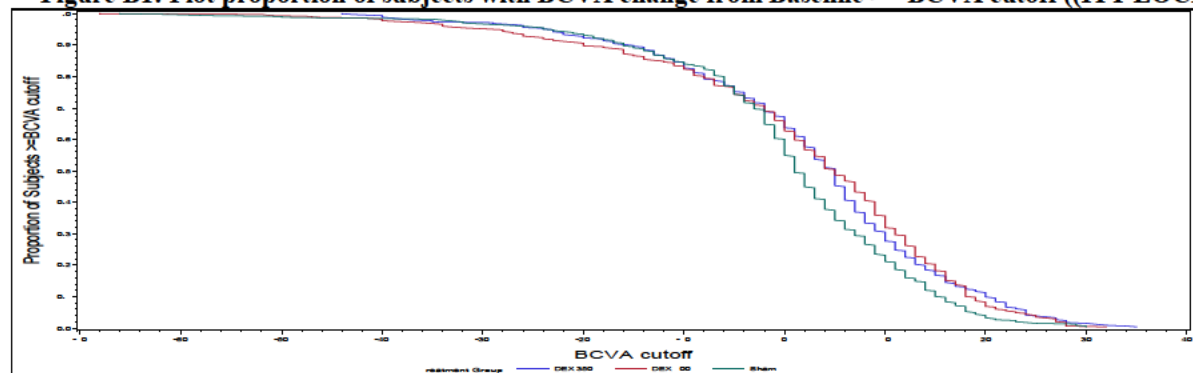
Table B3: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by Visit (ITT LOCF)

Visit	DEX 700 N=347	DEX 350 N=344	Sham N=349	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010				
Month 6	23(14.1%)	17(10.2%)	12(7.3%)	6.8% (0.2%, 13.5%)	3% (-3.1%, 9.0%)
Month 12	22(13.5%)	25(15.1%)	13(7.9%)	5.6% (-1%, 12.3%)	7.2% (0.4%, 14.0%)
Month 18	26(16%)	16(9.6%)	15(9.1%)	6.9% (-0.3%, 14%)	0.5% (-5.7%, 6.8%)
Month 24	21(12.9%)	25(15.1%)	15(9.1%)	3.8% (-3%, 10.6%)	6.0% (-1%, 13.0%)
Month 36	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1%, 16.5%)	9.0% (1.3%, 16.7%)
Month 39	34(20.9%)	31(18.7%)	19(11.5%)	9.3% (1.4%, 17.3%)	7.2% (-0.5%, 14.8%)
	Study 206207-011				
Month 6	16(8.5%)	11(6.1%)	6(3.2%)	5.3% (0.5%, 10%)	2.8% (-1.5%, 7.2%)
Month 12	23(12.2%)	17(9.4%)	17(9.2%)	3% (-3.2%, 9.3%)	0.2% (-5.7%, 6.2%)

Month 18	21(11.2%)	18(9.9%)	16(8.6%)	2.5%(-3.5%, 8.6%)	1.3%(-4.7%, 7.2%)
Month 24	31(16.5%)	15(8.3%)	18(9.7%)	6.8%(-0.1%, 13.6%)	-1.4%(-7.3%, 4.4%)
Month 36	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)
Month 39	38(20.2%)	31(17.1%)	19(10.3%)	9.9% (2.7%, 17.2%)	6.9%(-0.2%, 13.9%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy prior to a given visit were set as treatment failures in that and subsequent visits.

Figure B1: Plot proportion of subjects with BCVA change from Baseline \geq BCVA cutoff (ITT LOCF)



Source: Reviewer's Analysis

Table B4: Categorical Summary of BCVA Change from Baseline at Month 36 (ITT LOCF)

BCVA Change	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=188	DEX 350 N=181	Sham N=185
≥ 15 Letters Improvement	32 (19.6)	33(19.9)	18(10.9)	33(17.6)	28(15.5)	19 (10.3)
≥ 10 and < 15 Letters Improvement	27(16.6)	21(12.7)	15(9.1)	22(11.7)	17(9.4)	20(10.8)
≥ 5 and < 10 Letters Improvement	27(16.6)	31(18.7)	20(12.1)	21(11.2)	34(18.8)	18(9.7)
No Change (-5 to +5 Letters)	49 (30.1)	58(34.9)	85(51.5)	70(37.2)	55(30.4)	96(51.9)
≥ 5 and < 10 Letters Worsening	12(7.4)	12(7.2)	8(4.8)	9(4.8)	11(6.1)	10(5.4)
≥ 10 and < 15 Letters Worsening	5(3.1)	3(1.8)	6(3.6)	6(3.2)	11(6.1)	7(3.8)
≥ 15 Letters Worsening	11(6.7)	8(4.8)	13(7.9)	27(14.4)	25(13.8)	15(8.1)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set to the "no change" category.

Table B5: Summary of Area under the Curve (AUC) of the Change from Baseline BCVA

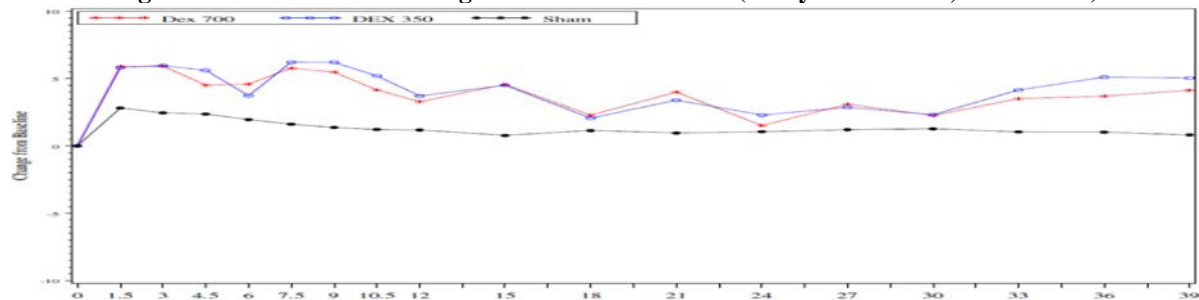
Studies	Treatment : Mean AUC (std)			Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	4.11 (8.26)	4.33 (8.49)	1.89 (7.74)	2.22 (0.48, 3.96)	2.45 (0.69,4.20)
010	2.90 (8.55)	2.94 (7.67)	2.02 (8.20)	0.88 (-0.83, 2.59)	0.91 (-0.72, 2.54)

Source: Table 11-1 of the applicant's submitted Study Reports.

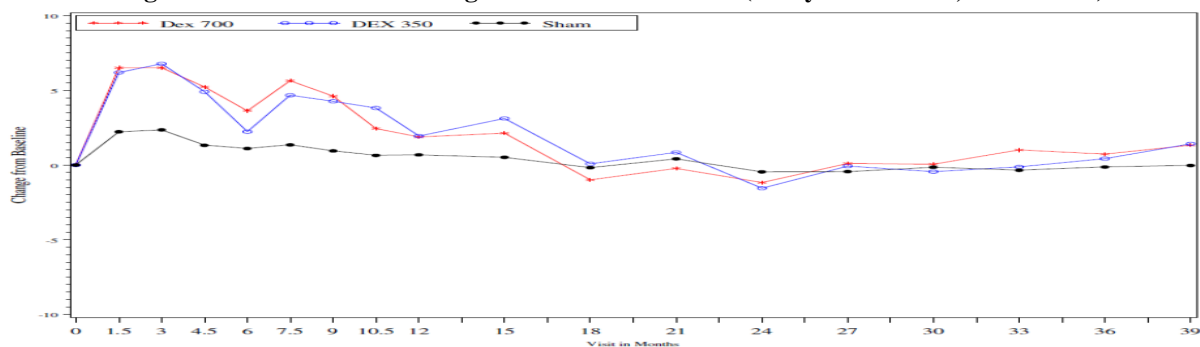
Table B6: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)

Visit	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Baseline*	56.2 (10.0)	55.9(9.6)	56.8(8.7)	-0.5 (-2.5, 1.5)	-0.9 (-2.9, 1.1)
Month 6	4.6(9)	3.7(9.1)	2(9)	2.6(0.7,4.6)	1.8(-0.2,3.7)
Month 12	3.3(10.7)	3.7(10.4)	1.2(10.2)	2.1(-0.2,4.4)	2.5(0.3,4.8)
Month 18	2.3(12.4)	2.1(11.3)	1.1(10.9)	1.1(-1.4,3.7)	0.9(-1.5,3.3)
Month 24	1.5(14.4)	2.3(14.7)	1.1(11.1)	0.5(-2.3,3.2)	1.2(-1.6,4.1)
Month 30	2.3(14.8)	2.3(15.2)	1.3(11.7)	1(-1.9,3.9)	1(-1.9,4)
Month 36	3.7(14.1)	5.1(12.3)	1(11.6)	2.7(-0.1,5.5)	4.1(1.5,6.7)
Month 39	4.1(13.9)	5(12)	0.8(11.9)	3.3(0.5,6.1)	4.2(1.7,6.8)
Study 206207-011					
Baseline*	55.9(9.8)	55.2(9.7)	57.0(8.8)	-1.1 (-3.0, 0.7)	-1.8 (-3.7, 0.1)
Month 6	3.6(8.6)	2.2(10.7)	1.1(10.2)	2.5(0.6,4.4)	1.1(-1,3.3)
Month 12	1.9(12.4)	1.9(11.2)	0.7(12.9)	1.2(-1.4,3.8)	1.3(-1.2,3.7)
Month 18	-1(14.7)	0.1(13.5)	-0.2(14.1)	-0.8(-3.8,2.1)	0.3(-2.6,3.1)
Month 24	-1.2(17.4)	-1.6(14.5)	-0.5(15.3)	-0.7(-4.1,2.6)	-1.1(-4.2,2)
Month 30	0.1(16.7)	-0.4(14.6)	-0.1(15.1)	0.2(-3,3.4)	-0.3(-3.3,2.7)
Month 36	0.7(17.2)	0.4(15.6)	-0.1(15.3)	0.9(-2.4,4.2)	0.6(-2.6,3.7)
Month 39	1.3(17)	1.4(15.2)	0(15.4)	1.4(-1.9,4.7)	1.4(-1.7,4.6)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. * Baseline measurement.

Figure B2: Plot of Mean Change from Baseline BCVA (Study 206207-010; ITT LOCF)

Source: Figure 11-1 of the applicant's submitted Study Reports. LOCF was used for imputing missing data.

Figure B3: Plot of Mean Change from Baseline BCVA (Study 206207-011; ITT LOCF)

Source: Figure 11-1 of the applicant's submitted Study Reports. LOCF was used for imputing missing data.

Table B7: Summary of Quartiles of Change in BCVA from Baseline at Month 36 (ITT LOCF)

Studies	Quartile	Treatment: N (%)			Diff (95% CI)	
		DEX 700 N=351	DEX 350 N=347	Sham N=350	DEX 700 vs. Sham	DEX 350 vs. Sham
010	Q1	-3.0	-1.0	-5.0	2.0 (-7,8.5)	4.0 (-3.99,11.5)
	Q2	6.0	5.0	1.0	5.0 (-1.4,14.4)	4.0 (-1.87,13.4)
	Q3	13.0	12.0	9.0	4.0 (-1.5,15)	3.0 (-1.49,11.2)
011	Q1	-7.0	-9.0	-5.0	-2.0 (-9.5,5.9)	-4.0 (-14.89,2.4)
	Q2	4.0	3.0	2.0	2.0 (-5,11.5)	1.0 (-3.89,10.9)
	Q3	12.0	10.0	9.0	3.0 (-3.2,11.5)	1.0 (-5.39,8.8)
Pooled	Q1	-5.0	-5.0	-5.0	0.0 (-8.5,8.7)	0.0 (-8.47,11.7)
	Q2	5.0	5.0	1.0	4.0 (-8,11.5)	4.0 (-7.45,4)
	Q3	13.0	11.0	9.0	4.0 (-4.7,11.5)	2.0 (-2.97,11.7)

Source: Reviewer's analysis. Q1, Q2 (Median) and Q3 correspond to first, second and third quartiles.

Table B8: Summary of Secondary Efficacy Outcomes: DEX 700 vs. Sham

Studies	Outcomes	Treatment : mean (std)		Mean Diff (95% CI)
		DEX 700	Sham	DEX 700 vs. Sham
010	Retinal thickness	-98.2 (178.9)	-52.1 (177.6)	-62.4 (-98.4, -26.5)
	Contrast sensitivity	-1.1 (8.0)	0.1 (4.5)	-1.1 (-2.5, 0.2)
011	Retinal thickness	-107.5 (228.3)	-71.3 (176.8)	-36.2 (-89.7, -5.1)
	Contrast sensitivity	-0.6 (8.4)	-0.7 (6.7)	-0.1 (-1.5,-1.6)
Pooled	Retinal thickness	-117.3 (208.1)	-62.1 (180.1)	-55.3 (-84.3,-26.2)
	Contrast sensitivity	-0.8 (8.3)	-0.3 (6.0)	-5.2 (-1.6,0.5)

Source: Table 14.2-6.2 and Table 14.2-9 of the applicant's submitted Study Reports.

Table B9: Summary of Secondary Efficacy Outcomes: DEX 350 vs. Sham

Studies	Outcomes	Treatment : mean (std)		Mean Diff (95% CI)
		DEX 350	Sham	DEX 350 vs. Sham
010	Retinal thickness	-109.0 (184.9)	-52.1 (177.6)	-62.6 (-98.3, -27.0)
	Contrast sensitivity	0.1 (6.4)	0.1 (4.5)	-0.3 (-1.7, 1.0)
011	Retinal thickness	-115.2 (202.3)	-71.3 (176.8)	-34.1 (-74.2, 5.9)
	Contrast sensitivity	-2.1 (7.8)	-0.7 (6.7)	-1.5 (-2.9, 0.0)
Pooled	Retinal thickness	-127.8 (196.7)	-62.0 (180.1)	-65.7 (-94.0,-37.5)
	Contrast sensitivity	-0.7 (7.1)	0.2 (6.0)	-0.5 (-1.4, 0.5)

Source: Table 14.2-6.2 and Table 14.2-9 of the applicant's submitted Study Reports.

Table B10: Summary of Correlations between Changes in Retinal Thickness and Contrast sensitivity and BCVA from Baseline at Month 36

Outcome	Correlation (95% CI)		
	Treatment Effects	Residuals	Outcomes
Retinal thickness	0.25 (0.00, 0.51)	0.34 (0.26, 0.41)	-0.35 (-0.45, -0.28)
Contrast sensitivity	0.78 (0.26, 0.87)	0.53 (0.46, 0.62)	0.54 (0.48, 0.59)

Source: Reviewer's analysis.

Table B11: Summary of Change in Patient Reported Outcomes from Baseline at Month 36: DEX 700 vs. Sham

Studies	Score	Treatment: mean (std)		Diff (95% CI)
		DEX 700	Sham	DEX 700 vs. Sham
	Composite Score	-1.08 (16.78)	-0.41 (14.34)	-0.66 (-4.19, 2.86)

010	General Vision Score	3.60 (20.07)	2.76 (15.95)	0.84 (-3.27, 4.94)
	Difficulty With Near Vision Score	4.44 (23.08)	4.24 (20.42)	0.19 (-4.73, 5.12)
	Difficulty With Far Vision Score	-1.52 (23.81)	-0.74 (19.35)	-0.78 (-5.68, 4.13)
	Mental Health Score	4.44 (23.08)	4.24 (20.42)	0.19 (-4.73, 5.12)
011	Composite Score	2.11 (18.18)	2.37 (16.03)	-0.26 (-3.89, 3.36)
	General Vision Score	5.96 (18.13)	6.39 (18.81)	-0.43 (-4.35, 3.49)
	Difficulty With Near Vision Score	6.71 (25.49)	4.33 (23.49)	2.37 (-2.81, 7.56)
	Difficulty With Far Vision Score	4.55 (25.88)	2.73 (21.76)	1.80 (-3.25, 6.86)
	Mental Health Score	7.04 (27.71)	5.63 (25.07)	1.41 (-4.18, 7.00)
Pooled	Composite Score	0.62 (17.6)	1.07 (15.3)	-0.45 (-3.0, 2.09)
	General Vision Score	4.86 (19.07)	4.69 (17.60)	0.17 (-2.67, 3.00)
	Difficulty With Near Vision Score	5.65 (24.38)	4.29 (22.08)	1.35 (-2.23, 4.94)
	Difficulty With Far Vision Score	1.72 (25.08)	1.12 (20.72)	0.59 (-2.95, 4.14)
	Mental Health Score	4.70 (26.39)	4.51 (23.70)	0.19 (-3.67, 4.06)

Source: Reviewer's analysis.

Table B12: Summary of Change in Patient Reported Outcomes from Baseline at Month 36: DEX 350 vs. Sham

Studies	Score	Treatment : mean (std)		Diff (95% CI)
		DEX 350	Sham	DEX 350 vs. Sham
010	Composite Score	1.32 (15.45)	-0.41 (14.34)	1.74 (-1.60, 5.08)
	General Vision Score	6.19 (16.36)	2.76 (15.95)	3.43 (-0.19, 7.06)
	Difficulty With Near Vision Score	5.56 (19.54)	4.24 (20.42)	1.31 (-3.17, 5.80)
	Difficulty With Far Vision Score	2.57 (19.35)	-0.74 (19.35)	3.31 (-1.04, 7.66)
	Mental Health Score	3.37 (24.38)	4.24 (20.42)	0.15 (-5.06, 5.37)
011	Composite Score	1.29 (16.09)	2.37 (16.03)	-1.08 (-4.50, 2.34)
	General Vision Score	6.54 (19.27)	6.39 (18.81)	0.15 (-3.93, 4.23)
	Difficulty With Near Vision Score	3.47 (20.90)	4.33 (23.49)	-0.87 (-5.61, 3.87)
	Difficulty With Far Vision Score	-1.50 (22.09)	2.73 (21.76)	-4.25 (-8.92, 0.42)
	Mental Health Score	4.44 (24.34)	5.63 (25.07)	-1.20 (-6.46, 4.07)
Pooled	Composite Score	1.31 (15.76)	1.07 (15.3)	0.23 (-2.16, 2.63)
	General Vision Score	6.37 (17.89)	4.69 (17.60)	1.68 (-1.06, 4.43)
	Difficulty With Near Vision Score	4.47 (20.25)	4.29 (22.08)	0.18 (-3.09, 3.45)
	Difficulty With Far Vision Score	0.45 (20.89)	1.12 (20.72)	-0.67 (-3.88, 2.54)
	Mental Health Score	3.92 (24.33)	4.51 (23.70)	-0.58 (-4.29, 3.12)

Source: Reviewer's analysis.

Table B13: Summary of Correlations between Changes in Patient Reported Scores and BCVA from Baseline at Month 36

Score	Correlation (95% CI)		
	Treatment Effects	Residuals	Outcomes
Composite Score	0.62 (0.20, 0.85)	0.26 (0.17, 0.33)	0.22 (0.16, 0.28)
General Vision Score	0.32 (-0.38, 0.60)	0.22 (0.14, 0.30)	0.20 (0.14, 0.25)
Near Vision Score	0.48 (-0.32, 0.75)	0.22 (0.14, 0.30)	0.23 (0.17, 0.29)
Far Vision Score	0.56 (-0.17, 0.80)	0.20 (0.14, 0.28)	0.17 (0.12, 0.23)
Mental Health Score	0.60 (0.1, 0.83)	0.20 (0.1, 0.26)	0.18 (0.12, 0.24)

Source: Reviewer's analysis.

- **Evaluation of Safety**

Table B14: Summary of Number of Injections

# of Injections	Treatment: N (%)		
	DEX 700 N=347	DEX 350 N=343	Sham N=350
1	44 (12.7%)	35 (10.2%)	105 (30.1%)
2	54 (15.6%)	45 (13.1%)	63 (18.1%)
3	39 (11.2%)	41 (11.9%)	41 (11.7%)
4	42 (12.1%)	40 (11.6%)	26 (7.4%)
5	49 (14.1%)	41 (11.9%)	29 (8.3%)
6	88 (25.4%)	105 (30.5%)	50 (14.3%)
7	31 (8.9%)	37 (10.8%)	35 (10.0%)
Mean (std)	4.11(1.95)	4.37 (1.93)	3.29 (2.15)
Median	4.0	5.0	3.0
Q1, Q3	2.0, 6.0	3.0, 6.0	1.0, 5.0

Source: Reviewer's analysis.

Table B15: Summary of Subjects Who Received Retreatment by Visit

Time to First Re-treatment	Treatment: N (%)		
	DEX 700 N=303*	DEX 350 N=308*	Sham N=245*
Month 6	227(74.9%)	247(80.2%)	194(79.2%)
Month 7.5	26(8.6%)	21(6.8%)	15(6.1%)
Month 9	20(6.6%)	19(6.2%)	17(6.9%)
Month 10.5	6(2.0%)	4(1.3%)	4(1.6%)
Month 12	188(62%)	207(67.2%)	140(57.1%)
Month 15	40(13.2%)	36(11.7%)	27(11.0%)
Month 18	147(48.5%)	154(50%)	109(44.5%)
Month 21	46(15.2%)	56(18.2%)	25(10.2%)
Month 24	110(36.3%)	134(43.5%)	96(39.2%)
Month 27	59(19.5%)	49(15.9%)	25(10.2%)
Month 30	89(29.4%)	113(36.7%)	70(28.6%)
Month 33	69(22.8%)	60(19.5%)	32(13.1%)
Month 36	52(17.2%)	58(18.8%)	45(18.4%)
Month 39	1(0.3%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's analysis. * # of subjects who received at least one retreatment.

Table B16: Summary of First Time Retreatment

Time to First Re-treatment	Treatment: N (%)		
	DEX 700 N=303*	DEX 350 N=308*	Sham N=245*
Month 6	227(74.9%)	247(80.2%)	194(79.2%)
Month 7.5	26(8.6%)	21(6.8%)	15(6.1%)
Month 9	20(6.6%)	19(6.2%)	17(6.9%)
Month 10.5	4(1.3%)	3(1.0%)	4(1.6%)
Month 12	13(4.3%)	8(2.6%)	3(1.2%)

Month 15	2(0.7%)	2(0.6%)	3(1.2%)
Month 18	5(1.7%)	3(1.0%)	3(1.2%)
Month 21	3(1.0%)	0 (0.0%)	1(0.4%)
Month 24	2(0.7%)	3(1%)	3(1.2%)
Month 27	0 (0.0%)	2(0.6%)	0 (0.0%)
Month 30	0 (0.0%)	1(0.3%)	0 (0.0%)
Month 33	1(0.3%)	0 (0.0%)	1(0.4%)

Source: Reviewer's analysis. * # of subjects who received at least one retreatment.

Table B17: Summary of Adverse Events (AE) (All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=347	DEX 350 N=343	Sham N=350	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	333 (96.0%)	334 (97.4%)	281 (80.3%)	15.7% (11.0%, 20.3%)	17.1% (12.6%, 21.6%)
Any Ocular AE	296 (85.3%)	303 (88.3%)	203 (58.0%)	27.3% (20.9%, 33.7%)	30.3% (24.2%, 36.5%)
Any Serious AE	115 (33.1%)	120 (35.0%)	83 (23.7%)	9.4% (2.8%, 16.1%)	11.3% (4.5%, 18.0%)
Any Ocular Serious AE	24 (6.9%)	14 (4.1%)	4 (1.1%)	5.8% (2.9%, 8.7%)	3.0% (0.6%, 5.3%)
Any Severe AE	164 (47.3%)	164 (47.8%)	108 (30.9%)	16.4% (9.3%, 23.5%)	17.7% (11.9%, 23.4%)
Any Ocular Severe AE	99 (28.5%)	81 (23.6%)	38 (10.9%)	17.7% (11.9%, 23.4%)	12.8% (7.2%, 18.3%)
Any IOP Related AE	125 (36.0%)	117 (34.1%)	18 (5.1%)	30.9% (25.3%, 36.4%)	29.0% (23.4%, 34.5%)
≥10 mm Hg IOP Change from Baseline at any visit	96 (27.7%)	85 (24.8%)	13 (3.7%)	24.0% (18.8%, 29.1%)	21.1% (16.1%, 26.0%)
≥25 mm Hg IOP at any visit	111 (32.0%)	94 (27.4%)	15 (4.3%)	27.7% (22.4%, 33.0%)	23.1% (17.9%, 28.3%)
≥35 mm Hg IOP at any visit	23 (6.6%)	18 (5.2%)	3 (0.9%)	5.8% (3.0%, 8.6%)	4.4% (1.8%, 6.9%)
Glaucoma	4 (1.2%)	3 (0.9%)	1 (0.3%)	0.9% (-0.4, 2.1%)	0.6% (-0.5%, 1.7%)
IOP Lowering Procedures	4 (1.1%)	1 (0.3%)	1 (0.3%)	0.9% (-0.4%, 2.1%)	0.0% (-0.8%, 0.8%)
Cataract Surgery in Baseline Phakic Subjects	155/262 (59.2%)	134/257 (52.1%)	18/250 (7.2%)	51.9% (45.2%, 58.7%)	44.9% (38.1%, 51.8%)
≥15 Letters Loss from Baseline	48 (13.8%)	37 (10.8%)	39 (11.1%)	2.7% (-2.2%, 7.6%)	-0.4% (-5.0%, 4.3%)
Death	9 (2.6%)	15 (4.4%)	5 (1.4%)	1.1% (-0.9%, 3.2%)	2.9% (0.4%, 5.4%)
Escape Therapy	34 (9.8%)	39 (11.4%)	67 (19.1%)	-9.3% (-14.5%, -4.2%)	-7.8% (-13.1%, -2.5%)

Source: Tables 12-4, 14.3-22 14.3-22.3 and 14.3-22.4 of the applicant's study report. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, lenticular opacities). IOP related AE (IOP increased, ocular hypertension, glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table B18: Summary of Relationship of AE to Study Medication and Delivery System

AE Related To	Treatment N (%)			Total N=559
	DEX 700 N=244	DEX 350 N=227	Sham N=88	
Applicator or Insertion	65 (26.6%)	82 (36.1%)	48 (54.5%)	195 (34.9%)
Drug	171 (70.1%)	142 (62.5%)	37 (42.0%)	350 (62.6%)
Both	8 (3.3%)	2 (0.9%)	2 (2.3%)	12 (2.1%)
Unknown	0 (0.0%)	1 (0.4%)	1 (1.1%)	2 (0.3%)

Source: Reviewer's Analysis.

Table B19: Summary of Number of Subjects who had Cataract Surgery

Time of Surgery	Treatment: N (%)			Total N=307
	DEX 700 N=155	DEX 350 N=134	Sham N=18	
Month <=12	26(16.8%)	20(14.9%)	5(27.8%)	51 (16.6%)
Month 15	12(7.7%)	11(8.2%)	3(16.7%)	26 (8.4%)
Month 18	21(13.5%)	18(13.4%)	1(5.6%)	40 (13.0%)
Month 21	28(18.1%)	18(13.4%)	2(11.1%)	48 (15.6%)
Month 24	22(14.2%)	24(17.9%)	2(11.1%)	48 (15.6%)
Month 27	20(12.9%)	14(10.4%)	1(5.6%)	35 (11.4%)
Month 30	12(7.7%)	12(9.0%)	0(0.0%)	24 (7.8%)
Month 33	9(5.8%)	13(9.7%)	1(5.6%)	23 (7.5%)
Month 36	4(2.6%)	4(3.0%)	3(16.7%)	11 (3.6%)
Month 39	1(0.6%)	0(0.0%)	0(0.0%)	1 (0.3%)

Source: Reviewer's analysis.

Table B20: Summary of Number of who had Cataract Surgery by Study

Time of Cataract Surgery	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=72	DEX 350 N=72	Sham N=8	DEX 700 N=83	DEX 350 N=62	Sham N=10
Month <=12	14(19.4%)	10(13.9%)	1(12.5%)	12(14.5%)	10(16.1%)	4(40.0%)
Month 15	7(9.7%)	8(11.1%)	0(0.0%)	5(6.0%)	3(4.8%)	3(30.0%)
Month 18	6(8.3%)	8(11.1%)	0(0.0%)	15(18.1%)	10(16.1%)	1(10.0%)
Month 21	14(19.4%)	11(15.3%)	1(12.5%)	14(16.9%)	7(11.3%)	1(10.0%)
Month 24	7(9.7%)	15(20.8%)	2(25%)	15(18.1%)	9(14.5%)	0(0.0%)
Month 27	12(16.7%)	6(8.3%)	1(12.5%)	8(9.6%)	8(12.9%)	0(0.0%)
Month 30	5(6.9%)	7(9.7%)	0(0%)	7(8.4%)	5(8.1%)	0(0.0%)
Month 33	4(5.6%)	5(6.9%)	1(12.5%)	5(6%)	8(12.9%)	0(0.0%)
Month 36	2(2.8%)	2(2.8%)	2(25%)	2(2.4%)	2(3.2%)	1(10%)
Month 39	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

Source: Reviewer's analysis.

Table B21: Summary of the Mean Change from Baseline in BCVA within 9 Months of Cataract Surgery

Time of Surgery	Number of Months relative to Time of Surgery: Mean (Std)						
	-9	-6	-3	0	+3	+6	+9
Month 15	3.4 (6.5)	1.8 (11.1)	-5.8 (8.8)	-3.7 (14.0)	4.7 (10.4)	8.6 (13.0)	6.3 (12.2)
Month 18	3.7 (10.9)	-2.2 (14.8)	-6.1 (16.1)	-9.4 (16.3)	6.3 (11.5)	4.9 (10.5)	7.1 (10.8)

Month 21	1.2 (9.4)	2.1 (9.8)	-8.2 (15.2)	-4.6 (16.0)	1.8 (12.1)	4.8 (12.6)	4.1 (12.2)
Month 24	4.0 (10.4)	-3.4 (13.7)	-8.2 (14.2)	-11.0 (22.1)	3.1 (12.9)	4.3 (13.4)	4.9 (13.6)
Month 27	-1.7 (12.4)	-5.2 (13.7)	-16.9 (16.5)	-15.1 (19.5)	-4.8 (16.3)	-3.7 (16.7)	-2.8 (17.1)
Month 30	1.7 (8.1)	-10.6 (20.9)	5.3 (15.5)	-10.6 (20.9)	3.5 (10.1)	5.7 (15.6)	5.3 (15.5)
Month 33	-0.5 (10.9)	-4.3 (12.3)	-19.3 (18.8)	-9.7 (22.5)	3.1 (14.9)	5.2 (11.2)	
Month 36	-4.4 (12.9)	-5.8 (14.5)	-15 (19.6)	-9.0 (22.6)	-4.6 (19.4)		

Source: Reviewer's analysis. Positive and negative reflect # of month pre and post-surgery. Zero corresponds to time of surgery.

Table B22: Summary of the Proportion of Subjects with a Positive Change from Baseline in BCVA within 9 Months of Cataract Surgery

Time of Surgery	Number of Months relative to Time of Surgery: N (%)						
	-9	-6	-3	0	+3	+6	+9
Month 15	18/26 (69.2%)	16/26 (61.5%)	7/26 (26.9%)	11/26 (42.3%)	17/26 (65.4%)	21/26 (80.8%)	18/26 (69.2%)
Month 18	27/40 (67.5%)	18/40 (45.0%)	16/40 (40.0%)	11/40 (27.5%)	27/40 (67.5%)	24/40 (60.0%)	29/40 (72.5%)
Month 21	27/48 (56.2%)	28/48 (58.3%)	19/48 (39.6%)	22/48 (45.8%)	28/48 (58.3%)	35/48 (72.9%)	32/48 (66.7)
Month 24	35/48 (72.9%)	24/48 (50.0%)	15/48 (31.2%)	18/48 (37.5%)	30/48 (62.5%)	33/48 (68.7%)	36/48 (75.0%)
Month 27	17/35 (48.6%)	12/35 (34.3%)	5/35 (14.3%)	8/35 (22.9%)	16/35 (45.7)	16/35 (45.7)	19/35 (54.3%)
Month 30	17/24 (70.8%)	9/24 (37.5%)	6/24 (25.0%)	5/24 (20.8%)	17/24 (70.8%)	20/24 (83.3%)	20/24 (83.3%)
Month 33	12/23 (52.2%)	8/23 (34.8%)	3/23 (13.0%)	10/23 (43.5%)	18/23 (78.3%)	17/23 (73.9%)	
Month 36	5/11 (45.5%)	4/11 (36.4%)	2/11 (18.2%)	5/11 (45.5%)	6/11 (54.5%)		

Source: Reviewer's analysis. Positive and negative reflect # of month pre and post-surgery. Zero corresponds to time of surgery.

Table B23: Summary of Subjects who had surgery among baseline Phakic subjects who reported Cataract AE

Studies	Treatment N(%)		
	DEX 700	DEX 350	Sham
010	65/81 (80.2%)	66/83 (79.5%)	8/19 (42.1%)
011	76/101 (75.2%)	59/85 (69.4%)	8/37 (21.6%)
Pooled	141/ 182 (77.5%)	125/168 (74.4%)	16/56 (28.6%)

Source: Reviewer's analysis. 14 subjects in DEX700, 2 subjects in Sham and 9 subjects in DEX 350 did not report Cataract AE but had surgery.

Table B24: Summary of Number of IOP events reported

# of IOP events	Treatment: N (%)		
	DEX 700 N=125	DEX 350 N=117	Sham N=18
1	62(49.6%)	65(55.6%)	13(72.2%)

2	30(24.0%)	30(25.6%)	4(22.2%)
3	13(10.4%)	12(10.3%)	0(0.0%)
4	10(8.0%)	8(6.8%)	0(0.0%)
5	8(6.4%)	0(0.0%)	1(5.6%)
6	2(1.6%)	1(0.9%)	0(0.0%)
7	0(0.0%)	1(0.9%)	0(0.0%)

Source: Reviewer's analysis.

Table B25: Summary of First time IOP related AE

Time to First IOP Related Adverse Event	Treatment: N (%)		
	DEX 700 N=125	DEX 350 N=117	Sham N=18
Month <=3	73(58.4%)	62(53%)	5(27.8%)
Month 4.5	0(0.0%)	1(0.9%)	2(11.1%)
Month 6	3(2.4%)	3(2.6%)	0(0.0%)
Month 7.5	14(11.2%)	16(13.7%)	3(16.7%)
Month 9	10(8%)	7(6.0%)	1(5.6%)
Month 10.5	4(3.2%)	2(1.7%)	0(0.0%)
Month 12	5(4.0%)	5(4.3%)	1(5.6%)
Month 15	8(6.4%)	7(6.0%)	1(5.6%)
Month 18	1(0.8%)	2(1.7%)	2(11.1%)
Month 21	4(3.2%)	3(2.6%)	0(0.0%)
Month 24	0(0.0%)	3(2.6%)	0(0.0%)
Month 27	0(0.0%)	3(2.6%)	1(5.6%)
Month 30	2(1.6%)	0(0.0%)	1(5.6%)
Month 33	0(0.0%)	1(0.9%)	0(0.0%)
Month 36	0(0.0%)	2(1.7%)	1(5.6%)
Month 39	1(0.8%)	0(0.0%)	0(0.0%)

Source: Reviewer's analysis.

Table B26: Summary of Cross tabulation of Number of Injections and Number of IOP Related AEs

# of Injections	Number of reported IOP AEs							Total
	1	2	3	4	5	6	7	
1	22(91.7%)	1(4.2%)	0(0.0%)	1(4.2%)	0(0.0%)	0(0.0%)	0(0.0%)	24
2	22(73.3%)	5(16.7%)	1(3.3%)	2(6.7%)	0(0.0%)	0(0.0%)	0(0.0%)	30
3	12(54.5%)	9(40.9%)	0(0.0%)	1(4.5%)	0(0.0%)	0(0.0%)	0(0.0%)	22
4	16(48.5%)	9(27.3%)	4(12.1%)	4(12.1%)	0(0.0%)	0(0.0%)	0(0.0%)	33
5	13(44.8%)	8(27.6%)	3(10.3%)	2(6.9%)	1(3.4%)	1(3.4%)	1(3.4%)	29
6	32(39.5%)	22(27.2%)	15(18.5%)	7(8.6%)	4(4.9%)	1(1.2%)	0(0.0%)	81
7	10(43.5%)	6(26.1%)	2(8.7%)	1(4.3%)	3(13%)	1(4.3%)	0(0.0%)	23

Source: Reviewer's analysis. Only subjects who received either DEX 700 or DEX 350 were included.

Table B27: Formula for Computing Area under the Curve

Let t_{ij} be the visit time (in days) for the patient i at visit j , and y_{ij} be the corresponding observed BCVA, where $i = 1, 2, \dots, N$, $j = 0, 1, 2, \dots, n_i$, where n_i is the number of visits with non-missing BCVA for patient i , $j = 0$ corresponds to baseline visits.

Define BCVA change from baseline at visit j for the patient i

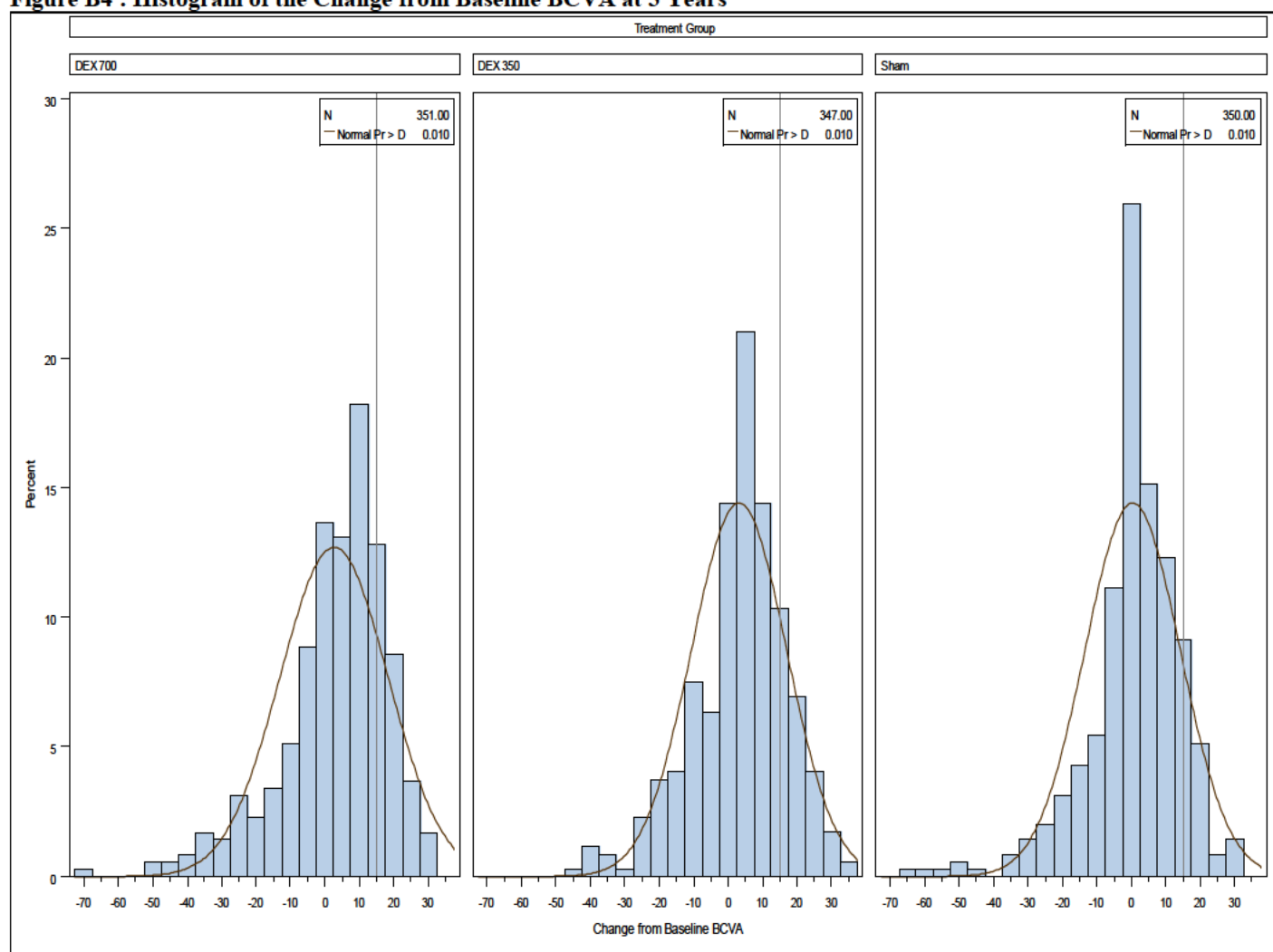
$$\Delta y_{ij} = y_{ij} - y_{i0}, \quad j > 0$$

$$AUC_i = \sum_{j=1}^{n_i} (\Delta y_{ij} + \Delta y_{i(j-1)}) \times \left(\frac{t_{ij} - t_{i(j-1)}}{2} \right), \quad j = 1, \dots, n_i, \quad \Delta y_{i0} = 0$$

Average change from baseline in BCVA for patient $i = AUC_i / (t_{in_i} - t_{i0})$.

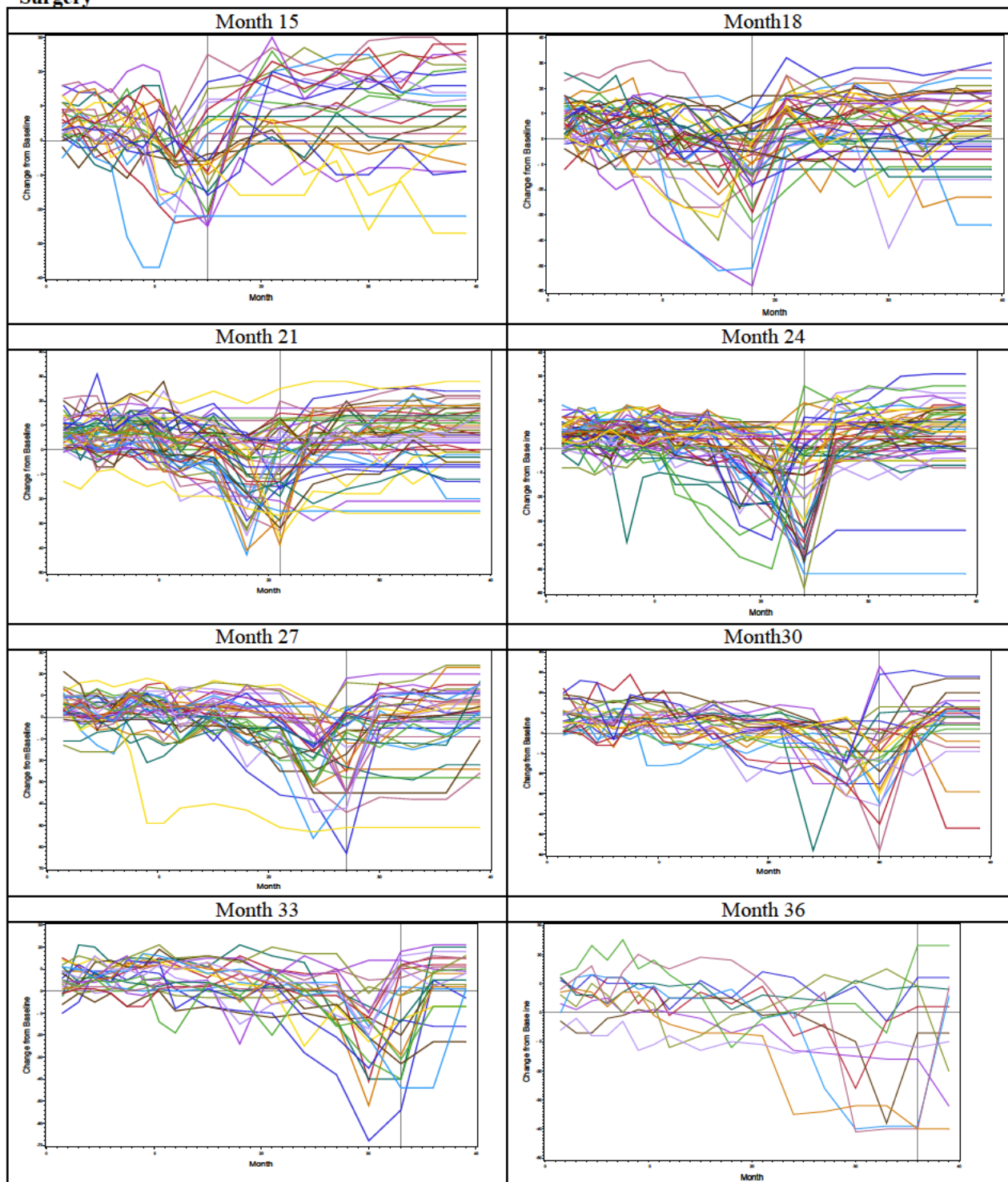
Source: Applicant's Statistical analysis plan.

Figure B4 : Histogram of the Change from Baseline BCVA at 3 Years



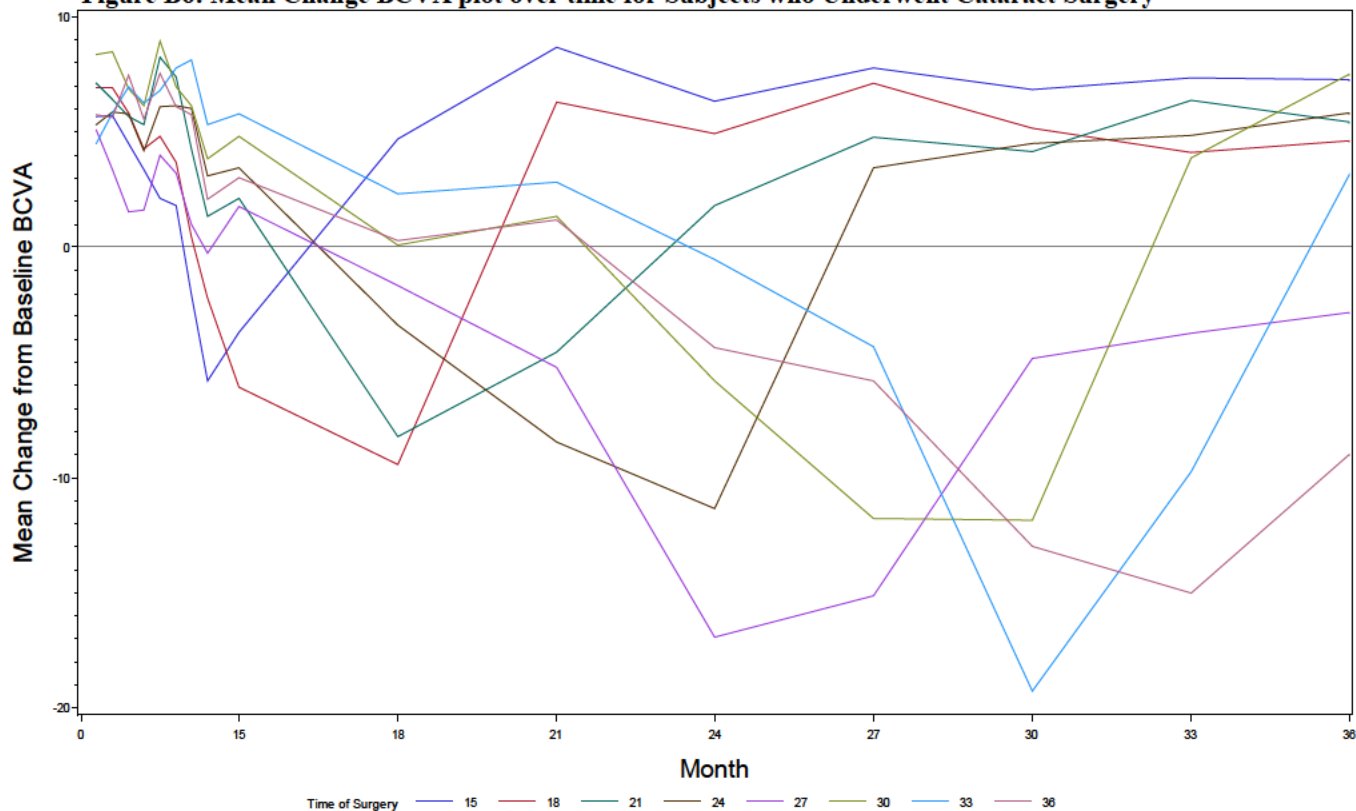
Source: Reviewer's Analysis. Vertical line corresponds to a BCVA change from baseline of 15 letters. P-value is from a Kolmogorov-Smirnov D test for normality.

Figure B5: Plot of Change from Baseline BCVA for Subjects who had Cataract Surgery by Month of Surgery



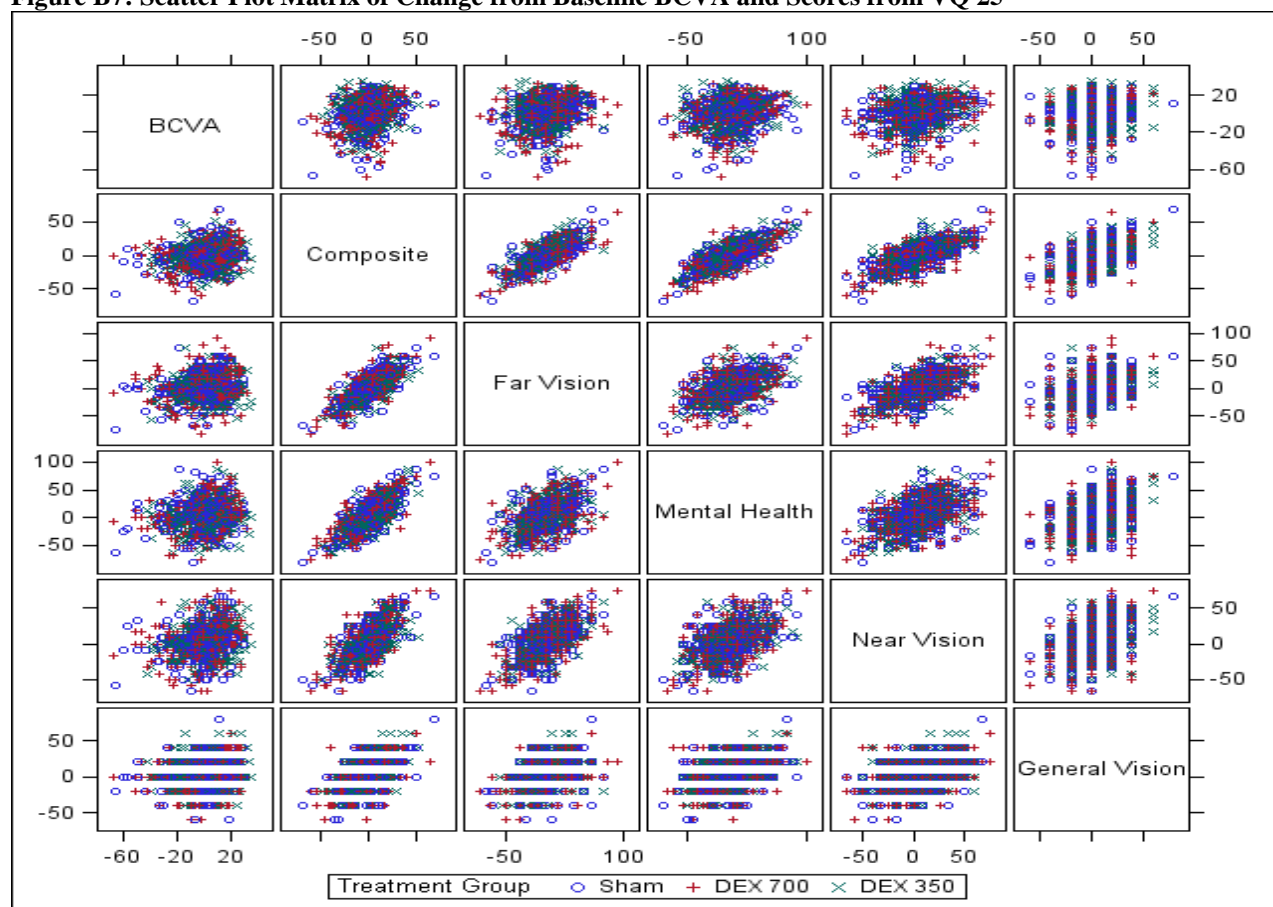
Source: Reviewer's Analysis. Vertical lines refer to the reported Month of surgery.

Figure B6: Mean Change BCVA plot over time for Subjects who Underwent Cataract Surgery



Source: Reviewer's analysis.

Figure B7: Scatter Plot Matrix of Change from Baseline BCVA and Scores from VQ 25



Source: Reviewer's Analysis.

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/s/

ABEL T ESHETE
06/26/2014

YAN WANG
06/26/2014
See my review.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA022315

Drug Name: OZURDEX: Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)

Indication(s): Treatment of Diabetic Macular Edema

Applicant: ALLERGAN INC.

Date(s): Stamp date: June 6, 2013
PDUFA date: April 7, 2014

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Keywords: Best corrected Visual Acuity, Intraocular Pressure and cataract surgery.

Table of Contents

1	EXECUTIVE SUMMARY	5
2	INTRODUCTION	7
2.1	OVERVIEW.....	7
2.1.1	<i>Drug Class and Indication.....</i>	7
2.1.2	<i>History of Drug Development.....</i>	7
2.1.3	<i>Studies Reviewed.....</i>	8
2.2	DATA SOURCES	10
3	STATISTICAL EVALUATION.....	10
3.1	DATA AND ANALYSIS QUALITY.....	10
3.2	EVALUATION OF EFFICACY.....	10
3.2.1	<i>Study Design and Endpoints.....</i>	10
3.2.2	<i>Statistical Methods.....</i>	12
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics.....</i>	14
3.2.4	<i>Results and Conclusions.....</i>	17
3.3	EVALUATION OF SAFETY	23
3.3.1	<i>Cataract Surgery.....</i>	27
3.3.2	<i>IOP-Related AE.....</i>	30
4	RISK BENEFIT ANALYSIS.....	31
4.1	RISK-BENEFIT ANALYSIS AT SUBJECT LEVEL	31
4.2	RISK-BENEFIT ANALYSIS AT POPULATION LEVEL.....	32
5	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	37
5.1	AGE GENDER RACE AND COUNTRY.....	38
5.2	OTHER SPECIAL/SUBGROUP POPULATIONS.....	40
6	SUMMARY AND CONCLUSIONS	43
6.1	STATISTICAL ISSUES	43
6.2	COLLECTIVE EVIDENCE	43
6.3	CONCLUSIONS AND RECOMMENDATIONS	44
6.4	LABELING RECOMMENDATIONS	44
7	APPENDIX.....	46
8	REFERENCES.....	64

LIST OF TABLES

Table 1: Summary of Pivotal Studies Reviewed.....	9
Table 2: Baseline and Demographics: Study 206207-010 (ITT population)	14
Table 3: Baseline and Demographics: Study 206207-011 (ITT population)	15
Table 4: Patient Disposition.....	16
Table 5: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years	17
Table 6: Sensitivity Analysis for the Primary Efficacy Endpoint.....	17
Table 7: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by Visit (ITT LOCF) ..	18
Table 8: Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF).....	19
Table 9: Summary of Area under the Curve (AUC) of the Change from Baseline BCVA	19
Table 10: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)	20
Table 11: Summary of Quartiles of Change in BCVA from Baseline at 3 Years (ITT LOCF).....	21
Table 12: Summary of Secondary Efficacy Outcomes: DEX 700 vs. Sham	21
Table 13: Summary of Secondary Efficacy Outcomes: DEX 350 vs. Sham	21
Table 14: Summary of Correlations between Changes in Retinal Thickness and Contrast sensitivity and BCVA from Baseline at 3 years.....	22

Table 15: Summary of Change in Patient Reported Outcomes from Baseline at 3 Years: DEX 700 vs. Sham	22
Table 16: Summary of Change in Patient Reported Outcomes from Baseline at 3 Years: DEX 350 vs. Sham	23
Table 17: Summary of Correlations between Changes in Patient Reported Scores and BCVA from Baseline at 3 Years.....	23
Table 18: Summary of Number of Injections	24
Table 19: Summary of Subjects Who Received Retreatment by Visit	24
Table 20: Summary of First Time Retreatment	25
Table 21: Summary of Adverse Events (AE) (All Treated Subjects).....	26
Table 22: Summary of Relationship of AE to Study Medication and Delivery System	26
Table 23: Summary of Number of Subjects who had Cataract Surgery	27
Table 24: Summary of Number of who had Cataract Surgery by Study	27
Table 25: Summary of the Mean Change from Baseline in BCVA within 9 Months of Cataract Surgery.....	28
Table 26: Summary of the Proportion of Subjects with a Positive Change from Baseline in BCVA within 9 Months of Cataract Surgery	29
Table 27: Summary of Subjects who had surgery among baseline Phakic subjects who reported Cataract AE.....	30
Table 28: Summary of Number of IOP events reported	30
Table 29: Summary of First time IOP related AE.....	30
Table 30: Summary of Cross tabulation of Number of Injections and Number of IOP Related AEs.....	31
Table 31: Summary of Risk-Benefit Analysis (Safety Population)	34
Table 32: Summary of Risk-Benefit Analysis for Psuedophakic subjects.....	36
Table 33: Summary of Population level Risk-Benefit Measures (Safety Population).....	37
Table 34: Proportion of subjects with ≥ 15 letters gain from baseline (ITT LOCF).....	46
Table 35: Proportion of subjects with ≥ 15 letters gain from baseline (Complete Cases)	47
Table 36: Summary of Mean change from Baseline BCVA (ITT LOCF).....	48
Table 37: Summary of the Mean Change from Baseline BCVA (Complete Cases).....	48
Table 38: Summary of Adverse Events for baseline Pseudophakic subjects	52
Table 39: Summary of Adverse Events Reported in $\geq 2\%$ of Subjects (All Treated Subjects)	52
Table 40: Summary of Treatment-Related Ocular AE in the Study Eye Reported in $\geq 2\%$ of Subjects	53
Table 41: Summary of Serious adverse Events Reported in ≥ 1 Subject (All Treated Subjects).....	53
Table 42: Formula for Computing Area under the Curve	64

LIST OF FIGURES

Figure 1: Plot proportion of subjects with BCVA change from Baseline \geq BCVA cutoff ((ITT LOCF).....	18
Figure 2: Plot of Mean Change from Baseline BCVA (Study 206207-010; ITT LOCF)	20
Figure 3: Plot of Mean Change from Baseline BCVA (Study 206207-011; ITT LOCF)	20
Figure 4: Summary plot for Risk-Benefit Analysis (Safety Population)	33
Figure 5: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 700 vs. Sham	38
Figure 6: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at 3 Year: DEX 700 vs. Sham	39
Figure 7: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 350 vs. Sham	39
Figure 8: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at 3 Year: DEX 350 vs. Sham	40
Figure 9: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 700 vs. Sham.....	41
Figure 10: Additional Subgroup Analysis by Baseline Disease Characteristics for Mean Change from Baseline BCVA at 3 Years: DEX 700 vs. Sham	41
Figure 11: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 350 vs. Sham.....	42
Figure 12: Additional Subgroup Analysis by Baseline Disease Characteristics for Mean Change from Baseline BCVA at 3 Years: DEX 350 vs. Sham	42
Figure 13: Plot of Mean change in BCVA from Baseline (Complete Case).....	50
Figure 14: Plot of Mean change in BCVA from Baseline (Per-Protocol).....	51
Figure 15 : Histogram of the Change from Baseline BCVA at 3 Years	55

Figure 16: Plot of Change from Baseline BCVA over time for Subjects who had Cataract Surgery by Month of Surgery.....	56
Figure 17: Mean Change BCVA plot over time for Subjects who Underwent Cataract Surgery	58
Figure 18: Mean plot of change from baseline BCVA for subjects who had no surgery or had cataract surgery within a year after randomization	59
Figure 19: Mean plot of change from baseline BCVA for subjects Without Cataract AE	60
Figure 20: Mean plot of change from baseline BCVA by Surgery Status among Subjects who reported cataract AE	61
Figure 21: Scatter Plot Matrix of Change from Baseline BCVA and Scores from VFQ 25	62
Figure 22: Cumulative Probability of first time elevated IOP AE	63

1 EXECUTIVE SUMMARY

This NDA included data from two Phase 3, double-masked, Sham-controlled, randomized studies (2062070-10 and 2062070-11). The applicant is seeking approval of OZURDEX, a Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) that releases a total dose of approximately 700 µg dexamethasone for the treatment of Diabetic Macular Edema (DME). The two studies shared a common protocol and a statistical analysis plan. A total of 1048 subjects (494 in 2062070-10 and 554 in 2062070-11) were randomized in a 1:1:1 ratio to receive either a Sham injection using a needle-less DEX PS DDS applicator or DEX PS DDS that released a total dose of approximately 350 µg dexamethasone (DEX 350) or 700 µg dexamethasone (DEX 700). The primary efficacy endpoint was the proportion of subjects with a 15 letter or more improvement in the best corrected visual acuity (BCVA) from baseline at Month 36 (3 Years). The primary efficacy analysis was conducted on all randomized subjects using a Chi-square test. Missing data were imputed using the Last Observation Carried Forward (LOCF) method. Subjects, who required escape therapies for macular edema other than the assigned study medication, were set as treatment failures in the primary efficacy analysis.

The primary efficacy results were consistent across the two studies. There was an approximate 8% difference in the proportion of subjects with a 15 letter or more gain from baseline BCVA at 3 years between the DEX 700 and Sham in favor of DEX 700 (19.6% vs. 10.9% in Study 2062070-10 and 17.6% vs. 10.3% in Study 2062070-11, resulting in a treatment difference of 8.7% (95% CI: 1.0%, 16.5%) in Study 2062070-10 and 7.3% (95% CI: 0.3%, 14.3%) in Study 2062070-11; Table 5). There was however no statistically significant difference between DEX 700 and Sham in the mean change from baseline BCVA at 3 years, the secondary efficacy endpoint, in either of the two studies. The treatment difference was only 2.7 (95% CI: -0.1, 5.5) letters in Study 2062070-10 and only 0.9 (95% CI: -2.4, 4.2) letters in Study 2062070-11 (Table 10).

With respect to safety, a substantially large proportion of subjects in the two DEX arms reported several adverse events compared to subjects in the Sham arm. The safety population consisted of 1040 subjects who received at least one study treatment. The proportion of subjects who reported at least one ocular adverse event in the study eye was 296/347 (85.3%), 303/343 (88.3%) and 203/350 (58.0%) in the DEX 700, DEX 350 and Sham arms respectively. Cataract surgery and Intraocular Pressure (IOP)-related AEs were the two most commonly reported AEs. The IOP-related AEs included elevated IOP, ocular hypertension and glaucoma. A significantly higher proportion of subjects in the DEX 700 (125/347; 36.0%) and DEX 350 (117/343; 34.1%) arms reported IOP-related AEs compared to (18/350; 5.1%) in the Sham arm. Among baseline Phakic subjects (subjects with natural lenses at baseline), a significantly higher proportion of subjects in the DEX 700 (155/262, 59.2%) and DEX 350 (134/257, 52.1%) arms required cataract surgery in the study eye compared to only 18/249 (7.2%) subjects in the Sham arm. The proportion of subjects who reported at least one serious ocular AE in the study eye was significantly higher in the DEX 700 24/347 (6.9%) and DEX 350 arms 14/343 (4.1%) compared to the Sham arm 4/350 (1.1%). A total of 29/1040 (2.8%) subjects, 9 (2.6%) in DEX 700, 15 (4.4%) in DEX 350 and 5 (1.4%) in the Sham arm died during the study (Table 21).

The reviewer conducted risk-benefit analyses both at the subject and population levels. The subject level risk-benefit analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best case scenario, is the case in which a pre-specified level of BCVA improvement was observed without incurring an AE. The worst case scenario is incurring an AE without achieving a pre-specified level of improvement in BCVA from baseline at 3 years. The other two scenarios are having benefit with AE, and no benefit and no AE. For the risk-benefit analysis at population level, the number needed to treat (NNT), the Number Needed to Harm (NNH) and the Benefit-to-Risk Ratio ($BRR=NNH/NNT$) were computed for each benefit and risk combination.

Compared to Sham, the DEX 700 arm had a higher proportion of subjects with the worst case scenario, and lower or only slightly higher proportion of subjects with the best case scenario for the majority of risks considered. The DEX 700 arm also had a higher proportion of subjects who had a ≥ 15 letter gain in BCVA from baseline at 3 years but incurred an AE. When IOP related AE and cataract surgery for Phakic subjects were considered as important risks, a significantly higher proportion of subjects in the DEX 700 arm fell into the worst case scenario. The proportion of subjects in the DEX 700 arm who reported at least one IOP-related AE without achieving a ≥ 15 letter gain in BCVA at 3 years was 29.1% compared to only 4.9% in the Sham arm (Figure 4 and Table 31). Similarly, over 47% of baseline Phakic subjects in the DEX 700 arm failed to achieve a ≥ 15 letter gain in BCVA from baseline at 3 years and had cataract surgery compared to only 6.0% in the Sham arm. On the other hand, DEX 700 and Sham were comparable with respect to the proportion of subjects with the best case scenario, i.e. a ≥ 15 letter gain in BCVA from baseline at 3 years without reporting any IOP related AE (11.8 vs. 10.3%;). Additionally, for the majority of risks considered, the BRR values were less than one or equivalently the NNT was larger than the NNH. The BRR values of 0.26 and 0.14 corresponding to IOP related AE and Cataract Surgery for Phakic subjects show that for every subject with a ≥ 15 letter gain in BCVA due to DEX 700, 4 subjects had at least one IOP related AE and 7 baseline Phakic subjects required cataract surgery, respectively (Table 33).

In conclusion, this NDA has provided evidence that a significantly higher proportion of subjects in the DEX 700 arm gained 15 or more letters from baseline at 3 year compared to subjects in the Sham arm. However, the difference between DEX 700 and Sham in the mean BCVA change from baseline at 3 years was small (approximately 2 letters) and not statistically significant. Additionally, a substantially large proportion of subjects in the DEX 700 arm reported adverse events, including elevated IOP and cataract formation that led to cataract surgery. Although the review's risk-benefit analyses suggested that the observed benefit might not outweigh the risk, the final evaluation of the risk-benefit outlook and the subsequent recommendation for approval of this product will have to be done in consultation with the clinical and other review teams.

2 INTRODUCTION

This NDA included data from two phase 3 studies (2062070-10 and 2062070-11) to support the safety and efficacy of Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) for the treatment of diabetic macular edema. The two pivotal studies shared a common protocol and a statistical analysis plan. These two studies were the main focus of this review.

2.1 Overview


This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the specific studies reviewed.

2.1.1 Drug Class and Indication

The Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System is an intraocular drug delivery system developed for treatment of diabetic macular edema and other retinal diseases. The active ingredient, dexamethasone, is a potent corticosteroid with marked anti-inflammatory activity. Dexamethasone is combined with biodegradable polymers and extruded into a small implant suitable for delivery into the posterior segment of the eye through a specifically designed applicator.

2.1.2 History of Drug Development

OZURDEX® was approved in the US for the treatment of macular edema on 17 June 2009, and for non-infectious uveitis affecting the posterior segment of the eye on 24 September 2010. OZURDEX was also approved in Europe for the treatment of adult subjects with macular oedema on 27 July 2010, and inflammation of the posterior segment of the eye presenting as non-infectious uveitis on 16 June 2011.

 (b) (4)
hile releasing dexamethasone, the implant gradually degrades completely over time so there is no need to remove the implant.

The applicant had an End-of-Phase 2 meeting with the agency on September 8, 2003 to discuss the development program for DEX PS DDS Applicator System. During the meeting, the agency recommended 3 years study duration and suggested that a 15 or more letters improvement in BCVA should be considered as clinically significant as opposed to the 10 letter or more improvement suggested by the applicant. The agency also indicated that a vehicle, placebo or alternative low dose of dexamethasone is the preferred control as opposed to the Sham injection suggested by the applicant. Note that a Sham injection is the control arm used in the two studies reviewed under this NDA. The agency accepted the applicant's proposed analysis for the primary and secondary efficacy endpoints and stated that both the intent-to-treat and per-protocol analyses should be conducted and the results submitted.

In a briefing package submitted on November 3, 2011, the applicant requested the use of the area under the curve, which is the current primary efficacy endpoint for European and other regulatory agencies, as the primary efficacy endpoint. The Agency however stated that, this endpoint does not differentiate the short term treatment effect (prior to 36-month) from the long term treatment effect. Arguing that an earlier treatment success is not necessarily a good indicator of later success, the agency recommended that the treatment effect of the test product be demonstrated at a time point of at least 36 month or later. The agency also provided the following additional comment regarding risk and benefit:

“Because this study is being proposed with multiple potential intravitreal steroid injections over a 3 year period for a class of drug (steroids) that has significant risks of cataract formation (with subsequent cataract surgery) and elevated IOP as adverse events, there is significant concern the benefits of using this drug product may not outweigh its risks when treating DME. Additionally, this class of products (steroids) is also likely to impair healing and reduce the eyes ability to recover from infections. This is potentially problematic for a diabetic population. The benefit over these risks needs to be demonstrated.”

2.1.3 Studies Reviewed

In this NDA, data from two phase 3 studies (206207-010 and 206207-011) were included to support the safety and efficacy of DEX PS DDS in the treatment of Diabetic Macular Edema. The two studies were both Phase 3, double-masked, Sham-controlled, and randomized. The two studies shared a common protocol and a statistical analysis plan and included sites from the US and abroad. The brief summaries of these studies are given in Table 1.

In both studies, subjects were randomly allocated in a 1:1:1 ratio to Sham, DEX 700 or DEX 350. In Study 206207010, a total of 494 subjects from 10 countries, of which 88 (17.8%) from the United States, were involved. The other sites were located in 9 countries (Australia, Canada, Czech Republic, Germany, Spain, Israel, Philippines Portugal, and South Africa). Similarly, in Study 206207011, a total of 554 subjects from 14 countries of which 207 (37.4%) from sites within the United States were involved. The remaining sites in this study were located in the following countries: (Brazil, Canada, Columbia, France, Great Britain, Hungry, India, Italy, Korea, New Zealand, Poland, Singapore and Taiwan).

Table 1: Summary of Pivotal Studies Reviewed

Study #	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
206207-010	A Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Subjects with Diabetic Macular Edema	<ul style="list-style-type: none"> – DEX 700: N=163 – DEX 350: N=166 – Sham : N=165 <p>Note: Study drug containing an extruded dosage form of 700 µg or 350 µg dexamethasone in an inactive biodegradable polymer matrix of poly [lactic-glycolic] acid (PLGA) was administered into the vitreous through the pars plana into the study eye only using the DEX PS DDS Applicator System.</p>	<p>Primary: The proportion of subjects with \geq 15-letter BCVA improvement at year 3.</p> <p>The primary analysis was a statistical evaluation of superiority of the two dose arms to Sham with respect to the primary efficacy variable. A gate-keeping procedure was used to control the overall type I error at 5%. The comparison of DEX 700 versus Sham was considered significant if the p-value was \leq 0.05. Only if the comparison of DEX 700 versus Sham was significant, was the comparison of DEX 350 versus Sham to be performed at a significance level of 0.05. A Pearson's chi-square test was used to compare the arms.</p>	<p>The primary endpoint of proportion of subjects with \geq 15-letter BCVA improvement at year 3 was significantly higher with DEX 700 (19.6%) compared with Sham (10.9%), $p = 0.0280$. Following the gate-keeping procedure, the comparison of DEX 350 (19.9%) versus Sham (10.9%) was statistically significant ($p = 0.0238$).</p>
206207-011	A Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Subjects with Diabetic Macular Edema	<ul style="list-style-type: none"> – DEX 700: N=188 – DEX 350: N=181 – Sham : N=185 <p>Note: Study drug containing an extruded dosage form of 700 µg or 350 µg dexamethasone in an inactive biodegradable polymer matrix of poly [lactic-glycolic] acid (PLGA) was administered into the vitreous through the pars plana into the study eye only using the DEX PS DDS Applicator System.</p>	<p>Primary: The proportion of subjects with \geq 15-letter BCVA improvement at year 3</p> <p>The primary analysis was a statistical evaluation of superiority of the two dose arms to Sham with respect to the primary efficacy variable. A gate-keeping procedure was used to control the overall type I error at 5%. The comparison of DEX 700 versus Sham was considered significant if the p-value was \leq 0.05. Only if the comparison of DEX 700 versus Sham was significant, was the comparison of DEX 350 versus Sham to be performed at a significance level of 0.05. A Pearson's chi-square test was used to compare the arms.</p>	<p>The primary endpoint of proportion of subjects with \geq 15-letter BCVA improvement at year 3 was statistically significantly higher with DEX 700 (17.6%) compared with Sham (10.3%), $p = 0.0423$. Following the gate-keeping procedure, the comparison of DEX 350 versus Sham was not statistically significant (15.5% versus 10.3%, $p = 0.1377$).</p>

2.2 Data Sources

The data sources for this review included the applicant's clinical study reports for both studies and the integrated safety and efficacy analysis reports. Additionally, the applicant submitted SAS datasets electronically. Both SDTM and ADAM data formats were used. The data sets used in this review are located at \\Cdsub1\evsprod\NDA022315\0064\m5\datasets\ise\analysis. The change from baseline best correct visual acuity (BCVA) and the actual BCVA both at baseline and subsequent measurement times were included in the "va.xpt" dataset with variable names *CHG* and *AVAL* respectively. For the primary efficacy analysis, the binary indicator *IMP15L* which assumes a value of "Yes" when the change from baseline BCVA was ≥ 15 and "No" otherwise was used. The treatment variable, given both as numeric (*TRTCD*) and character (*TRTGRP*), was also included in the above dataset. The adverse events and the first time the subject used a rescue therapy were included in the "ae.xpt" dataset. The information regarding concurrent procedures including cataract surgery was included in the "cp.xpt" dataset. For the risk-benefit analysis the "va.xpt" and "ae.xpt" datasets were merged by unique subject identification number (*USBJID*). From the resulting dataset, the risk-benefit outcome (four possible scenarios) was created for each risk-benefit combination.

3 STATISTICAL EVALUATION

This section provides a detailed review of the two pivotal studies.

3.1 Data and Analysis Quality

The data were generally of good quality. The applicant submitted data using the standard SDTM and ADAM formats. The final statistical analysis plan and the amended protocols were all submitted.

3.2 Evaluation of Efficacy

This section summarizes the design of the two studies and the corresponding efficacy results submitted by the applicant and the reviewer's analysis.

3.2.1 Study Design and Endpoints

In Study 206207-010, a total of 494 subjects who signed the informed consent and met the inclusion/exclusion criteria were randomized to receive DEX 700, DEX 350 or Sham (166, 165 and 163 respectively). Similarly in Study 206207-010, a total of 554 subjects (188, 181 and 185 respectively) were randomized to receive DEX 700, DEX 350 or Sham.

According to the protocol, the studies were to enroll patients with diabetic macular edema in at least 1 eye. If both eyes were eligible for the study, the eligible eye with shorter duration of macular edema was selected as the study eye. The study eye were identified at the qualification/baseline visit and remained the same throughout the entire study duration. Only the study eye was treated in the study.

The protocol specified scheduled visits consisted of the Qualification/Baseline (Day -14 to -4), randomization (Day 0), post-insertion safety visits (Days 1, 7 and 21, after treatment or re-treatment), Year 1 (Months 1.5, 3, 4.5, 6, 7.5, 9, 10.5, and 12), Year 2 (Months 15, 18, 21, and 24) and Year 3 (Months 27, 30, 33 and 36). Starting from the Month 6 visit, subjects were evaluated for retreatment eligibility every 3 months. The study protocol specified that a subject is eligible for retreatment with the same assigned study medication if the retinal thickness in the 1 mm central macular subfield by optical coherence tomography (OCT) was $>175\text{ }\mu\text{m}$ (determined by the site) or upon investigator interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the center subfield). However, the study treatment procedure would not be performed more often than every 6 months. The applicant specified primary objective was to investigate the safety and efficacy of the 700 μg DEX PS DDS Applicator System (700 μg dexamethasone) and 350 μg DEX PS DDS Applicator System (350 μg dexamethasone) compared with a Sham DEX PS DDS Applicator System (needle-less applicator) in subjects with diabetic macular edema. The primary efficacy endpoint was the proportion of subjects with an improvement of 15 or more letters in BCVA in the study eye from baseline at Month 36.

There were 5 protocol amendments for Studies 206207-010 and 206207-011 on the following dates:

Protocol Version	Allergan Internal Approval Date
Protocol	19 November 2004
Amendment #1	16 October 2005
Amendment #2	01 May 2007
Amendment #3	11 February 2009
Amendment #4	08 May 2010
Amendment #5	14 November 2011

Protocol amendment 4 included three major changes: (1) subjects who met re-treatment criteria were allowed to receive a re-treatment at Month 36 visit; (2) a Month 39 visit was added to provide an assessment of efficacy and safety for subjects who received a re-treatment at Month 36 visit; and (3) the primary efficacy analysis of the proportion of subjects who had a 15 letter or more gain in BCVA from baseline was changed from Month 24 to final study visit (Month 39 or earlier), i.e. the primary efficacy endpoint was defined as the proportion of subjects with a 15 letter or more gain from baseline at Month 39/Final.

During the review process, the clinical reviewer sent the following information request to the applicant on October 31, 2013:

“Please provide an explanation for the marked difference in the number of patients (N) at the Month 36 Visit versus the Month 39/Final Visit in Table 14.2-4.3 (Study 206207-010) and Table 14.2-4.3 (Study 206207-011).”

The applicant's response submitted on November 8, 2013 and located at \\Cdsesub1\evsprod\NDA022315\0073) is given below:

In Amendment 4, the primary analysis was changed to month 36 from month 24 to ensure that the cumulative risks and benefits to patients with diabetic macular edema would be best evaluated over a period of 3 years. Also, as per the Amendment 4, patients were allowed to receive a study treatment at month 36 as needed by retreatment criteria, and a month 39 visit was added to provide an assessment of efficacy and safety from any month 36 retreatment. By the time all sites received ethics committee approval to initiate Amendment 4, 52.4% (549/1048) of patients had either prematurely exited the study or completed the month 36 visit and exited the study. Only patients who were continued in the study and received injections at month 36 (following Amendment 4) continued to month 39. Thus the sample sizes for the month 39 timepoint are lower than those for the month 36 timepoint for the overall population.

Reviewer's Remarks: Because only a few [173 (16.5%)] of the 1048 randomized subjects completed the Month 39 visit and even less randomized subjects (15.3%) had a BCVA measurement at the Month 39 visit, the primary efficacy endpoint in this statistical review was the proportion of subjects with a 15 letter or more gain in BCVA from baseline at 3 years (Month 36). It should also be noted that FDA recommended this endpoint as the primary endpoint to the applicant at the End-of-Phase 2 meeting in September 2003 as well as in a Type C meeting in September 2011.

Mean BCVA change from baseline, the Area under the curve (AUC) of the change from baseline BCVA, central retinal thickness using OCT, contrast sensitivity and Patient's perception regarding their vision and general health collected using a Visual Functioning Questionnaire (VFQ-25) were some of the secondary efficacy endpoints. Note that, the applicant used the AUC of the change from baseline BCVA as the primary efficacy endpoint for submissions made to other regulatory agencies.

3.2.2 Statistical Methods

The DEX 700 and DEX 350 arms were compared against the Sham arm with respect to the primary efficacy outcome using the chi-square test. Confidence intervals for the treatment differences were computed using the normal approximation for binomial distribution. For the secondary and safety outcomes, a Chi-square test for dichotomous or non-ordered categorical response measures and t-test for continuous variables and ordered categorical response measures were employed. A gate-keeping approach was used to adjust for multiple comparisons resulting from the comparison of the DEX arms against Sham with respect to the primary efficacy endpoint. Specifically, the DEX 350 arm was compared to Sham only when the DEX 700 arm showed a statistically significant effect compared to Sham at a 5% level of significance. All secondary efficacy analyses were performed based on a 2-sided hypothesis test with a significance level of 0.05.

Unless stated otherwise, all analyses of efficacy were conducted on the ITT population, defined as all randomized subjects, and subjects were analyzed in the arm to which they were randomized. For the primary analysis, the Last Observation Carried Forward (LOCF) approach was used as a main tool to impute missing values. In the applicant's analysis, for subjects who

received an escape medication prior to the final visit, the observed outcomes after the date of receiving escape medication were set as missing, and LOCF was used to impute the missing values. Section 5.5.2 of the study protocol however states that subjects who require escape therapy are treated as treatment failures. Thus, the reviewer's analysis considers all subjects who received a rescue therapy as treatment failures. Both the reviewer and the applicant performed the analysis of the per-protocol population (including all subjects with no major protocol violation), and the ITT analysis with multiple imputation approach used for missing data. For the multiple imputations, a two-step approach was followed. In the first step, the change from baseline BCVA was imputed using the Markov chain Monte Carlo (MCMC) method to create a monotone missing pattern. In the second step, a regression approach in which the change from baseline BCVA value at a particular visit used as a response and all measures prior to that visit used as covariates was applied. The resulting imputed values were then converted into binary outcomes.

The reviewer conducted risk-benefit analyses both at the subject and population levels. The subject level risk-benefit analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best case scenario, is the case in which a pre-specified level of BCVA improvement was observed without incurring an AE. The worst case scenario is incurring an AE without achieving a pre-specified level of improvement in BCVA from baseline at 3 years. The other two scenarios are having benefit with AE, and no benefit and no AE.

For the risk-benefit analysis at the population level, the unadjusted number needed to treat ($NNT = 1 / (P_{DEX} - P_{SHAM})$) and adverse event adjusted number needed to treat ($NNT_{adj} = 1 / ((P_{DEX} - P_{SHAM}) * (1 - (Q_{DEX} - Q_{SHAM})))$) together with the Number Needed to Harm ($NNH = 1 / (Q_{DEX} - Q_{SHAM})$) were computed for each benefit and risk combination. Here P_{DEX} and P_{SHAM} represent proportion of success and Q_{DEX} and Q_{SHAM} represent proportion of subjects with a given adverse event in the DEX 700 and Sham arms respectively. The unadjusted number needed to treat measures the average number of subjects that need to be treated to observe one improvement in BCVA. The adverse event adjusted number needed to treat is the average number of subjects that need to be treated to observe an improvement in BCVA without a treatment related adverse event. The Benefit-Risk Ratio ($BRR = (P_{DEX} - P_{SHAM}) / (Q_{DEX} - Q_{SHAM}) = NNH / NNT$) was also computed. The confidence intervals for the numbers needed to treat and harm were computed by inverting and exchanging the limits of a 95% confidence interval for the difference in proportion of success and the difference in the proportion of subjects with a given AE respectively [1 & 2].

The DEX 700 and DEX 350 arms were also compared against the Sham arm with respect to several secondary efficacy endpoints. The Mean change from baseline BCVA, the AUC of the mean change from baseline, change from baseline central retinal thickness using OCT, contrast sensitivity and Patient's perception regarding their vision and general health collected using a Visual Functioning Questionnaire (VFQ-25) were compared using a t-test. The formula for the AUC is given in the appendix.

Additionally, at the pre-NDA efficacy supplement meeting held on August 14, 2012, the agency indicated that retinal thickness was not validated for BCVA in response to the applicant's question regarding primary and secondary efficacy endpoints. This reviewer thus used the meta-analysis method for surrogate marker validation [3] to quantify the association between the

change from baseline BCVA and central retinal thickness using OCT and contrast sensitivity. The same surrogate marker validation methodology was used to quantify the associations between the change from baseline in patient reported scores and the change from baseline BCVA at 3 years. The correlation between the country level treatment effects and the correlation between treatment adjusted and unadjusted change in scores and BCVA from baseline at 3 years were computed. A strong correlation both at the treatment effects and outcome levels indicates a potential surrogacy which can be further investigated with additional data.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

There were no significant baseline imbalances between the three arms in the demographics of age, gender, race or study eye iris color. The mean age of participants in Study 206207-010 was slightly higher than those in Study 206207-011. In both studies, there were more male participants than female participants; and the majority of participants were Caucasian. The percentage of participants with dark iris was higher than light iris (Table 2 and Table 3).

Table 2: Baseline and Demographics: Study 206207-010 (ITT population)

	DEX 700 (N=163)	DEX 350 (N=166)	Sham (N=165)	Total (N=494)	P-value
Age(years)					0.696
Mean (SD)	63.1 (8.01)	63.3 (9.01)	62.6 (9.10)	63.0 (8.71)	
Range	33-84	27-82	26-83	26-84	
<45	4 (2.5%)	5(3.0%)	7(4.2%)	16 (3.2%)	
45-65	89 (54.6%)	97 (58.4%)	95 (57.6%)	281 (56.9%)	
>65	70 (42.9%)	64 (38.6%)	63 (38.2%)	197 (39.9%)	
Sex					0.906
Male	102 (62.6%)	100 (60.2%)	102 (61.8%)	304 (61.5%)	
Female	61 (37.4%)	66 (39.8%)	63 (38.2%)	190 (38.5%)	
Race					0.649
Caucasian	138 (84.7%)	140 (84.3%)	134 (81.2%)	412 (83.4%)	
Non-Caucasian	25 (15.3%)	26 (15.7%)	31 (18.8%)	82 (16.6%)	
Black	7 (4.3%)	7 (4.2%)	13 (7.9%)	27 (5.5%)	
Asian ^a	12 (7.4%)	14 (8.4%)	13 (7.9%)	39 (7.9%)	
Hispanic	1 (0.6%)	2 (1.2%)	2 (1.2%)	5 (1.0%)	
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	5 (3.1%)	3 (1.8%)	3 (1.8%)	11 (2.2%)	
Iris Color					0.907
Light	69 (42.3%)	74 (44.6%)	73 (44.2%)	216 (43.7%)	
Dark	94 (57.7%)	92 (55.4%)	92 (55.8%)	278 (56.3%)	
Baseline Lens Status					0.799
Phakic	119 (73.0%)	119 (71.7%)	115 (69.7%)	353 (71.5%)	
Pseudophakic	47 (28.3%)	47 (28.3%)	50 (30.3%)	141 (28.5%)	
Prior DME Treatment					
Laser	115 (70.6%)	116 (69.9%)	122 (73.9%)	353 (71.5%)	
Steroid Injection	28 (17.2%)	30 (18.1%)	23 (13.9%)	81 (16.4%)	
Anti-VEGF	17 (10.4%)	20 (12.0%)	13 (7.9%)	50 (10.1%)	
No prior treatment	40 (24.5%)	40 (24.1%)	38 (23.0%)	118 (23.9%)	
Weight (Kg)					0.337
Mean (SD)	84.3 (17.8)	85.1 (20.4)	82.2 (16.9)	83.8 (18.5)	
Range	48 -144	43 - 155	50 - 150	43 - 155	

Height (cm)					0.957
Mean (SD)	167.2 (9.3)	167.3 (10.1)	167.0 (8.8)	167.1 (9.4)	
Range	146 -188	139 -191	142- 188	139- 191	
Diabetes Duration ^b					0.142
Mean (SD)	17.2 (9.2)	16.2 (9.2)	15.3 (8.3)	16.2 (8.9)	
Median (Range)	16 (2-51)	15.5 (2-57)	15.5 (1-37)	16 (1-57)	
DME Duration ^c					0.582
Mean (SD)	24.0 (26.2)	24.9 (29.3)	27.2 (29.6)	25.4 (28.3)	
Median (Range)	15 (0-160)	14 (0-191)	16 (0-152)	15 (0-191)	
HbA1c					0.987
Mean (SD)	7.5 (1.1)	7.5 (1.1)	7.5 (1.1)	7.5 (1.1)	
Median (Range)	7.4 (5-10)	7.4 (5-10)	7.4 (5-10)		

Source: Tables 10.1 and 10.2 of Applicant's submitted Study Reports. ^aAsian race excludes Japanese. ^b Years ^c Months

Table 3: Baseline and Demographics: Study 206207-011 (ITT population)

	DEX 700 (N=188)	DEX 350 (N=181)	Sham (N=185)	Total (N=554)	P-value
Age(years)					0.558
Mean (SD)	61.9 (8.57)	61.3 (9.34)	62.4 (9.85)	61.9 (9.26)	
Range	40-85	25-84	29-88	25-88	
<45	2 (1.1%)	8 (4.4%)	6(3.2%)	16(2.9%)	
45-65	116 (61.7%)	109 (60.2%)	108 (58.4%)	333 (60.1%)	
>65	70 (37.2%)	64 (35.4%)	71 (38.4%)	205 (37.0%)	0.746
Sex					
Male	111 (59.0%)	106 (58.6%)	115 (62.2%)	332 (59.9%)	
Female	77 (41.0%)	75 (41.4%)	70 (37.8%)	222 (40.1%)	0.891
Race					
Caucasian	96 (51.1%)	94 (51.9%)	99 (53.5%)	289 (52.2%)	
Non-Caucasian	92 (48.9%)	87 (48.1%)	86 (46.5%)	265 (47.8%)	
Black	9 (4.8%)	9 (5.0%)	7 (3.8%)	25 (4.5%)	
Asian ^a	42 (22.3%)	42 (23.2%)	40 (21.6%)	124 (22.4%)	
Hispanic	34 (18.1%)	32 (17.7%)	31 (16.8%)	97 (17.5%)	
Japanese	1 (0.5%)	2 (1.1%)	1 (0.5%)	4 (0.7%)	
Other	6 (3.2%)	2 (1.1%)	7 (3.8%)	15 (2.7%)	0.582
Iris Color					
Light	58 (30.9%)	47 (26.0%)	53 (28.6%)	158 (28.5%)	
Dark	130 (69.1%)	134 (74.0%)	132 (71.4%)	396 (71.5%)	0.420
Baseline Lens Status					
Phakic	146 (77.7%)	140 (77.3%)	134 (72.4%)	420 (75.8%)	0.420
Pseudophakic	42 (22.3%)	41 (22.6%)	51 (38.1%)	134 (24.2%)	
Prior DME Treatment					
Laser	116 (61.7%)	108 (59.7%)	121 (65.4%)	345 (62.3%)	
Steroid Injection	30 (16.0%)	39 (21.5%)	38 (20.5%)	107 (19.3%)	
Anti-VEGF	8 (4.3%)	19 (10.5%)	13 (7.0%)	40 (7.2%)	
No prior treatment	64 (34.0%)	58 (32.0%)	51 (27.6%)	173 (31.2%)	
Weight (Kg)					0.483
Mean (SD)	81.2 (22.6)	79.0 (20.1)	78.9 (18.1)	79.7 (20.4)	
Range	41 -204	43 - 160	45 - 135	41 - 204	
Height (cm)					0.502
Mean (SD)	163.8 (9.4)	164.5 (9.7)	165.0 (9.51)	164.4 (9.5)	
Range	137 -196	135 -186	133- 190	133- 196	
Diabetes Duration ^b					0.642
Mean (SD)	15.9 (8.8)	15.5 (9.5)	16.4 (9.8)	15.9 (9.4)	
Range	1-43	1-61	1-54	1-61	

DME Duration ^c					0.738
Mean (SD)	23.2 (25.9)	25.5 (33.3)	24.8 (25.0)	24.5 (28.2)	
Median (Range)	15 (0-163)	17 (0-299)	19 (0-187)	17 (0-299)	
HbA1c					0.488
Mean (SD)	7.6 (1.2)	7.6 (1.2)	7.5 (1.0)	7.5 (1.1)	
Median (Range)	7.5 (4-10)	7.5 (5-10)	7.2 (5-10)	7.5 (4-10)	

Source: Tables 10.1 and 10.2 of Applicant's submitted Study Reports. ^a Asian race excludes Japanese. ^b Years, ^c Months

3.2.3.2 Patient Disposition

The percentage of subjects who completed the study was comparable across the three treatment arms. The percentage of subjects in the two DEX arms who terminated the study was lower than those in the Sham arm. Most people terminated the study due to lack of efficacy (Sham arm) and adverse events (DEX arms) (Table 4). Note that in the protocol, a subject was considered to have completed the study if he/she completed the Month 36 or 39 visits. The number of subjects with observed BCVA measurements at Month 36 (not carried forward) was 104 (63.8%), 107 (64.4%) and 63 (38.2%) in the DEX 700, DEX 350 and Sham respectively for Study 206207-010, and 107 (56.9%), 101 (55.8%) and 68 (36.7%) in the DEX 700, DEX 350 and Sham respectively for Study 206207-011.

Table 4: Patient Disposition

	DEX 700	DEX 350	Sham	Total
Study 206207-010				
Subjects Randomized	163 (32.9%)	166 (33.6%)	165 (33.4%)	494
Subjects Who completed the Study	107 (65.6%)	118 (71.1%)	70 (42.4%)	
Completed the Study at Month 36	77	78	48	203 (41.1%)
Completed the Study at Month 39	30	40	22	
Reason for Discontinuation				
Adverse Events	20/56 (35.7%)	18/48 (37.5%)	16/95 (16.8%)	
Lack of Efficacy	9/56 (16.1%)	14/48 (29.2%)	37/95 (38.9%)	
Lost-to-Follow-up	5/56 (8.9%)	5/48 (10.4%)	10/95 (10.5%)	
Personal Reason	7/56 (12.5%)	4/48 (8.3%)	16/95 (16.8%)	
Protocol Violations	2/56 (3.6%)	0/48 (0.0%)	0/95 (0.0%)	
Other ¹	13/56 (23.2%)	7/48 (14.6%)	16/95 (16.8%)	
Study 206207-011				
	DEX 700	DEX 350	Sham	Total
Subjects Randomized	188 (33.9%)	181 (32.7%)	185 (33.4%)	554
Subjects Who completed the Study	118 (62.8%)	112 (61.9%)	82 (44.3%)	
Completed the Study at Month 36	92	83	56	232 (41.9%)
Completed the Study at Month 39	26	29	26	
Reason for Discontinuation				
Adverse Events	25/70 (35.7%)	30/69 (43.5%)	23/103 (22.3%)	
Lack of Efficacy	14/70 (20.0%)	11/69 (15.9%)	47/103 (45.6%)	
Lost-to-Follow-up	6/70 (8.5%)	7/69 (10.1%)	8/103 (7.7%)	
Personal Reason	7/70 (10.0%)	6/69 (8.7%)	10/103 (9.7%)	
Protocol Violations	1/70 (1.4%)	3/69 (4.3%)	1/102 (0.9%)	
Other ¹	17/70 (24.3%)	12/69 (17.4%)	14/103 (13.6%)	

Source: Table 14.1-1.1 of Applicant's submitted Study Reports. ¹ Other reasons for early discontinuation of the study obtained from listing 16.2.1-2 include: Site closed, switched to alternative therapy, required escape therapy, consent withdrawal, unscheduled visit, poor compliance from patient, applicant request, patient relocation, patient participation in other trial, etc.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

3.2.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects with a 15 letter or more improvement in BCVA from baseline at 3 years. In both studies, DEX 700 had a significantly higher proportion of subjects with a 15 letter or more improvement from baseline at 3 years compared to the Sham, whereas a significant difference was observed between DEX 350 and Sham in only one of the two studies (Table 5).

Table 5: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
011	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

The sensitivity analyses results based on the multiple imputations and the per-protocol population (all subjects with no major protocol violation) were fairly consistent with the primary efficacy analysis results in terms of the direction and magnitude of the treatment effect (Table 6). For the multiple imputations, the proportion of subjects with an improvement of 15 or more letters from baseline at 3 years was in close agreement with the primary efficacy analyses results for both studies in the DEX 700 arm and in Study 206207-011 for the Sham arm. In Study 206207-010 however, the multiple imputations analysis resulted in relatively higher proportion of subjects with an improvement of 15 or more letters from baseline at 3 years for the Sham arm leading to a non-significant difference. The complete case analysis showed non-significant difference in both studies. This is mainly driven by the significantly lower number of subjects with complete BCVA at 3 Years especially in the Sham arm. In conclusion, it appears that the overall study conclusion regarding the primary efficacy endpoint does not seem to have been significantly impacted by the method used to handle missing data.

Table 6: Sensitivity Analysis for the Primary Efficacy Endpoint

Studies	Methods	Treatment: N (%)			%Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
206207-010	Multiple Imputation	34/163 (20.8%)	39/166 (23.4%)	25/165 (15.1%)	5.7% (-5.6%, 16.7%)	8.4% (-5.2%, 22.0%)
	Per-Protocol	31/144 (21.5%)	31/155 (20.0%)	18/143 (12.6%)	8.9% (0.3%, 17.6%)	7.4% (-0.9%, 15.7%)
	Complete Case	25/104 (24.0%)	29/107 (27.1%)	13/63 (20.6%)	3.4% (-9.5%, 16.3%)	6.5% (-6.6%, 19.5%)
206207-011	Multiple Imputation	35/188 (18.6%)	35/181 (19.3%)	19/185 (10.5%)	8.1% (0.8%, 16.4%)	9.0% (-0.01%, 18.1%)
	Per-Protocol	31/170 (18.2%)	27/159 (17.0%)	19/162 (11.7%)	6.5% (-1.0%, 14.1%)	5.2% (-2.4%, 12.9%)
	Complete Case	27/107 (25.2%)	25/101 (24.7%)	16/68 (23.5%)	1.7% (-11.3%, 14.7%)	1.2% (-11.9%, 14.4%)

Source: Reviewer's Analysis. For per-protocol analysis, LOCF was used to impute missing data for all subjects with missing data except for non-protocol violators. The complete case analysis is based on subjects who had a BCVA measurement at Month 36. For all analyses, subjects who received escape therapy prior to 3 years were set as treatment failures.

3.2.4.1.2 Secondary Efficacy Endpoints

3.2.4.1.2.1 Improvement in BCVA from Baseline by Visit

The comparison of the two DEX arms and the Sham arm with respect to the proportion of subjects with a 15 letter or more improvement at selected months is given in Table 7. The DEX 700 arm had a significantly higher proportion of subjects with a 15 letter or more improvement in BCVA from baseline at Months 6, 36 and 39 in both studies. Table 34 in the appendix provides the proportions of subjects with a 15 letters or more improvement at all measurement time points.

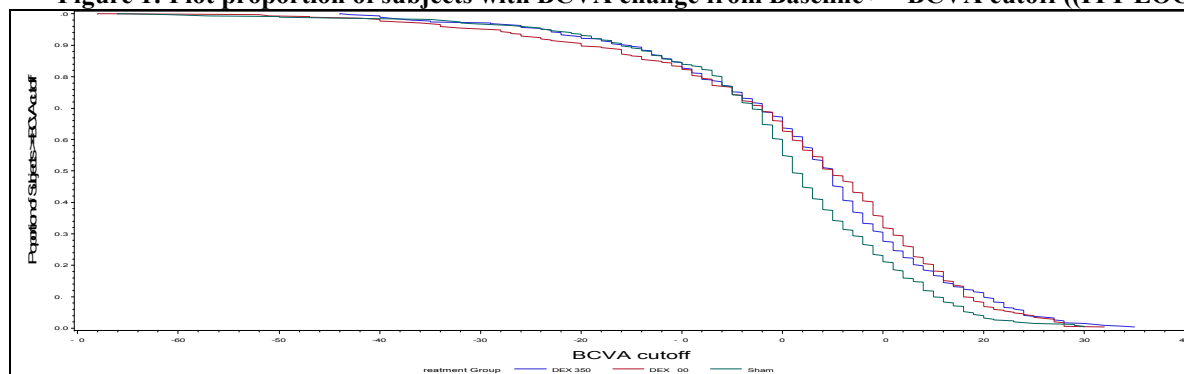
Table 7: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by Visit (ITT LOCF)

Visit	DEX 700 N=347	DEX 350 N=344	Sham N=349	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 206207-010				
Month 6	23(14.1%)	17(10.2%)	12(7.3%)	6.8% (0.2%, 13.5%)	3%(-3.1%, 9.0%)
Month 12	22(13.5%)	25(15.1%)	13(7.9%)	5.6% (-1%, 12.3%)	7.2% (0.4%, 14.0%)
Month 18	26(16%)	16(9.6%)	15(9.1%)	6.9% (-0.3%, 14%)	0.5%(-5.7%, 6.8%)
Month 24	21(12.9%)	25(15.1%)	15(9.1%)	3.8%(-3%, 10.6%)	6.0%(-1%, 13.0%)
Month 36	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1%, 16.5%)	9.0% (1.3%, 16.7%)
Month 39	34(20.9%)	31(18.7%)	19(11.5%)	9.3% (1.4%, 17.3%)	7.2%(-0.5%, 14.8%)
	Study 206207-011				
Month 6	16(8.5%)	11(6.1%)	6(3.2%)	5.3% (0.5%, 10%)	2.8%(-1.5%, 7.2%)
Month 12	23(12.2%)	17(9.4%)	17(9.2%)	3%(-3.2%, 9.3%)	0.2%(-5.7%, 6.2%)
Month 18	21(11.2%)	18(9.9%)	16(8.6%)	2.5%(-3.5%, 8.6%)	1.3%(-4.7%, 7.2%)
Month 24	31(16.5%)	15(8.3%)	18(9.7%)	6.8%(-0.1%, 13.6%)	-1.4%(-7.3%, 4.4%)
Month 36	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)
Month 39	38(20.2%)	31(17.1%)	19(10.3%)	9.9% (2.7%, 17.2%)	6.9%(-0.2%, 13.9%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy prior to a given visit were set as treatment failures in that and subsequent visits.

A plot of the proportions of subjects above different change from baseline BCVA cutoff points is given in Figure 1. The DEX 700 arm had consistently higher proportion of subjects with a positive change from baseline compared to Sham.

Figure 1: Plot proportion of subjects with BCVA change from Baseline \geq BCVA cutoff (ITT LOCF)



Source: Reviewer's Analysis

A summary of the change from baseline in BCVA at 3 years categorized into different levels of improvement and worsening is given in Table 8. For all arms, the largest proportion of subjects fell in the “no change” category, which the applicant defined as a change in BCVA of between -5 to 5 letters from baseline at 3 years. Compared to Sham, DEX 700 had higher proportion of subjects with a 15 letter or more improvement and significantly lower proportion of subjects with no change in BCVA (BCVA of between -5 to 5 letters) from baseline at 3 years. A similar pattern was observed for the comparison of DEX 350 against Sham (Table 8).

Table 8: Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF)

BCVA Change	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=188	DEX 350 N=181	Sham N=185
≥15 Letters Improvement	32 (19.6)	33(19.9)	18(10.9)	33(17.6)	28(15.5)	19 (10.3)
≥10 and <15 Letters Improvement	27(16.6)	21(12.7)	15(9.1)	22(11.7)	17(9.4)	20(10.8)
≥5 and <10 Letters Improvement	27(16.6)	31(18.7)	20(12.1)	21(11.2)	34(18.8)	18(9.7)
No Change (-5 to +5 Letters)	49 (30.1)	58(34.9)	85(51.5)	70(37.2)	55(30.4)	96(51.9)
>=5 and <10 Letters Worsening	12(7.4)	12(7.2)	8(4.8)	9(4.8)	11(6.1)	10(5.4)
>=10 and <15 Letters Worsening	5(3.1)	3(1.8)	6(3.6)	6(3.2)	11(6.1)	7(3.8)
>=15 Letters Worsening	11(6.7)	8(4.8)	13(7.9)	27(14.4)	25(13.8)	15(8.1)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set to the “no change” category.

3.2.4.1.2.2 Area under the curve (AUC) and Mean of change from baseline BCVA

The applicant used the mean area under the curve (AUC) of the change from baseline BCVA as the primary efficacy endpoint for other regulatory agencies. For each subject, the area under the curve was computed (see Table 42 in the appendix for the formula for AUC). The mean AUC for each treatment arm was subsequently computed and compared using a t-test. Compared to the Sham arm, both DEX arms showed a significantly higher mean AUC of the change from baseline BCVA in Study 206207-010 but not in Study 206207-011 (Table 9).

Table 9: Summary of Area under the Curve (AUC) of the Change from Baseline BCVA

Studies	Treatment : Mean AUC (std)			Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	4.11 (8.26)	4.33 (8.49)	1.89 (7.74)	2.22 (0.48, 3.96)	2.45 (0.69,4.20)
010	2.90 (8.55)	2.94 (7.67)	2.02 (8.20)	0.88 (-0.83, 2.59)	0.91 (-0.72, 2.54)

Source: Table 11-1 of the applicant's submitted Study Reports.

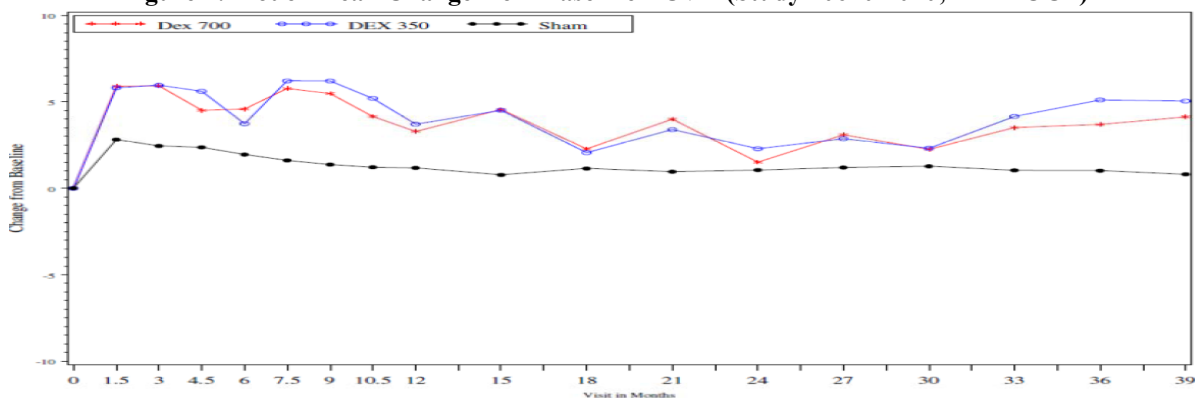
The summary of the mean change in BCVA and the mean plots of the change in BCVA from baseline over time are given in Table 10, Figure 2 and Figure 3. For Study 206207-010, the Sham arm had consistently lower mean change from baseline for all measurement times. For Study 206207-011, however, there was no noticeable separation between the three arms between months 15 and 36. Section 3.3.1 of this review attempts to provide an explanation as to why there was no separation between months 15 and 36 in study 206207-011.

Table 10: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)

Visit	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Baseline*	56.2 (10.0)	55.9(9.6)	56.8(8.7)	-0.5 (-2.5, 1.5)	-0.9 (-2.9, 1.1)
Month 6	4.6(9)	3.7(9.1)	2(9)	2.6(0.7,4.6)	1.8(-0.2,3.7)
Month 12	3.3(10.7)	3.7(10.4)	1.2(10.2)	2.1(-0.2,4.4)	2.5(0.3,4.8)
Month 18	2.3(12.4)	2.1(11.3)	1.1(10.9)	1.1(-1.4,3.7)	0.9(-1.5,3.3)
Month 24	1.5(14.4)	2.3(14.7)	1.1(11.1)	0.5(-2.3,3.2)	1.2(-1.6,4.1)
Month 30	2.3(14.8)	2.3(15.2)	1.3(11.7)	1(-1.9,3.9)	1(-1.9,4)
Month 36	3.7(14.1)	5.1(12.3)	1(11.6)	2.7(-0.1,5.5)	4.1(1.5,6.7)
Month 39	4.1(13.9)	5(12)	0.8(11.9)	3.3(0.5,6.1)	4.2(1.7,6.8)
Study 206207-011					
Baseline*	55.9(9.8)	55.2(9.7)	57.0(8.8)	-1.1 (-3.0, 0.7)	-1.8 (-3.7, 0.1)
Month 6	3.6(8.6)	2.2(10.7)	1.1(10.2)	2.5(0.6,4.4)	1.1(-1,3.3)
Month 12	1.9(12.4)	1.9(11.2)	0.7(12.9)	1.2(-1.4,3.8)	1.3(-1.2,3.7)
Month 18	-1(14.7)	0.1(13.5)	-0.2(14.1)	-0.8(-3.8,2.1)	0.3(-2.6,3.1)
Month 24	-1.2(17.4)	-1.6(14.5)	-0.5(15.3)	-0.7(-4.1,2.6)	-1.1(-4.2,2)
Month 30	0.1(16.7)	-0.4(14.6)	-0.1(15.1)	0.2(-3,3.4)	-0.3(-3.3,2.7)
Month 36	0.7(17.2)	0.4(15.6)	-0.1(15.3)	0.9(-2.4,4.2)	0.6(-2.6,3.7)
Month 39	1.3(17)	1.4(15.2)	0(15.4)	1.4(-1.9,4.7)	1.4(-1.7,4.6)

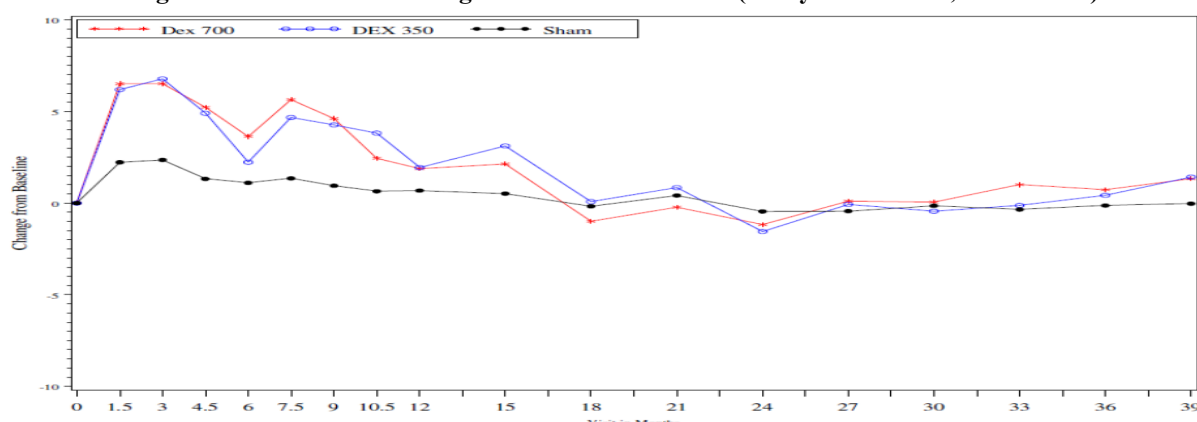
Source: Reviewer's Analysis. LOCF was used for imputing missing data. * Baseline measurement.

Figure 2: Plot of Mean Change from Baseline BCVA (Study 206207-010; ITT LOCF)



Source: Figure 11-1 of the applicant's submitted Study Reports. LOCF was used for imputing missing data.

Figure 3: Plot of Mean Change from Baseline BCVA (Study 206207-011; ITT LOCF)



Source: Figure 11-1 of the applicant's submitted Study Reports. LOCF was used for imputing missing data.

The two DEX arms were also compared with respect to the median, first and third quartiles of the change from baseline in BCVA at 3 years. There was no significant difference between either of the two DEX arms and the Sham arm in any of the quartiles. The point estimates for the median and the third quartile however were slightly higher for the two DEX arms compared to the Sham arm (Table 11).

Table 11: Summary of Quartiles of Change in BCVA from Baseline at 3 Years (ITT LOCF)

Studies	Quartile	Treatment: N (%)			Diff (95% CI)	
		DEX 700 N=351	DEX 350 N=347	Sham N=350	DEX 700 vs. Sham	DEX 350 vs. Sham
010	Q1	-3.0	-1.0	-5.0	2.0 (-7,8.5)	4.0 (-3.99,11.5)
	Q2	6.0	5.0	1.0	5.0 (-1.4,14.4)	4.0 (-1.87,13.4)
	Q3	13.0	12.0	9.0	4.0 (-1.5,15)	3.0 (-1.49,11.2)
011	Q1	-7.0	-9.0	-5.0	-2.0 (-9.5,5.9)	-4.0 (-14.89,2.4)
	Q2	4.0	3.0	2.0	2.0 (-5,11.5)	1.0 (-3.89,10.9)
	Q3	12.0	10.0	9.0	3.0 (-3.2,11.5)	1.0 (-5.39,8.8)
Pooled	Q1	-5.0	-5.0	-5.0	0.0 (-8.5,8.7)	0.0 (-8.47,11.7)
	Q2	5.0	5.0	1.0	4.0 (-8,11.5)	4.0 (-7.45,4)
	Q3	13.0	11.0	9.0	4.0 (-4.7,11.5)	2.0 (-2.97,11.7)

Source: Reviewer's analysis. Q1, Q2 (Median) and Q3 correspond to first, second and third quartiles.

3.2.4.1.2.3 Contrast sensitivity and Retinal thickness at center field

Additional secondary efficacy endpoints including changes from baseline contrast sensitivity and retinal thickness at center field were also assessed. The two DEX arms had significantly higher decline in retinal thickness from baseline at 3 years compared to the Sham arm. There was however no significant difference in the change from baseline contrast sensitivity at 3 years between the two DEX arms and the Sham arm (Table 12 and Table 13).

Table 12: Summary of Secondary Efficacy Outcomes: DEX 700 vs. Sham

Studies	Outcomes	Treatment : mean (std)		Mean Diff (95% CI)
		DEX 700	Sham	DEX 700 vs. Sham
010	Retinal thickness	-98.2 (178.9)	-52.1 (177.6)	-62.4 (-98.4, -26.5)
	Contrast sensitivity	-1.1 (8.0)	0.1 (4.5)	-1.1 (-2.5, 0.2)
011	Retinal thickness	-107.5 (228.3)	-71.3 (176.8)	-36.2 (-89.7, -5.1)
	Contrast sensitivity	-0.6 (8.4)	-0.7 (6.7)	-0.1 (-1.5,-1.6)
Pooled	Retinal thickness	-117.3 (208.1)	-62.1 (180.1)	-55.3 (-84.3,-26.2)
	Contrast sensitivity	-0.8 (8.3)	-0.3 (6.0)	-5.2 (-1.6,0.5)

Source: Table 14.2-6.2 and Table 14.2-9 of the applicant's submitted Study Reports.

Table 13: Summary of Secondary Efficacy Outcomes: DEX 350 vs. Sham

Studies	Outcomes	Treatment : mean (std)		Mean Diff (95% CI)
		DEX 350	Sham	DEX 350 vs. Sham
010	Retinal thickness	-109.0 (184.9)	-52.1 (177.6)	-62.6 (-98.3, -27.0)
	Contrast sensitivity	0.1 (6.4)	0.1 (4.5)	-0.3 (-1.7, 1.0)
011	Retinal thickness	-115.2 (202.3)	-71.3 (176.8)	-34.1 (-74.2, 5.9)
	Contrast sensitivity	-2.1 (7.8)	-0.7 (6.7)	-1.5 (-2.9, 0.0)
Pooled	Retinal thickness	-127.8 (196.7)	-62.0 (180.1)	-65.7 (-94.0,-37.5)
	Contrast sensitivity	-0.7 (7.1)	0.2 (6.0)	-0.5 (-1.4, 0.5)

Source: Table 14.2-6.2 and Table 14.2-9 of the applicant's submitted Study Reports.

In responses to the applicant's question regarding primary and secondary efficacy endpoints at the pre-NDA efficacy supplement meeting held on August 14, 2012, the agency indicated that retinal thickness was not validated for BCVA. The reviewer thus used the meta-analysis method for validation of surrogate endpoints to quantify the correlations between the raw outcomes, treatment adjusted outcomes (residuals) and the country level treatment differences between DEX 700 and Sham on the changes in BCVA, retinal thickness at center field and contrast sensitivity from baseline at 3 years. There appears to be a weak correlation between changes from baseline at 3 years BCVA and retinal thickness at center field both at the country specific treatment effect level and outcomes. There was a relatively strong correlation between changes from baseline at 3 years BCVA and contrast sensitivity both at country specific treatment effect level and outcomes (Table 14).

Table 14: Summary of Correlations between Changes in Retinal Thickness and Contrast sensitivity and BCVA from Baseline at 3 years

Outcome	Correlation (95% CI)		
	Treatment Effects	Residuals	Outcomes
Retinal thickness	0.25 (0.00, 0.51)	0.34 (0.26, 0.41)	-0.35 (-0.45, -0.28)
Contrast sensitivity	0.78 (0.26, 0.87)	0.53 (0.46, 0.62)	0.54 (0.48, 0.59)

Source: Reviewer's analysis.

3.2.4.1.2.4 Visual Functioning Questionnaire (VFQ-25)

Patient's perception regarding their vision and general health was collected using a Visual Functioning Questionnaire (VFQ-25) both at baseline and at 3 years. The VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. Subjects' responses were converted to scores from zero to hundred. A zero score implies complete dissatisfaction and a 100 implies complete satisfaction. Four of the 11 subscales which measure vision health, namely, General vision, Difficulty with short vision, Difficulty with long vision and Mental health issues related to vision were selected. There was no significant difference between the two DEX arms and Sham with respect to the change from baseline composite score and the four selected subscales at 3 years (Table 15 and Table 16).

Table 15: Summary of Change in Patient Reported Outcomes from Baseline at 3 Years: DEX 700 vs. Sham

Studies	Score	Treatment: mean (std)		Diff (95% CI)
		DEX 700	Sham	DEX 700 vs. Sham
010	Composite Score	-1.08 (16.78)	-0.41 (14.34)	-0.66 (-4.19, 2.86)
	General Vision Score	3.60 (20.07)	2.76 (15.95)	0.84 (-3.27, 4.94)
	Difficulty With Near Vision Score	4.44 (23.08)	4.24 (20.42)	0.19 (-4.73, 5.12)
	Difficulty With Far Vision Score	-1.52 (23.81)	-0.74 (19.35)	-0.78 (-5.68, 4.13)
	Mental Health Score	4.44 (23.08)	4.24 (20.42)	0.19 (-4.73, 5.12)
011	Composite Score	2.11 (18.18)	2.37 (16.03)	-0.26 (-3.89, 3.36)
	General Vision Score	5.96 (18.13)	6.39 (18.81)	-0.43 (-4.35, 3.49)
	Difficulty With Near Vision Score	6.71 (25.49)	4.33 (23.49)	2.37 (-2.81, 7.56)
	Difficulty With Far Vision Score	4.55 (25.88)	2.73 (21.76)	1.80 (-3.25, 6.86)
	Mental Health Score	7.04 (27.71)	5.63 (25.07)	1.41 (-4.18, 7.00)
Pooled	Composite Score	0.62 (17.6)	1.07 (15.3)	-0.45 (-3.0, 2.09)
	General Vision Score	4.86 (19.07)	4.69 (17.60)	0.17 (-2.67, 3.00)
	Difficulty With Near Vision Score	5.65 (24.38)	4.29 (22.08)	1.35 (-2.23, 4.94)
	Difficulty With Far Vision Score	1.72 (25.08)	1.12 (20.72)	0.59 (-2.95, 4.14)
	Mental Health Score	4.70 (26.39)	4.51 (23.70)	0.19 (-3.67, 4.06)

Source: Reviewer's analysis.

Table 16: Summary of Change in Patient Reported Outcomes from Baseline at 3 Years: DEX 350 vs. Sham

Studies	Score	Treatment : mean (std)		Diff (95% CI)
		DEX 350	Sham	DEX 350 vs. Sham
010	Composite Score	1.32 (15.45)	-0.41 (14.34)	1.74 (-1.60, 5.08)
	General Vision Score	6.19 (16.36)	2.76 (15.95)	3.43 (-0.19, 7.06)
	Difficulty With Near Vision Score	5.56 (19.54)	4.24 (20.42)	1.31 (-3.17, 5.80)
	Difficulty With Far Vision Score	2.57 (19.35)	-0.74 (19.35)	3.31 (-1.04, 7.66)
	Mental Health Score	3.37 (24.38)	4.24 (20.42)	0.15 (-5.06, 5.37)
011	Composite Score	1.29 (16.09)	2.37 (16.03)	-1.08 (-4.50, 2.34)
	General Vision Score	6.54 (19.27)	6.39 (18.81)	0.15 (-3.93, 4.23)
	Difficulty With Near Vision Score	3.47 (20.90)	4.33 (23.49)	-0.87 (-5.61, 3.87)
	Difficulty With Far Vision Score	-1.50 (22.09)	2.73 (21.76)	-4.25 (-8.92, 0.42)
	Mental Health Score	4.44 (24.34)	5.63 (25.07)	-1.20 (-6.46, 4.07)
Pooled	Composite Score	1.31 (15.76)	1.07 (15.3)	0.23 (-2.16, 2.63)
	General Vision Score	6.37 (17.89)	4.69 (17.60)	1.68 (-1.06, 4.43)
	Difficulty With Near Vision Score	4.47 (20.25)	4.29 (22.08)	0.18 (-3.09, 3.45)
	Difficulty With Far Vision Score	0.45 (20.89)	1.12 (20.72)	-0.67 (-3.88, 2.54)
	Mental Health Score	3.92 (24.33)	4.51 (23.70)	-0.58 (-4.29, 3.12)

Source: Reviewer's analysis.

Here also, the reviewer used the meta-analysis method for validation of surrogate endpoints to compute the correlation between the country level treatment differences between DEX 700 and Sham on the change in BCVA from baseline at 3 years and the patient reported scores. Additionally, the correlations between the raw changes from baseline and correlation between the changes from baseline after adjusting for treatment (residuals) were also computed. The scatter plot of the changes from baseline in BCVA and the patient reported scores is given in the appendix Figure 21. There was a weak correlation between the change from baseline BCVA at 3 years and the subjects reported scores both at the outcome level as well as the country specific treatment effect level (Table 17).

Table 17: Summary of Correlations between Changes in Patient Reported Scores and BCVA from Baseline at 3 Years

Score	Correlation (95% CI)		
	Treatment Effects	Residuals	Outcomes
Composite Score	0.62 (0.20, 0.85)	0.26 (0.17, 0.33)	0.22 (0.16, 0.28)
General Vision Score	0.32 (-0.38, 0.60)	0.22 (0.14, 0.30)	0.20 (0.14, 0.25)
Near Vision Score	0.48 (-0.32, 0.75)	0.22 (0.14, 0.30)	0.23 (0.17, 0.29)
Far Vision Score	0.56 (-0.17, 0.80)	0.20 (0.14, 0.28)	0.17 (0.12, 0.23)
Mental Health Score	0.60 (0.1, 0.83)	0.20 (0.1, 0.26)	0.18 (0.12, 0.24)

Source: Reviewer's analysis.

3.3 Evaluation of Safety

Out of the 1048 randomized subjects, five subjects in Study 206207-010 and 3 subjects in Study 206207-011 did not receive their respective treatments and thus were excluded from the safety population. The safety population in the two studies combined thus consisted of 1040 subjects (347, 343, and 350 subjects in the DEX 700, DEX 350 and Sham arm respectively) who received at least one injection. Eighty-eight of the 347 subjects in the DEX 700 arm and 105 of the 343 subjects in the DEX 350 arm received 6 injections during the course of the study (Table 18). Subjects in the DEX arms had a slightly higher average number of injections compared to subjects in the Sham arm.

Table 18: Summary of Number of Injections

# of Injections	Treatment: N (%)		
	DEX 700 N=347	DEX 350 N=343	Sham N=350
1	44 (12.7%)	35 (10.2%)	105 (30.1%)
2	54 (15.6%)	45 (13.1%)	63 (18.1%)
3	39 (11.2%)	41 (11.9%)	41 (11.7%)
4	42 (12.1%)	40 (11.6%)	26 (7.4%)
5	49 (14.1%)	41 (11.9%)	29 (8.3%)
6	88 (25.4%)	105 (30.5%)	50 (14.3%)
7	31 (8.9%)	37 (10.8%)	35 (10.0%)
Mean (std)	4.11(1.95)	4.37 (1.93)	3.29 (2.15)
Median	4.0	5.0	3.0
Q1, Q3	2.0, 6.0	3.0, 6.0	1.0, 5.0

Source: Reviewer's analysis.

Starting from the Month 6 visit, subjects were evaluated for retreatment eligibility every 3 months and those who qualified were retreated with the same assigned study medication. The study protocol specified that a subject was eligible for retreatment if the retinal thickness in the 1 mm central macular subfield by optical coherence tomography (OCT) was a $> 175 \mu\text{m}$ (determined by the site) or upon investigator interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the center subfield).

From Table 18, we can deduce that a total of 303, 308 and 245 subjects in the DEX 700, DEX 350 and Sham arm respectively, received at least one retreatment (2 or more injections). The summary of the number of subjects who received retreatment at a given study visit and the summary of the time at which the first retreatment was provided is presented in Table 19 and Table 20 respectively. In each treatment arm, over 75% of the subjects who had at least one retreatment received their first retreatment at Month 6, which corresponds to the protocol defined earliest possible time for retreatment.

Table 19: Summary of Subjects Who Received Retreatment by Visit

Time to First Re-treatment	Treatment: N (%)		
	DEX 700 N=303*	DEX 350 N=308*	Sham N=245*
Month 6	227(74.9%)	247(80.2%)	194(79.2%)
Month 7.5	26(8.6%)	21(6.8%)	15(6.1%)
Month 9	20(6.6%)	19(6.2%)	17(6.9%)
Month 10.5	6(2.0%)	4(1.3%)	4(1.6%)
Month 12	188(62%)	207(67.2%)	140(57.1%)
Month 15	40(13.2%)	36(11.7%)	27(11.0%)
Month 18	147(48.5%)	154(50%)	109(44.5%)
Month 21	46(15.2%)	56(18.2%)	25(10.2%)
Month 24	110(36.3%)	134(43.5%)	96(39.2%)
Month 27	59(19.5%)	49(15.9%)	25(10.2%)
Month 30	89(29.4%)	113(36.7%)	70(28.6%)
Month 33	69(22.8%)	60(19.5%)	32(13.1%)

Month 36	52(17.2%)	58(18.8%)	45(18.4%)
Month 39	1(0.3%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's analysis. * # of subjects who received at least one retreatment.

Table 20: Summary of First Time Retreatment

Time to First Re-treatment	Treatment: N (%)		
	DEX 700 N=303*	DEX 350 N=308*	Sham N=245*
Month 6	227(74.9%)	247(80.2%)	194(79.2%)
Month 7.5	26(8.6%)	21(6.8%)	15(6.1%)
Month 9	20(6.6%)	19(6.2%)	17(6.9%)
Month 10.5	4(1.3%)	3(1.0%)	4(1.6%)
Month 12	13(4.3%)	8(2.6%)	3(1.2%)
Month 15	2(0.7%)	2(0.6%)	3(1.2%)
Month 18	5(1.7%)	3(1.0%)	3(1.2%)
Month 21	3(1.0%)	0 (0.0%)	1(0.4%)
Month 24	2(0.7%)	3(1%)	3(1.2%)
Month 27	0 (0.0%)	2(0.6%)	0 (0.0%)
Month 30	0 (0.0%)	1(0.3%)	0 (0.0%)
Month 33	1(0.3%)	0 (0.0%)	1(0.4%)

Source: Reviewer's analysis. * # of subjects who received at least one retreatment.

The proportion of subjects who reported at least one ocular AE in the study eye was 296/347 (85.3%), 303/343 (88.3%) and 203/350 (58.0%) in the DEX 700, DEX 350 and Sham arm respectively. The two frequently reported AEs were cataract formation and Intraocular Pressure (IOP)-related AEs. The IOP-related AEs included elevated IOP, ocular hypertension and glaucoma. A significantly higher proportion of subjects in the DEX 700 (125/347; 36.0%) and DEX 350 (117/343; 34.1%) arms had IOP-related AEs compared to Sham (18/350; 5.1%). The proportion of subjects with an IOP change from baseline of at least a 10 mm Hg and the proportion of subjects with at least a 25 mm Hg and 35 mm Hg of IOP in the study eye at any time during the study period was significantly higher in the two DEX arms compared to Sham. Among subjects with natural lens at baseline (Phakic subjects), a significantly higher proportion in the DEX 700 (155/262, 59.2%) and DEX 350 (134/257, 52.1%) arms required cataract surgery in the study eye compared to only 18/249 (7.2%) in the Sham arm.

A higher proportion of subjects reported at least one serious AE (ocular or non-ocular) in the DEX 700 arm (115/347, 33.1%) and the DEX 350 arm (120/343, 35.0%) compared to the Sham arm (83/350, 23.7%). The proportion of subjects who reported at least one serious ocular AE in the study eye was significantly higher in the DEX 700 arm (24/347, 6.9%) and the DEX 350 arm (14/343, 4.1%) compared to the Sham arm (4/350, 1.1%). A total of 29/1040 (2.8%) subjects, 9 (2.6%) in DEX 700, 15 (4.4%) in DEX 350 and 5 (1.4%) in the Sham arm died during the study. The proportion of subjects who lost 15 letter or more from baseline at 3 years was comparable between the two DEX arms and the Sham arm (46/347 (13.3%), 37/343 (10.8%), 39/350 (11.1%) in DEX 700, 350 and Sham respectively). The proportion of subjects who required escape therapy was significantly higher in the Sham arm compared to the two DEX arms (Table 21).

Table 21: Summary of Adverse Events (AE) (All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=347	DEX 350 N=343	Sham N=350	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	333 (96.0%)	334 (97.4%)	281 (80.3%)	15.7% (11.0%, 20.3%)	17.1% (12.6%, 21.6%)
Any Ocular AE	296 (85.3%)	303 (88.3%)	203 (58.0%)	27.3% (20.9%, 33.7%)	30.3% (24.2%, 36.5%)
Any Serious AE	115 (33.1%)	120 (35.0%)	83 (23.7%)	9.4% (2.8%, 16.1%)	11.3% (4.5%, 18.0%)
Any Ocular Serious AE	24 (6.9%)	14 (4.1%)	4 (1.1%)	5.8% (2.9%, 8.7%)	3.0% (0.6%, 5.3%)
Any Severe AE	164 (47.3%)	164 (47.8%)	108 (30.9%)	16.4% (9.3%, 23.5%)	17.7% (11.9%, 23.4%)
Any Ocular Severe AE	99 (28.5%)	81 (23.6%)	38 (10.9%)	17.7% (11.9%, 23.4%)	12.8% (7.2%, 18.3%)
Any IOP Related AE	125 (36.0%)	117 (34.1%)	18 (5.1%)	30.9% (25.3%, 36.4%)	29.0% (23.4%, 34.5%)
≥10 mm Hg IOP Change from Baseline at any visit	96 (27.7%)	85 (24.8%)	13 (3.7%)	24.0% (18.8%, 29.1%)	21.1% (16.1%, 26.0%)
≥25 mm Hg IOP at any visit	111 (32.0%)	94 (27.4%)	15 (4.3%)	27.7% (22.4%, 33.0%)	23.1% (17.9%, 28.3%)
≥35 mm Hg IOP at any visit	23 (6.6%)	18 (5.2%)	3 (0.9%)	5.8% (3.0%, 8.6%)	4.4% (1.8%, 6.9%)
Glaucoma	4 (1.2%)	3 (0.9%)	1 (0.3%)	0.9% (-0.4, 2.1%)	0.6% (-0.5%, 1.7%)
IOP Lowering Procedures	4 (1.1%)	1 (0.3%)	1 (0.3%)	0.9% (-0.4%, 2.1%)	0.0% (-0.8%, 0.8%)
Cataract Surgery in Baseline Phakic Subjects	155/262 (59.2%)	134/257 (52.1%)	18/249 (7.2%)	51.9% (45.2%, 58.7%)	44.9% (38.1%, 51.8%)
≥15 Letters Loss from Baseline	48 (13.8%)	37 (10.8%)	39 (11.1%)	2.7% (-2.2%, 7.6%)	-0.4% (-5.0%, 4.3%)
Death	9 (2.6%)	15 (4.4%)	5 (1.4%)	1.1% (-0.9%, 3.2%)	2.9% (0.4%, 5.4%)
Escape Therapy	34 (9.8%)	39 (11.4%)	67 (19.1%)	-9.3% (-14.5%, -4.2%)	-7.8% (-13.1%, -2.5%)

Source: Tables 12-4, 14.3-22 14.3-22.3 and 14.3-22.4 of the applicant's study report. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

The summary of the relationship of the reported AEs to the study medication and the applicator system is summarized in Table 22. The majority of the reported treatment related AEs in the two DEX arms were related to the study medication rather than the applicator. It is not however clear how subjects in the Sham arm would have treatment-related AEs due to the study medication given that a needle-less injection without any study medication was used for this arm.

Table 22: Summary of Relationship of AE to Study Medication and Delivery System

AE Related To	Treatment N (%)			Total N=559
	DEX 700 N=244	DEX 350 N=227	Sham N=88	
Applicator or Insertion	65 (26.6%)	82 (36.1%)	48 (54.5%)	195 (34.9%)
Drug	171 (70.1%)	142 (62.5%)	37 (42.0%)	350 (62.6%)
Both	8 (3.3%)	2 (0.9%)	2 (2.3%)	12 (2.1%)
Unknown	0 (0.0%)	1 (0.4%)	1 (1.1%)	2 (0.3%)

Source: Reviewer's Analysis.

A summary of adverse events for baseline Pseudophakic subjects only is presented in Table 38 in the appendix. Summaries of ocular adverse events and treatment related ocular adverse events reported in $\geq 2\%$ of subjects in any of the three treatment arms, and serious ocular adverse events are given in Table 39--Table 41 in the appendix. The two DEX arms had a consistently higher proportion of subjects with ocular adverse events compared to the Sham arm. The majority of subjects reported cataract as a serious adverse event.

3.3.1 Cataract Surgery

As discussed in the previous section, one of the two most common AEs was cataract surgery. A summary of the number of subjects who underwent cataract surgery by the month at which the surgery was performed is presented in Table 23 for the two studies combined and in Table 24 for each study separately. Note that the applicant used different intervals of days to define the month at which a subject had surgery and the month at which the subject had a BCVA measurement. For example, for the time of surgery, Month 30 refers to 810-989 days after randomization, whereas, the BCVA measurement taken between Days 855-944 was assigned to Month 30 measurement. To ease comparison of analysis results, this reviewer applied the interval used to define the month at which a BCVA measurement was taken to determine the time of surgery. Thus, results reported in the applicant's submission might be slightly different from the summary provided here. In the combined studies, 51 (16.6%) subjects had surgery within the first 12 months. Most subjects had cataract surgery between Months 18 and 27. In Study 206207-010, 14 (19.1%) baseline phakic subjects who received DEX 700 had surgery within the first 12 months, and the corresponding figure for Study 206207-011 was 12 (14.5%). Most subjects in Study 206207-010 had surgery prior to 12 month or at Months 21 and 27. Similarly in Study 206207-011, most subjects had surgery either prior to Month 12 or at Months 18, 21 and 24.

Table 23: Summary of Number of Subjects who had Cataract Surgery

Time of Surgery	Treatment: N (%)			Total N=307
	DEX 700 N=155	DEX 350 N=134	Sham N=18	
Month ≤ 12	26(16.8%)	20(14.9%)	5(27.8%)	51 (16.6%)
Month 15	12(7.7%)	11(8.2%)	3(16.7%)	26 (8.4%)
Month 18	21(13.5%)	18(13.4%)	1(5.6%)	40 (13.0%)
Month 21	28(18.1%)	18(13.4%)	2(11.1%)	48 (15.6%)
Month 24	22(14.2%)	24(17.9%)	2(11.1%)	48 (15.6%)
Month 27	20(12.9%)	14(10.4%)	1(5.6%)	35 (11.4%)
Month 30	12(7.7%)	12(9.0%)	0(0.0%)	24 (7.8%)
Month 33	9(5.8%)	13(9.7%)	1(5.6%)	23 (7.5%)
Month 36	4(2.6%)	4(3.0%)	3(16.7%)	11 (3.6%)
Month 39	1(0.6%)	0(0.0%)	0(0.0%)	1 (0.3%)

Source: Reviewer's analysis.

Table 24: Summary of Number of who had Cataract Surgery by Study

Time of Cataract Surgery	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=72	DEX 350 N=72	Sham N=8	DEX 700 N=83	DEX 350 N=62	Sham N=10
Month ≤ 12	14(19.4%)	10(13.9%)	1(12.5%)	12(14.5%)	10(16.1%)	4(40.0%)
Month 15	7(9.7%)	8(11.1%)	0(0.0%)	5(6.0%)	3(4.8%)	3(30.0%)
Month 18	6(8.3%)	8(11.1%)	0(0.0%)	15(18.1%)	10(16.1%)	1(10.0%)
Month 21	14(19.4%)	11(15.3%)	1(12.5%)	14(16.9%)	7(11.3%)	1(10.0%)

Month 24	7(9.7%)	15(20.8%)	2(25%)	15(18.1%)	9(14.5%)	0(0.0%)
Month 27	12(16.7%)	6(8.3%)	1(12.5%)	8(9.6%)	8(12.9%)	0(0.0%)
Month 30	5(6.9%)	7(9.7%)	0(0%)	7(8.4%)	5(8.1%)	0(0.0%)
Month 33	4(5.6%)	5(6.9%)	1(12.5%)	5(6%)	8(12.9%)	0(0.0%)
Month 36	2(2.8%)	2(2.8%)	2(25%)	2(2.4%)	2(3.2%)	1(10%)
Month 39	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

Source: Reviewer's analysis.

The individual plots of the change from baseline in BCVA over time and the mean change from baseline for subjects who had cataract surgeries from the combined studies is given in Appendix: Figure 16 and Figure 17 respectively. It appears that for the majority of subjects who required cataract surgery, the change from baseline BCVA declines starting within weeks of randomization through the reported time of surgery and then starts to increase after surgery. The summary of the mean change from baseline and the proportion of subjects with a positive change from baseline within 9 month before and after surgery are summarized in Table 25 and Table 26 and support this observation. Except for subjects who had surgery at Month 27 and Month 36, the mean change from baseline in BCVA was negative within 6 month prior to surgery and at the time of surgery. The change however becomes positive and remains positive starting from the next measurement time, i.e., 3 months after surgery. Similarly for those subjects who had surgery at Month 27, and 36, although the mean change is not positive 3 months after surgery, there appears to be a substantial improvement compared to the mean BCVA change at the time of surgery (Table 25). There appears to be a general pattern in that the proportion of subjects with a positive change from baseline declines leading to the time of surgery and increases after surgery. For example, out of the 26 subjects who had cataract surgery at Month 15, 7 (26.9%) had a positive change from baseline 3 months prior to surgery but this number climbs to 17 (65.4%) 3 months after surgery (Table 26).

Table 25: Summary of the Mean Change from Baseline in BCVA within 9 Months of Cataract Surgery

Time of Surgery	Number of Months relative to Time of Surgery: Mean (Std)						
	-9	-6	-3	0	+3	+6	+9
Month 15	3.4 (6.5)	1.8 (11.1)	-5.8 (8.8)	-3.7 (14.0)	4.7 (10.4)	8.6 (13.0)	6.3 (12.2)
Month 18	3.7 (10.9)	-2.2 (14.8)	-6.1 (16.1)	-9.4 (16.3)	6.3 (11.5)	4.9 (10.5)	7.1 (10.8)
Month 21	1.2 (9.4)	2.1 (9.8)	-8.2 (15.2)	-4.6 (16.0)	1.8 (12.1)	4.8 (12.6)	4.1 (12.2)
Month 24	4.0 (10.4)	-3.4 (13.7)	-8.2 (14.2)	-11.0 (22.1)	3.1 (12.9)	4.3 (13.4)	4.9 (13.6)
Month 27	-1.7 (12.4)	-5.2 (13.7)	-16.9 (16.5)	-15.1 (19.5)	-4.8 (16.3)	-3.7 (16.7)	-2.8 (17.1)
Month 30	1.7 (8.1)	-10.6 (20.9)	5.3 (15.5)	-10.6 (20.9)	3.5 (10.1)	5.7 (15.6)	5.3 (15.5)
Month 33	-0.5 (10.9)	-4.3 (12.3)	-19.3 (18.8)	-9.7 (22.5)	3.1 (14.9)	5.2 (11.2)	
Month 36	-4.4 (12.9)	-5.8 (14.5)	-15 (19.6)	-9.0 (22.6)	-4.6 (19.4)		

Source: Reviewer's analysis. Positive and negative reflect # of month pre and post-surgery. Zero corresponds to time of surgery.

Table 26: Summary of the Proportion of Subjects with a Positive Change from Baseline in BCVA within 9 Months of Cataract Surgery

Time of Surgery	Number of Months relative to Time of Surgery: N (%)						
	-9	-6	-3	0	+3	+6	+9
Month 15	18/26 (69.2%)	16/26 (61.5%)	7/26 (26.9%)	11/26 (42.3%)	17/26 (65.4%)	21/26 (80.8%)	18/26 (69.2%)
Month 18	27/40 (67.5%)	18/40 (45.0%)	16/40 (40.0%)	11/40 (27.5%)	27/40 (67.5%)	24/40 (60.0%)	29/40 (72.5%)
Month 21	27/48 (56.2%)	28/48 (58.3%)	19/48 (39.6%)	22/48 (45.8%)	28/48 (58.3%)	35/48 (72.9%)	32/48 (66.7)
Month 24	35/48 (72.9%)	24/48 (50.0%)	15/48 (31.2%)	18/48 (37.5%)	30/48 (62.5%)	33/48 (68.7%)	36/48 (75.0%)
Month 27	17/35 (48.6%)	12/35 (34.3%)	5/35 (14.3%)	8/35 (22.9%)	16/35 (45.7)	16/35 (45.7)	19/35 (54.3%)
Month 30	17/24 (70.8%)	9/24 (37.5%)	6/24 (25.0%)	5/24 (20.8%)	17/24 (70.8%)	20/24 (83.3%)	20/24 (83.3%)
Month 33	12/23 (52.2%)	8/23 (34.8%)	3/23 (13.0%)	10/23 (43.5%)	18/23 (78.3%)	17/23 (73.9%)	
Month 36	5/11 (45.5%)	4/11 (36.4%)	2/11 (18.2%)	5/11 (45.5%)	6/11 (54.5%)		

Source: Reviewer's analysis. Positive and negative reflect # of month pre and post-surgery. Zero corresponds to time of surgery.

The mean plots of the change from baseline BCVA excluding subjects who had surgery 12 months after randomization are presented in Figure 18 in the appendix. For Study 206207-011, there was an improved separation among the three treatment groups, however no improvement was observed for Study 206207-011 compared to when all subjects were included. When a similar plot was produced excluding all subjects who reported cataract-related AE regardless of whether they had surgery or not, there was an improved separation among the three treatment groups with the two DEX arms having higher mean change from baseline BCVA values in both studies (Figure 19).

In Study 206207-011, 101 baseline phakic subjects who received DEX 700 reported cataract AE. Of these, 76 (75.2%) had cataract surgery compared to 65 (80.2%) of the 81 baseline phakic subjects who received DEX 700 and reported cataract AE in study 206207-010 (Table 27). Figure 20 in the appendix depicts mean plots of the change from baseline BCVA for subjects who reported at least one cataract-related AE classified by surgery or no surgery. It appears that, between Months 6 and 24, which also corresponds to the time the majority of subjects had cataract surgery; subjects who underwent cataract surgery had lower mean BCVA compared to those who did not have surgery. After Month 24 however, subjects who underwent cataract surgery have a substantial increase in the mean change from baseline BCVA while those who reported cataract related AE but did not have surgery had a sharp decline. It thus appears that, the relatively higher number of subjects who reported cataract AE but had not undergone surgery in Study 206207-011 might have contributed to the observed lower mean change in BCVA, and thus excluding these set of subjects might have resulted in an improved treatment difference as the majority are in the DEX arms. Additionally, in Study 206207-011, there was a much sharper decline in the mean change from baseline in BCVA among subjects who reported cataract AE but did not have surgery compared to the same set of subjects in study 206207-010.

In conclusion, from the above analyses, it appears that, cataract formation resulted in a decline in BCVA over time. Although cataract surgery reversed this decline to some degree, it did not result

in a large enough improvement in the mean change from baseline BCVA to completely overcome the decline. Additionally, not all subjects who reported cataract-related AEs had surgery, thus, the large decline in BCVA in these subjects might have contributed to the overall lower mean change in BCVA in the two DEX groups especially in Study 206207-011.

Table 27: Summary of Subjects who had surgery among baseline Phakic subjects who reported Cataract AE

Studies	Treatment N(%)		
	DEX 700	DEX 350	Sham
010	65/81 (80.2%)	66/83 (79.5%)	8/19 (42.1%)
011	76/101 (75.2%)	59/85 (69.4%)	8/37 (21.6%)
Pooled	141/ 182 (77.5%)	125/168 (74.4%)	16/56 (28.6%)

Source: Reviewer's analysis. 14 subjects in DEX700, 2 subjects in Sham and 9 subjects in DEX 350 did not report Cataract AE but had surgery.

3.3.2 IOP-Related AE

The second most commonly reported adverse event was related to IOP. As indicated earlier, there were a total of 260 subjects (125 in DEX 700, 117 in DEX 350 and 18 in the Sham arm) who reported at least one IOP-related AE during the study period. The summary of the number of IOP related AEs reported is given in Table 28. The majority of subjects from the three treatment arms had only one incident of IOP related AE. The summary of the time at which the first IOP-related AE was reported is provided in Table 29. The cumulative probability of first time IOP-related AE is given in Figure 22 in the appendix. From Table 29 and the cumulative plot, it appears that, for all study arms, the first elevated IOP incidences appeared in the first few months. A cross-tabulation of the number of injections and the number of IOP-related AEs reported is given in Table 30. There appears to be a slight association between the number of injections and the number of times a subject had an elevated IOP related AE; with higher number of injections resulting in a relatively higher number of IOP AEs reported.

Table 28: Summary of Number of IOP events reported

# of IOP events	Treatment: N (%)		
	DEX 700 N=125	DEX 350 N=117	Sham N=18
1	62(49.6%)	65(55.6%)	13(72.2%)
2	30(24.0%)	30(25.6%)	4(22.2%)
3	13(10.4%)	12(10.3%)	0(0.0%)
4	10(8.0%)	8(6.8%)	0(0.0%)
5	8(6.4%)	0(0.0%)	1(5.6%)
6	2(1.6%)	1(0.9%)	0(0.0%)
7	0(0.0%)	1(0.9%)	0(0.0%)

Source: Reviewer's analysis.

Table 29: Summary of First time IOP related AE

Time to First IOP Related Adverse Event	Treatment: N (%)		
	DEX 700 N=125	DEX 350 N=117	Sham N=18
Month <=3	73(58.4%)	62(53%)	5(27.8%)
Month 4.5	0(0.0%)	1(0.9%)	2(11.1%)
Month 6	3(2.4%)	3(2.6%)	0(0.0%)
Month 7.5	14(11.2%)	16(13.7%)	3(16.7%)

Month 9	10(8%)	7(6.0%)	1(5.6%)
Month 10.5	4(3.2%)	2(1.7%)	0(0.0%)
Month 12	5(4.0%)	5(4.3%)	1(5.6%)
Month 15	8(6.4%)	7(6.0%)	1(5.6%)
Month 18	1(0.8%)	2(1.7%)	2(11.1%)
Month 21	4(3.2%)	3(2.6%)	0(0.0%)
Month 24	0(0.0%)	3(2.6%)	0(0.0%)
Month 27	0(0.0%)	3(2.6%)	1(5.6%)
Month 30	2(1.6%)	0(0.0%)	1(5.6%)
Month 33	0(0.0%)	1(0.9%)	0(0.0%)
Month 36	0(0.0%)	2(1.7%)	1(5.6%)
Month 39	1(0.8%)	0(0.0%)	0(0.0%)

Source: Reviewer's analysis.

Table 30: Summary of Cross tabulation of Number of Injections and Number of IOP Related AEs

# of Injections	Number of reported IOP AEs							Total
	1	2	3	4	5	6	7	
1	22(91.7%)	1(4.2%)	0(0.0%)	1(4.2%)	0(0.0%)	0(0.0%)	0(0.0%)	24
2	22(73.3%)	5(16.7%)	1(3.3%)	2(6.7%)	0(0.0%)	0(0.0%)	0(0.0%)	30
3	12(54.5%)	9(40.9%)	0(0.0%)	1(4.5%)	0(0.0%)	0(0.0%)	0(0.0%)	22
4	16(48.5%)	9(27.3%)	4(12.1%)	4(12.1%)	0(0.0%)	0(0.0%)	0(0.0%)	33
5	13(44.8%)	8(27.6%)	3(10.3%)	2(6.9%)	1(3.4%)	1(3.4%)	1(3.4%)	29
6	32(39.5%)	22(27.2%)	15(18.5%)	7(8.6%)	4(4.9%)	1(1.2%)	0(0.0%)	81
7	10(43.5%)	6(26.1%)	2(8.7%)	1(4.3%)	3(13%)	1(4.3%)	0(0.0%)	23

Source: Reviewer's analysis. Only subjects who received either DEX 700 or DEX 350 were included.

4 Risk Benefit Analysis

The reviewer conducted two types of risk-benefit analyses: one at subject level and one at population level. Subjects who received one study treatment were included in these analyses and were analyzed according to the treatment to which they were randomized. The analysis results are presented in Tables 34-36. These results demonstrated unfavorable risk-benefit profile for the test product.

4.1 Risk-benefit Analysis at Subject Level

For a given benefit and risk of interest, this analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best case scenario is the case in which a pre-specified level of BCVA improvement was observed without incurring an AE. The worst case scenario is incurring an AE without achieving a pre-specified level of improvement in BCVA from baseline at 3 years. The other two scenarios are having benefit with AE, and no benefit and no AE.

Compared to Sham, the DEX 700 arm had a higher proportion of subjects with the worst case scenario, and lower or only slightly higher proportion of subjects with the best case scenario for the majority of risks considered. Additionally, the DEX 700 arm also had a higher proportion of subjects who achieved improvement in BCVA but incurred an AE and lower proportion of subjects with no benefit and no AE compared to Sham (Table 31).

A significantly higher proportion of subjects in the DEX 700 arm failed to achieve a 15 letter or more improvement in BCVA from baseline at 3 years but reported at least one IOP related AE (Worst Case Scenario) compared to subjects in the Sham arm (101 (29.1%) vs. 17 (4.9%)). On the other hand, the proportion of subjects with the best case scenario i.e., ≥ 15 letters improvement without reporting any IOP related AE was comparable in the DEX 700 and Sham arm [41(11.8%) vs. 36 (10.3%); Figure 4].

For baseline Phakic subjects, a significantly higher proportion of subjects underwent cataract surgery but failed to achieve a 15 letter or more BCVA improvement from baseline at 3 years (Worst Case Scenario) in the DEX 700 arm compared to Sham (125 (47.7%) vs. 15 (6.0%)). The proportion of baseline Phakic subjects with a 15 letter or more BCVA improvement from baseline at 3 years without requiring cataract surgery (Best Case Scenario) however was slightly lower in the DEX 700 arm compared to Sham (16 (6.1%) vs. 23 (9.2%)) (Figure 4 and Table 31).

A similar risk-benefit analysis for baseline pseudophakic subjects was performed with IOP related AE as the assumed risk. Because of an improved treatment effect and slightly lower risk estimate, the risk-benefit profile for this subgroup of subjects appears to be slightly better than the whole population. For this subgroup of subjects, in the DEX 700 arm, 21/85 (24.7%) subjects failed to achieve a 15 letter or more improvement in BCVA from baseline at 3 years but reported at least one IOP related AE (Worst Case Scenario) compared to 8/100 (8.0%) in the Sham arm. On the other hand, the proportion of subjects with the best case scenario i.e., ≥ 15 letters improvement without reporting any IOP related AE was 15/85 (17.6%) in the DEX 700 arm compared to 11/100 (11.0%) in the Sham arm (Table 32).

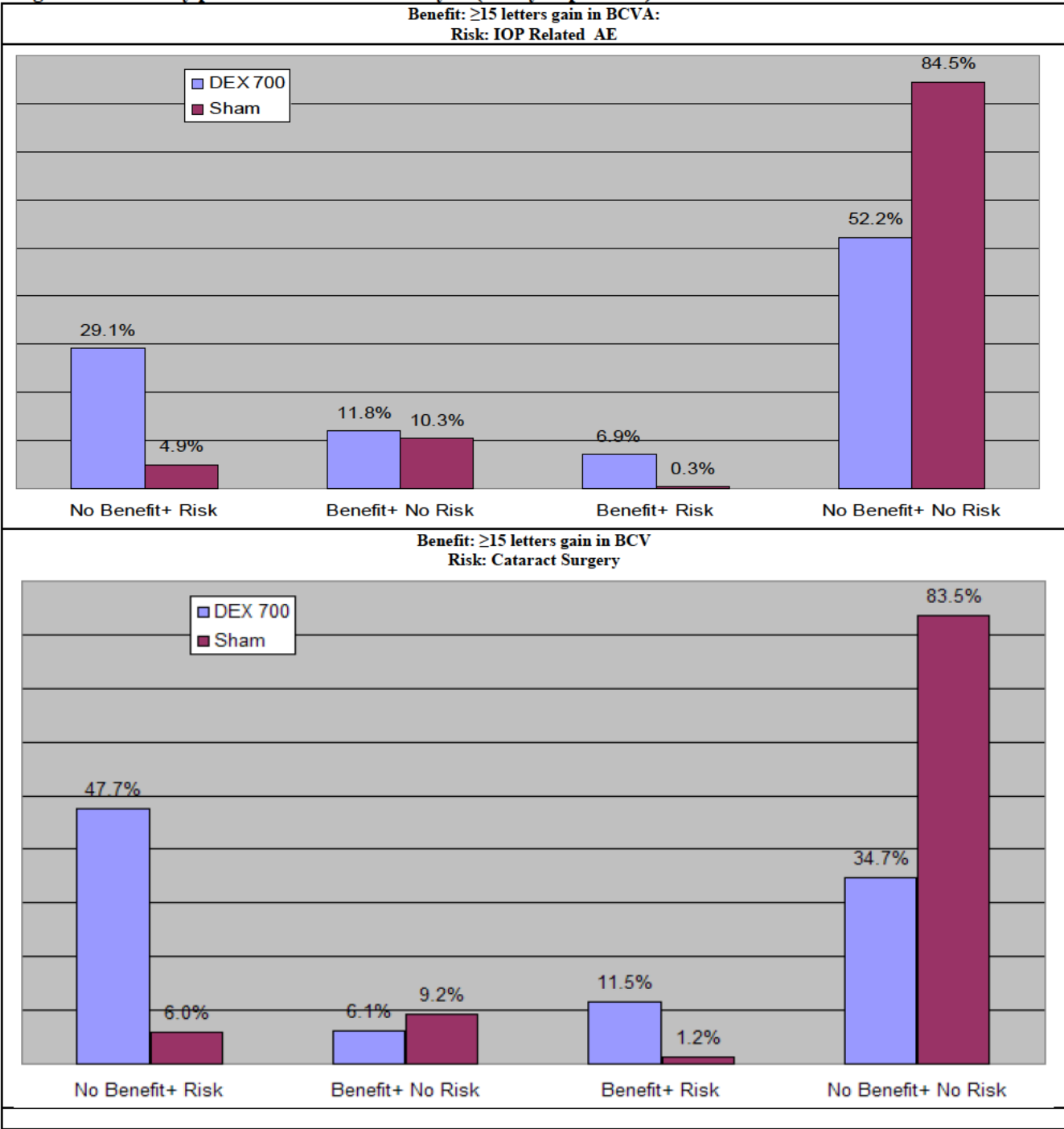
4.2 Risk-benefit Analysis at Population Level

For the risk-benefit analysis at population level, the unadjusted number needed to treat ($NNT = 1 / (P_{DEX} - P_{SHAM})$) and adverse event adjusted number needed to treat ($NNT_{adj} = 1 / ((P_{DEX} - P_{SHAM}) * (1 - (Q_{DEX} - Q_{SHAM})))$) together with the Number Needed to Harm ($NNH = 1 / (Q_{DEX\ 700} - Q_{SHAM})$) were computed for each benefit and risk combination. Here P_{DEX} and P_{SHAM} represent the proportion of success and Q_{DEX} and Q_{SHAM} represent the proportion of subjects with a given adverse event in the DEX 700 and Sham arms, respectively. The unadjusted number needed to treat measures the average number of subjects that need to be treated to observe one improvement in BCVA. The adverse event adjusted number needed to treat is the average number of subjects that need to be treated to observe an improvement in BCVA without treatment related adverse event. The Benefit-Risk Ratio ($BRR = (P_{DEX} - P_{SHAM}) / (Q_{DEX} - Q_{SHAM}) = NNH / NNT$) was also computed.

For the majority of risks considered, the BRR values were less than one or equivalently the Number NNT was larger than the NNH. This implies that fewer subjects were needed to be treated using DEX 700 to observe an AE compared to the number needed to be treated to observe one subject with a 15 letter or more BCVA improvement from baseline at 3 years. For example, the BRR values of 0.26 and 0.14 corresponding to Any IOP related AE and Cataract Surgery for Phakic subjects imply that for every subject with a 15 letter or more BCVA improvement due to DEX 700, 4 subjects had at least one IOP related AE and 7 Phakic subjects required cataract surgery, respectively. The IOP related AE adjusted number needed to treat was 45% higher than the unadjusted value, i.e., compared to Sham, more subjects need to be treated using DEX 700 to

observe a 15 letter or more improvement in BCVA without incurring an IOP related AE (Table 33).

Figure 4: Summary plot for Risk-Benefit Analysis (Safety Population)



Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Table 31: Summary of Risk-Benefit Analysis (Safety Population)

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 700 N=347	Sham N=349	DEX 700 N=347	Sham N=349	DEX 700 N=347	Sham N=349	DEX 700 N=347	Sham N=349
BCVA improvement of ≥ 15 letters	Any AE	2 (0.6%)	0.0(0.0%)	270(77.8%)	243(69.6%)	63(18.2%)	37(10.6%)	12(3.5%)	69(19.8%)
	Any Ocular AE	11(3.2%)	11(3.2%)	242(69.7%)	176(50.4%)	54(15.6%)	26(7.4%)	40(11.5%)	136(39.0%)
	Any Serious AE	40(11.5%)	23(6.6%)	90(25.9%)	68(19.5%)	25(7.2%)	14(4.0%)	192(55.3%)	244(69.9%)
	Any Ocular Serious AE	61(17.6%)	36(10.3%)	20(5.8%)	2(0.6%)	4(1.2%)	1(0.3%)	262(75.5%)	310(88.8%)
	Any Severe AE	30(8.6%)	22(6.3%)	129(37.2%)	92(26.4%)	35(10.1%)	15(4.3%)	153(44.1%)	220(63.0%)
	Any Severe Ocular AE	47(13.5%)	36(10.3%)	81(23.3%)	36(10.3%)	18(5.2%)	1(0.3%)	201(57.9%)	276(79.1%)
	Any IOP Related AE	41(11.8%)	36(10.3%)	101(29.1%)	17(4.9%)	24(6.9%)	1(0.3%)	181(52.2%)	295(84.5%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	50(14.4%)	37(10.6%)	81(23.3%)	13(3.7%)	15(4.3%)	0(0.0%)	201(57.9%)	299(85.7%)
	≥ 25 mm Hg IOP at any visit	48(13.8%)	37(10.6%)	94(27.1%)	15(4.3%)	17(4.9%)	0(0%)	188(54.2%)	297(85.1%)
	≥ 35 mm Hg IOP at any visit	62(17.9%)	37(10.6%)	20(5.8%)	3(0.9%)	3(0.9%)	0(0%)	262(75.5%)	309(88.5%)
	Cataract Surgery in Phakic Subjects	16(6.1%)	23(9.2%)	125(47.7%)	15(6%)	30(11.5%)	3(1.2%)	91(34.7%)	208(83.5%)
BCVA improvement of ≥ 10 letters	Any AE	4(1.2%)	5(1.4%)	223(64.3%)	213(61%)	110(31.7%)	67(19.2%)	10(2.9%)	64(18.3%)
	Any Ocular AE	18(5.2%)	26(7.4%)	200(57.6%)	156(44.7%)	96(27.7%)	46(13.2%)	33(9.5%)	121(34.7%)
	Any Serious AE	70(20.2%)	53(15.2%)	71(20.5%)	63(18.1%)	44(12.7%)	19(5.4%)	162(46.7%)	214(61.3%)
	Any Ocular Serious AE	110(31.7%)	71(20.3%)	20(5.8%)	2(0.6%)	4(1.2%)	1(0.3%)	213(61.4%)	275(78.8%)
	Any Severe AE	60(17.3%)	51(14.6%)	110(31.7%)	86(24.6%)	54(15.6%)	21(6%)	123(35.4%)	191(54.7%)
	Any Severe Ocular AE	86(24.8%)	68(19.5%)	71(20.5%)	33(9.5%)	28(8.1%)	4(1.1%)	162(46.7%)	244(69.9%)
	Any IOP Related AE	72(20.7%)	67(19.2%)	83(23.9%)	13(3.7%)	42(12.1%)	5(1.4%)	150(43.2%)	264(75.6%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	84(24.2%)	70(20.1%)	66(19%)	11(3.2%)	30(8.6%)	2(0.6%)	167(48.1%)	266(76.2%)
	≥ 25 mm Hg IOP at any visit	80(23.1%)	70(20.1%)	77(22.2%)	13(3.7%)	34(9.8%)	2(0.6%)	156(45%)	264(75.6%)
	≥ 35 mm Hg IOP at any visit	106(30.5%)	72(20.6%)	15(4.3%)	3(0.9%)	8(2.3%)	0(0%)	218(62.8%)	274(78.5%)
	Cataract Surgery in Phakic Subjects	25(9.5%)	47(18.9%)	101(38.5%)	13(5.2%)	54(20.6%)	5(2%)	82(31.3%)	184(73.9%)
BCVA improvement of ≥ 1 letters	Any AE	7(2.0%)	29(8.3%)	139(40.1%)	150(43%)	194(55.9%)	130(37.2%)	7(2%)	40(11.5%)
	Any Ocular AE	31(8.9%)	72(20.6%)	126(36.3%)	115(33%)	170(49%)	87(24.9%)	20(5.8%)	75(21.5%)
	Any Serious AE	129(37.2%)	115(33%)	43(12.4%)	38(10.9%)	72(20.7%)	44(12.6%)	103(29.7%)	152(43.6%)
	Any Ocular Serious AE	191(55%)	157(45%)	14(4%)	1(0.3%)	10(2.9%)	2(0.6%)	132(38%)	189(54.2%)
	Any Severe AE	109(31.4%)	110(31.5%)	72(20.7%)	58(16.6%)	92(26.5%)	49(14%)	74(21.3%)	132(37.8%)
	Any Severe Ocular AE	149(42.9%)	146(41.8%)	47(13.5%)	24(6.9%)	52(15%)	13(3.7%)	99(28.5%)	166(47.6%)
	Any IOP Related AE	123(35.4%)	148(42.4%)	47(13.5%)	7(2%)	78(22.5%)	11(3.2%)	99(28.5%)	183(52.4%)

	≥10 mm Hg IOP Change from Baseline at any visit	144(41.5%)	153(43.8%)	39(11.2%)	7(2%)	57(16.4%)	6(1.7%)	107(30.8%)	183(52.4%)
	≥25 mm Hg IOP at any visit	132(38%)	151(43.3%)	42(12.1%)	7(2%)	69(19.9%)	8(2.3%)	104(30%)	183(52.4%)
	≥35 mm Hg IOP at any visit	184(53%)	157(45%)	6(1.7%)	1(0.3%)	17(4.9%)	2(0.6%)	140(40.3%)	189(54.2%)
	Cataract Surgery in Phakic Subjects	50(19.1%)	104(41.8%)	60(22.9%)	11(4.4%)	95(36.3%)	7(2.8%)	57(21.8%)	127(51%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Summary of Risk-Benefit Analysis (Continued)

Benefit	Risk	Differences: DEX 700- Sham (95% CI)			
		Benefit + No Risk (Best Case Scenario)	No Benefit + Risk (Worst Case Scenario)	Benefit + Risk	No Benefit + No Risk
BCVA improvement of ≥15 letters	Any AE	0.6% (-0.2%, 1.4%)	8.2% (1.7%, 14.7%)	7.6% (2.4%, 12.7%)	-16.3% (-20.9%, -11.7%)
	Any Ocular AE	0% (-2.6%, 2.6%)	19.3% (12.2%, 26.4%)	8.1% (3.4%, 12.8%)	-27.4% (-33.6%, -21.3%)
	Any Serious AE	4.9% (0.7%, 9.2%)	6.5% (0.2%, 12.7%)	3.2% (-0.2%, 6.6%)	-14.6% (-21.7%, -7.5%)
	Any Ocular Serious AE	7.3% (2.1%, 12.4%)	5.2% (2.6%, 7.8%)	0.9% (-0.4%, 2.1%)	-13.3% (-18.9%, -7.7%)
	Any Severe AE	2.3% (-1.6%, 6.2%)	10.8% (3.9%, 17.7%)	5.8% (2%, 9.6%)	-18.9% (-26.2%, -11.7%)
	Any Ocular Severe AE	3.2% (-1.6%, 8%)	13% (7.6%, 18.5%)	4.9% (2.5%, 7.3%)	-21.2% (-27.9%, -14.4%)
	Any IOP Related AE	1.5% (-3.2%, 6.2%)	24.2% (18.9%, 29.5%)	6.6% (3.9%, 9.4%)	-32.4% (-38.8%, -25.9%)
	≥10 mm Hg IOP Change from Baseline at any visit	3.8% (-1.1%, 8.7%)	19.6% (14.7%, 24.5%)	4.3% (2.2%, 6.5%)	-27.7% (-34.1%, -21.4%)
	≥25 mm Hg IOP at any visit	3.2% (-1.6%, 8.1%)	22.8% (17.7%, 27.9%)	4.9% (2.6%, 7.2%)	-30.9% (-37.4%, -24.5%)
	≥35 mm Hg IOP at any visit	7.3% (2.1%, 12.4%)	4.9% (2.3%, 7.5%)	0.9% (-0.1%, 1.8%)	-13% (-18.7%, -7.4%)
BCVA improvement of ≥10 letters	Cataract Surgery in Phakic Subjects	-3.1% (-7.7%, 1.5%)	41.7% (35%, 48.4%)	10.2% (6.2%, 14.3%)	-48.8% (-56.2%, -41.4%)
	Any AE	-0.3% (-2%, 1.4%)	3.2% (-3.9%, 10.4%)	12.5% (6.1%, 18.9%)	-15.5% (-19.9%, -11%)
	Any Ocular AE	-2.3% (-5.9%, 1.3%)	12.9% (5.6%, 20.3%)	14.5% (8.6%, 20.4%)	-25.2% (-31%, -19.3%)
	Any Ocular Serious AE	5% (-0.7%, 10.6%)	2.4% (-3.4%, 8.3%)	7.2% (3%, 11.5%)	-14.6% (-22%, -7.3%)
	Any Ocular Serious AE	11.4% (4.9%, 17.8%)	5.2% (2.6%, 7.8%)	0.9% (-0.4%, 2.1%)	-17.4% (-24.1%, -10.7%)
	Any Severe AE	2.7% (-2.8%, 8.1%)	7.1% (0.4%, 13.7%)	9.5% (5%, 14.1%)	-19.3% (-26.5%, -12%)
	Any Ocular Severe AE	5.3% (-0.9%, 11.5%)	11% (5.8%, 16.2%)	6.9% (3.8%, 10%)	-23.2% (-30.3%, -16.1%)
	Any IOP Related AE	1.6% (-4.4%, 7.5%)	20.2% (15.3%, 25.1%)	10.7% (7%, 14.3%)	-32.4% (-39.3%, -25.5%)
	≥10 mm Hg IOP Change from Baseline at any visit	4.2% (-2%, 10.3%)	15.9% (11.4%, 20.4%)	8.1% (5%, 11.1%)	-28.1% (-35%, -21.2%)
	≥25 mm Hg IOP at any visit	3% (-3.1%, 9.1%)	18.5% (13.7%, 23.3%)	9.2% (6%, 12.5%)	-30.7% (-37.6%, -23.8%)
	≥35 mm Hg IOP at any visit	9.9% (3.5%, 16.4%)	3.5% (1.1%, 5.8%)	2.3% (0.7%, 3.9%)	-15.7% (-22.4%, -9%)
	Cataract Surgery in Phakic Subjects	-9.3% (-15.4%, -3.3%)	33.3% (26.8%, 39.8%)	18.6% (13.4%, 23.8%)	-42.6% (-50.4%, -34.8%)

BCVA improvement of ≥ 1 letters	Any AE	-6.3% (-9.5%, -3%)	-2.9% (-10.2%, 4.4%)	18.7% (11.4%, 25.9%)	-9.4% (-13.1%, -5.8%)
	Any Ocular AE	-11.7% (-16.9%, -6.5%)	3.4% (-3.7%, 10.4%)	24.1% (17.1%, 31%)	-15.7% (-20.7%, -10.8%)
	Any Ocular Serious AE	4.2% (-2.9%, 11.3%)	1.5% (-3.3%, 6.3%)	8.1% (2.6%, 13.6%)	-13.9% (-21%, -6.8%)
	Any Ocular Serious AE	10.1% (2.7%, 17.4%)	3.7% (1.6%, 5.9%)	2.3% (0.4%, 4.2%)	-16.1% (-23.4%, -8.8%)
	Any Severe AE	-0.1% (-7%, 6.8%)	4.1% (-1.7%, 9.9%)	12.5% (6.6%, 18.4%)	-16.5% (-23.2%, -9.8%)
	Any Ocular Severe AE	1.1% (-6.2%, 8.4%)	6.7% (2.2%, 11.1%)	11.3% (7%, 15.5%)	-19% (-26.1%, -12%)
	Any IOP Related AE	-7% (-14.2%, 0.3%)	11.5% (7.6%, 15.4%)	19.3% (14.6%, 24.1%)	-23.9% (-31%, -16.8%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	-2.3% (-9.7%, 5%)	9.2% (5.6%, 12.9%)	14.7% (10.6%, 18.8%)	-21.6% (-28.7%, -14.5%)
	≥ 25 mm Hg IOP at any visit	-5.2% (-12.5%, 2.1%)	10.1% (6.4%, 13.8%)	17.6% (13.1%, 22.1%)	-22.5% (-29.6%, -15.3%)
	≥ 35 mm Hg IOP at any visit	8% (0.6%, 15.4%)	1.4% (0%, 2.9%)	4.3% (1.9%, 6.7%)	-13.8% (-21.2%, -6.5%)
	Cataract Surgery in Phakic Subjects	-22.7% (-30.4%, -14.9%)	18.5% (12.8%, 24.2%)	33.4% (27.3%, 39.6%)	-29.2% (-37.2%, -21.3%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

Table 32: Summary of Risk-Benefit Analysis for Psuedophakic subjects

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 700 N=85	Sham N=100	DEX 700 N=85	Sham N=100	DEX 700 N=85	Sham N=100	DEX 700 N=85	Sham N=100
BCVA improvement of ≥ 15 letters	Any AE	0 (0.0%)	0 (0.0%)	62(72.9%)	75(75.0%)	19(22.4%)	11(11.0%)	4(4.7%)	14(14.0%)
	Any Ocular AE	4(4.7%)	3(3.0%)	48(56.5%)	53(53.0%)	15(17.6%)	8(8.0%)	18(21.2%)	36(36.0%)
	Any Serious AE	8(9.4%)	6(6.0%)	20(23.5%)	31(31.0%)	11(12.9%)	5(5.0%)	46(54.1%)	58(58.0%)
	Any Ocular Serious AE	19(22.4%)	11(11.0%)	2(2.4%)	0(0.0%)	0 (0.0%)	0 (0.0%)	64(75.3%)	89(89.0%)
	Any Severe AE	7(8.2%)	6(6.0%)	26(30.6%)	33(33.0%)	12(14.1%)	5(5.0%)	40(47.1%)	56(56.0%)
	Any Severe Ocular AE	16(18.8%)	11(11.0%)	8(9.4%)	8(8.0%)	3(3.5%)	0(0.0%)	58(68.2%)	81(81.0%)
	Any IOP Related AE	15(17.6%)	10(10.0%)	21(24.7%)	8(8.0%)	4(4.7%)	1(1.0%)	45(52.9%)	81(81.0%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	16(18.8%)	11(11.0%)	17(20.0%)	2(2.0%)	3(3.5%)	0(0.0%)	49(57.6%)	87(87.0%)
	≥ 25 mm Hg IOP at any visit	16(18.8%)	11(11.0%)	18(21.2%)	6(6.0%)	3(3.5%)	0(0.0%)	48(56.5%)	83(83.0%)
	≥ 35 mm Hg IOP at any visit	18(21.2%)	11(11.0%)	5(5.9%)	1(1.0%)	1(1.2%)	0(0.0%)	61(71.8%)	88(88.0%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures.

Table 33: Summary of Population level Risk-Benefit Measures (Safety Population)

Benefit	Risk	Estimates (95% CI)			
		NNT	NNTadj	NNH	BRR
BCVA improvement of ≥15 letters	Any AE	12.3 (7.5, 34.4)	14.6 (9.4, 38.7)	6.4(4.9, 9.0)	0.52
	Any Ocular AE	12.3 (7.5, 34.4)	16.9 (11.3, 43.6)	3.6 (3.0, 4.8)	0.30
	Any Serious AE	12.3 (7.5, 34.4)	13.6 (8.9, 35.5)	10.4 (6.1, 33.5)	0.84
	Any Ocular Serious AE	12.3 (7.5, 34.4)	13.1 (8.2, 35.5)	16.5 (11.2, 31.1)	1.34
	Any Severe AE	12.3 (7.5, 34.4)	14.7 (9.8, 38)	6 (4.2, 10.6)	0.49
	Any Ocular Severe AE	12.3 (7.5, 34.4)	15 (9.8, 39.2)	5.6 (4.2, 8.2)	0.45
	Any IOP Related AE	12.3 (7.5, 34.4)	17.8 (11.8, 46.1)	3.2 (2.7, 4)	0.26
	≥10 mm Hg IOP Change from Baseline at any visit	12.3 (7.5, 34.4)	16.2 (10.6, 42.4)	4.2 (3.4, 5.3)	0.34
	≥25 mm Hg IOP at any visit	12.3 (7.5, 34.4)	17 (11.2, 44.3)	3.6 (3.0, 4.5)	0.29
	≥35 mm Hg IOP at any visit	12.3 (7.5, 34.4)	13.1 (8.2, 35.5)	17.3 (11.7, 33.6)	1.41
	Cataract Surgery in Phakic Subjects	14.1 (7.6, 87.4)	29.2 (18.5, 159.3)	1.9 (1.7, 2.2)	0.14
BCVA improvement of ≥10 letters	Any AE	8.2 (5.3, 17.5)	9.7 (6.7, 19.7)	6.4 (4.9, 9.0)	0.78
	Any Ocular AE	8.2 (5.3, 17.5)	11.3 (8.1, 22.2)	3.6 (3.0, 4.8)	0.45
	Any Ocular Serious AE	8.2 (5.3, 17.5)	9.1 (6.4, 18.1)	10.4 (6.1, 33.5)	1.27
	Any Ocular Serious AE	8.2 (5.3, 17.5)	8.7 (5.9, 18.1)	16.5 (11.2, 31.1)	2.02
	Any Severe AE	8.2 (5.3, 17.5)	9.8 (7, 19.4)	6 (4.2, 10.6)	0.74
	Any Ocular Severe AE	8.2 (5.3, 17.5)	10 (7, 20)	5.6 (4.2, 8.2)	0.68
	Any IOP Related AE	8.2 (5.3, 17.5)	11.8 (8.4, 23.5)	3.2 (2.7, 4.0)	0.4
	≥10 mm Hg IOP Change from Baseline at any visit	8.2 (5.3, 17.5)	10.8 (7.5, 21.6)	4.2 (3.4, 5.3)	0.51
	≥25 mm Hg IOP at any visit	8.2 (5.3, 17.5)	11.3 (8, 22.6)	3.6 (3.0, 4.5)	0.44
	≥35 mm Hg IOP at any visit	8.2 (5.3, 17.5)	8.7 (5.8, 18.1)	17.3 (11.7, 33.6)	2.12
	Cataract Surgery in Phakic Subjects	10.8 (6, 56.8)	22.4 (14.4, 103.5)	1.9 (1.7, 2.2)	0.18
BCVA improvement of ≥1 letters	Any AE	8.1 (5.1, 20)	9.6 (6.4, 22.5)	6.4 (4.9, 9.0)	0.79
	Any Ocular AE	8.1 (5.1, 20)	11.1 (7.7, 25.3)	3.6 (3.0, 4.8)	0.45
	Any Ocular Serious AE	8.1 (5.1, 20)	8.9 (6.1, 20.6)	10.4 (6.1, 33.5)	1.28
	Any Ocular Serious AE	8.1 (5.1, 20)	8.6 (5.6, 20.7)	16.5 (11.2, 31.1)	2.04
	Any Severe AE	8.1 (5.1, 20)	9.7 (6.6, 22.1)	6 (4.2, 10.6)	0.74
	Any Ocular Severe AE	8.1 (5.1, 20)	9.9 (6.6, 22.8)	5.6 (4.2, 8.2)	0.69
	Any IOP Related AE	8.1 (5.1, 20)	11.7 (8, 26.8)	3.2 (2.7, 4.0)	0.4
	≥10 mm Hg IOP Change from Baseline at any visit	8.1 (5.1, 20)	10.6 (7.1, 24.6)	4.2 (3.4, 5.3)	0.52
	≥25 mm Hg IOP at any visit	8.1 (5.1, 20)	11.2 (7.6, 25.8)	3.6 (3, 4.5)	0.45
	≥35 mm Hg IOP at any visit	8.1 (5.1, 20)	8.6 (5.5, 20.6)	17.3 (11.7, 33.6)	2.14
	Cataract Surgery in Phakic Subjects	9.3 (5.2, 46.7)	19.3 (12.5, 85.1)	1.9 (1.7, 2.2)	0.21

Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. Let $P_{DEX\ 700}$ and P_{SHAM} be proportion of success and Q_{DEX} and Q_{SHAM} be proportion of subjects with adverse event in the DEX 700 and Sham arms respectively. BRR: Benefit-Risk Ratio= $(P_{DEX\ 700} - P_{SHAM}) / (Q_{DEX\ 700} - Q_{SHAM})$. NNT= $1 / (P_{DEX\ 700} - P_{SHAM})$: Number Need to be treated to observe one success. NTTadj= $1 / ((P_{DEX\ 700} - P_{SHAM}) * (1 - (Q_{DEX\ 700} - Q_{SHAM})))$: Number Need to be treated to observe one success without adverse event. NNH= $1 / (Q_{DEX\ 700} - Q_{SHAM})$: Number Needed Harm.

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

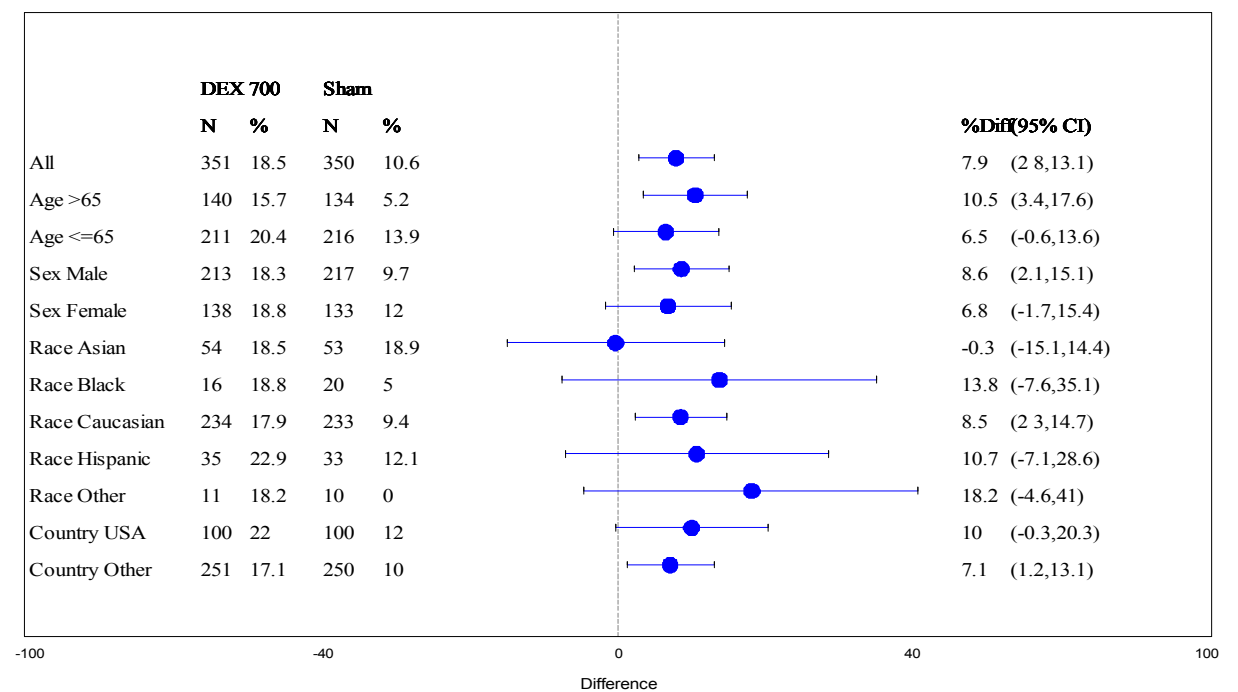
The summary results for the comparison of the DEX arms and Sham with respect to the primary efficacy endpoint of the proportion of subjects with a 15 letter or more gain from baseline at 3 years and the secondary efficacy endpoint of the mean change from baseline BCVA for

subgroup of subjects formed based on baseline demographics and disease characteristics are summarized below. These subgroup analyses are based on the pooled data from the two Phase 3 studies. The subgroup analysis results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Unless stated otherwise, all analyses are performed on the ITT population with LOCF used to impute missing data.

5.1 Age Gender Race and Country

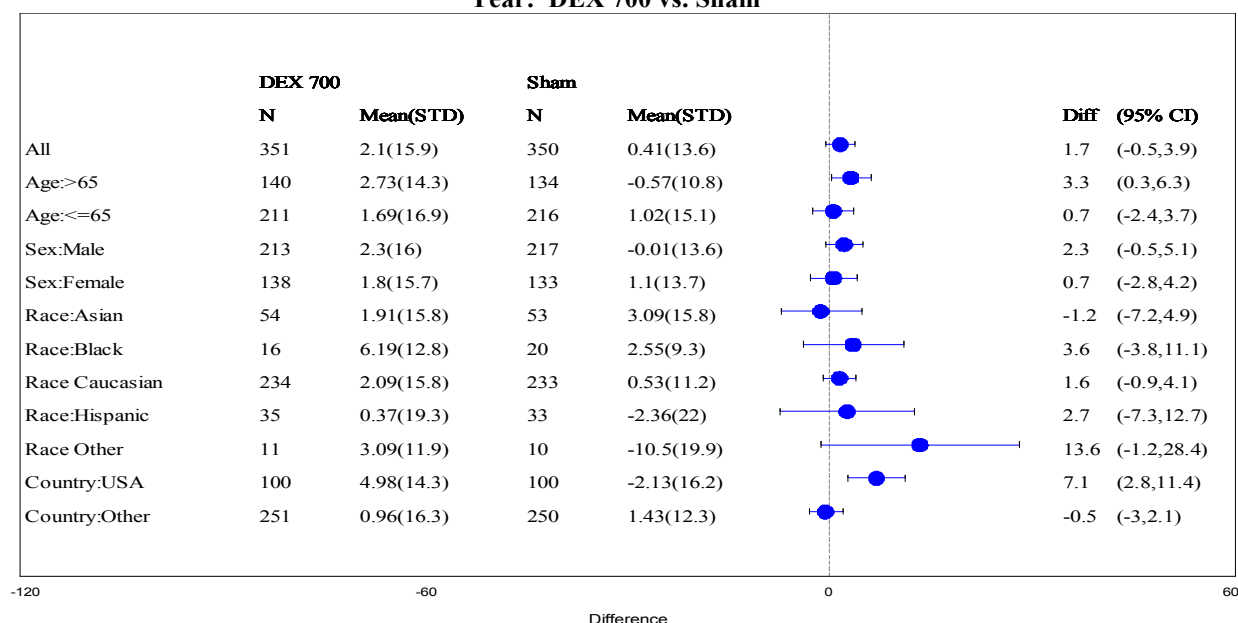
Overall, the subgroup analysis results based on baseline demographics were consistent with the primary efficacy analysis results. Although the observed treatment effects appear to be better in some subgroups (for example US subjects, subjects older than 65 years), conclusive statements regarding statistical significance could not be made on the magnitude of the treatment effect for any subgroup, as the studies were not designed to test the treatment effect for any subgroup (Figure 5- Figure 8).

Figure 5: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 700 vs. Sham



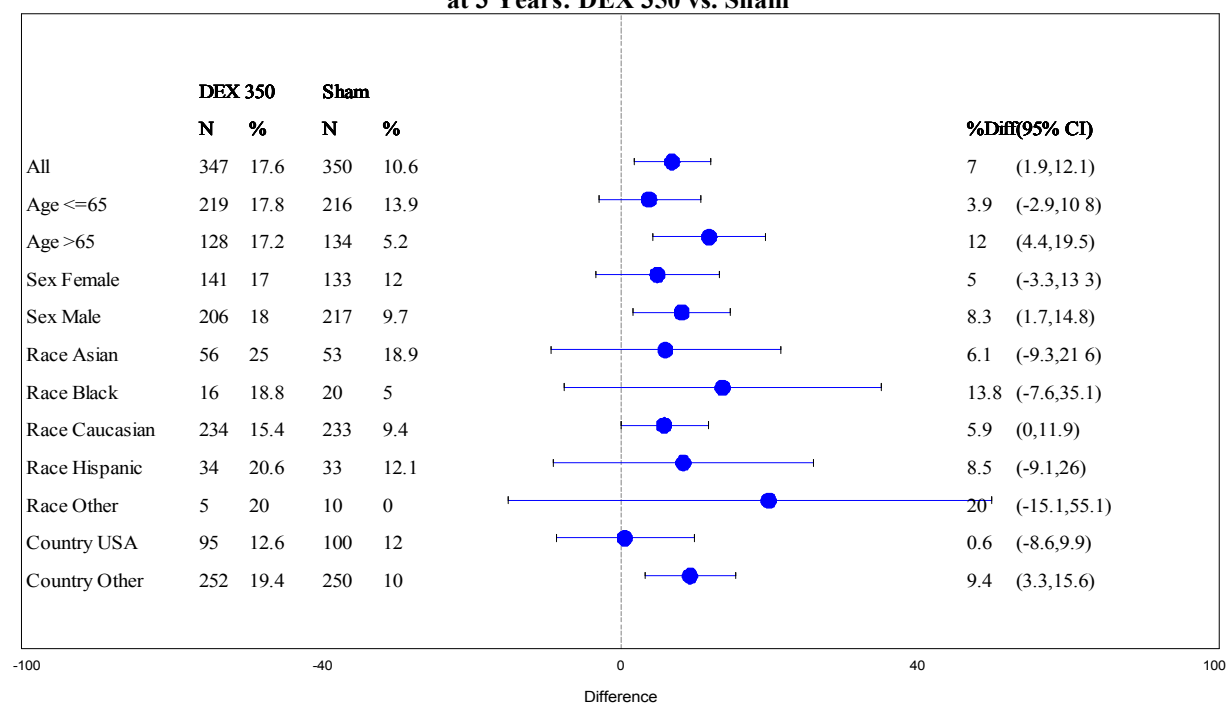
Source: Reviewer’s Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at 3 years in the subgroup.

Figure 6: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at 3 Year: DEX 700 vs. Sham



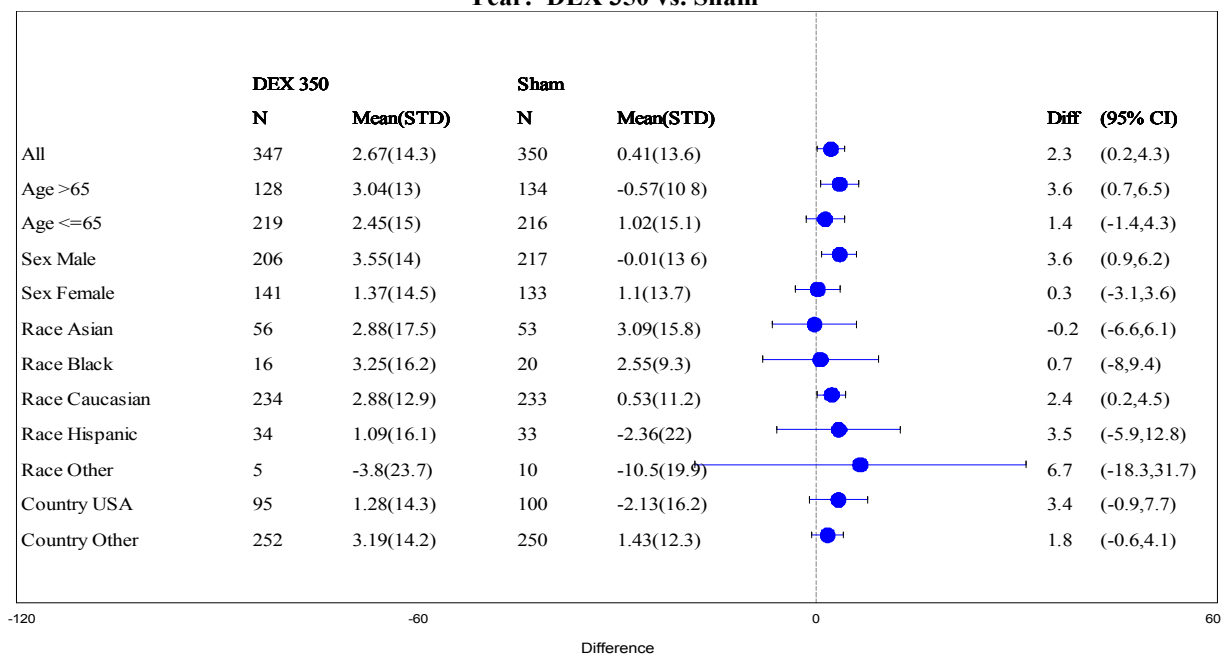
Source: Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at 3 years in the subgroup.

Figure 7: Subgroup Analysis for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 350 vs. Sham



Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at 3 Years in the subgroup.

Figure 8: Subgroup Analysis by Baseline Demographics for the Mean Change from Baseline BCVA at 3 Year: DEX 350 vs. Sham



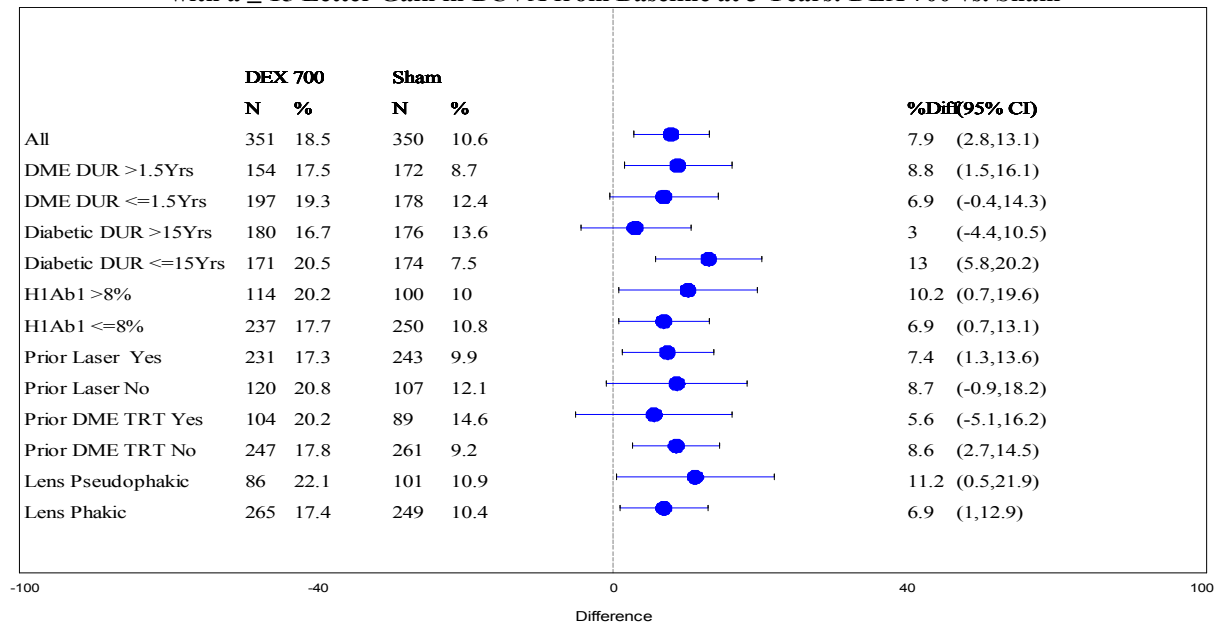
Source: Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at 3 years in the subgroup.

5.2 Other Special/Subgroup Populations

Additional subgroup analyses for subgroups formed based on duration of diabetes (≤ 15 years versus > 15 years), duration of DME (≤ 1.5 years versus > 1.5 years), baseline HbA1c ($\leq 8\%$ versus $> 8\%$), prior laser treatment (yes versus no), any prior treatment (yes versus no) and lens status at baseline (phakic study eye versus pseudophakic study eye) are summarized below.

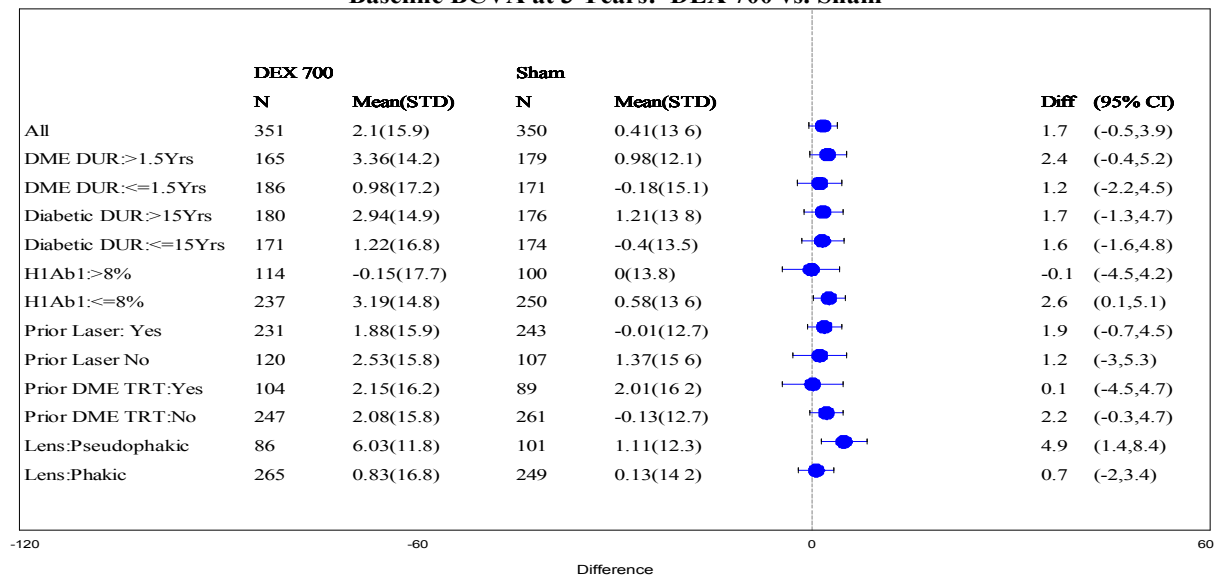
Here also, the subgroup analysis results were consistent with the primary efficacy analysis results. Observed treatment effects appear to be better in the subgroup of subjects with lower diabetic duration, subjects with higher H1Ab1 level and baseline pseudophakic subjects. Note that the DME duration was calculated as a difference between dates of DME onset and randomization divided by 30 and rounded to the nearest integer. If both date and month were missing, June 30 was imputed; and if only date was missing 15 was imputed.

Figure 9: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 700 vs. Sham



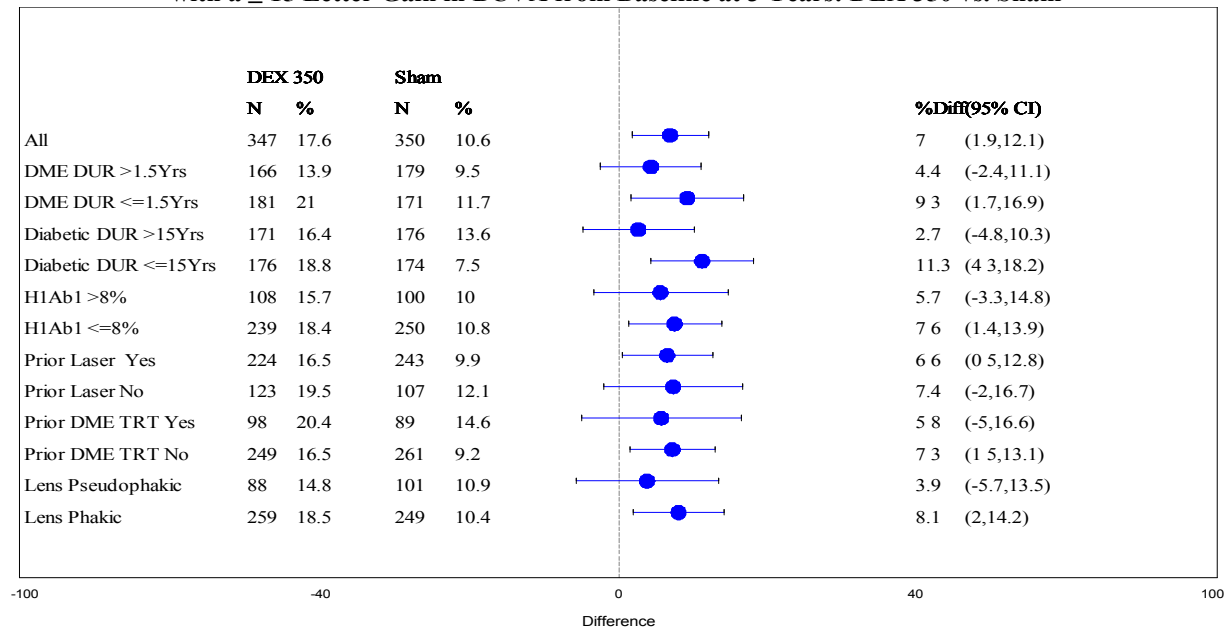
Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at 3 Years in the subgroup. Source:

Figure 10: Additional Subgroup Analysis by Baseline Disease Characteristics for Mean Change from Baseline BCVA at 3 Years: DEX 700 vs. Sham



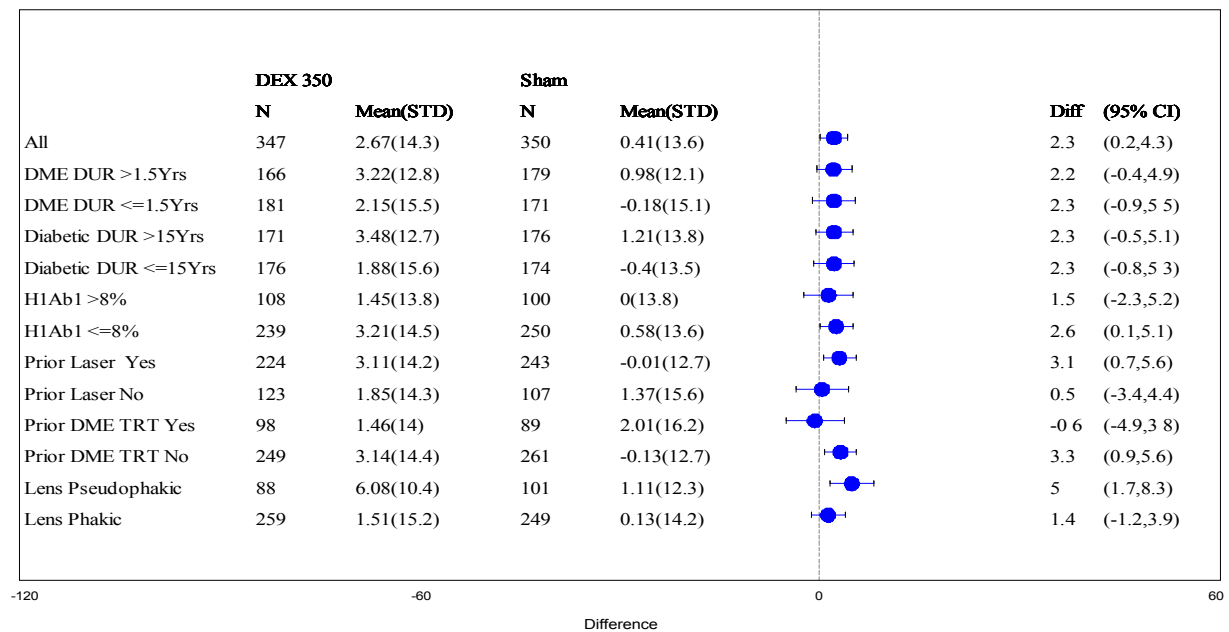
Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at 3 years in the subgroup.

Figure 11: Additional Subgroup Analysis by Baseline Disease Characteristics for the Proportion of Subjects with a ≥ 15 Letter Gain in BCVA from Baseline at 3 Years: DEX 350 vs. Sham



Source: Reviewer's Analysis. LOCF was used to impute missing values. Subjects who required escape therapy were set as treatment failures. N=number of subjects in the subgroup. %: percentage of subjects with 15 or more letters improvement from baseline at 3 Years in the subgroup.

Figure 12: Additional Subgroup Analysis by Baseline Disease Characteristics for Mean Change from Baseline BCVA at 3 Years: DEX 350 vs. Sham



Reviewer's Analysis. LOCF was used to impute missing values. N=number of subjects in the subgroup. Mean (STD): Mean and Standard deviation of BCVA change from baseline at 3 years in the subgroup.

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues

The first major statistical issue encountered in this review was related to the definition of the primary efficacy endpoint. Amendment 4 of the study protocol (08 May 2010) allowed a possible re-treatment at Month 36 visit and included an additional visit at a Month 39 to provide assessment of efficacy and safety for subjects who received a re-treatment at Month 36 visit. Consequentially, the applicant re-defined the primary efficacy endpoint as the proportion of subjects who had a 15 letter or more gain in BCVA from baseline at final study visit (Month 39 or earlier) to accommodate efficacy measures from the additional re-treatment. However, only 173 (16.5%) of the 1048 randomized subjects had completed the Month 39 visit, and only 161(15.3%) of the randomized subjects had a BCVA measurement at the Month 39 visit. Additionally, FDA recommended the primary endpoint to be evaluated at Month 36 at the End-of-Phase 2 meeting in September 2003 as well as in a Type C meeting in September 2011. This review therefore used the proportion of subjects with a 15 letter or more gain at Month 36 as the primary efficacy endpoint.

Substantially large proportion of subjects had missing BCVA measurement at 3 Years. The main reasons for missing data were treatment related (Adverse event in the case of the DEX 700 arm and lack of efficacy for the Sham arm). As discussed earlier, the LOCF was used for the primary efficacy analysis. This method however assumes that the outcomes of subjects do not change after they have dropped out and ignores the uncertainty of imputed values. Additionally, although Section 5.5.2 of the study protocol specified that subjects who received escape medication would be treated as treatment failures, in the applicant's primary efficacy analysis, the measurements taken after escape therapy were set as missing and were imputed using the LOCF method. This has resulted in some subjects who required escape therapy being treated as treatment successes. Note however that, the difference between the applicant's analysis and the reviewer's analysis which treated all subjects who received a rescue therapy as failures was negligible. Additionally, for this particular NDA, the results of the multiple imputations method which takes the uncertainty of the imputed values into consideration and has slightly less restrictive assumptions were consistent with the primary analysis results. Thus the overall study conclusion regarding the primary efficacy endpoint does not seem to have been significantly impacted by the method used to handle missing data.

6.2 Collective Evidence

The primary objective of the studies considered as part of this NDA submission was met. There were more subjects in the DEX 700 arm who gained at least 15 letters in BCVA from baseline at 3 years compared to subjects in the Sham arm. There was a statistically non-significant difference of about 2 letters in the mean change from baseline BCVA between DEX 700 and Sham. For DEX 700 arm, the treatment effect was consistent in the majority of the subgroups formed based on baseline characteristics. The DEX 700 arm also had a significantly positive

outcome with respect to the majority of the secondary efficacy endpoints compared to the Sham arm.

The two studies highlighted the safety issues associated with the study treatments. Two of the prominent adverse events associated with the study treatment were cataract formation and IOP related adverse events. The IOP-related adverse events included elevated IOP, ocular hypertension and glaucoma. A substantially large proportion of subjects in the two study treatments had IOP-related adverse events and required cataract surgery compared to the subjects randomized to the Sham arm. There were also more deaths in the two DEX arms compared to the Sham arm, although the applicant reported the deaths as not related to study treatment. The risk-benefit analysis showed that the DEX 700 arm had a less than favorable safety profile. For example, compared to the baseline Phakic subjects in the Sham arm, 41.7% more baseline Phakic subjects in the DEX 700 arm underwent cataract surgery but have not achieved a 15 letter improvement in BCVA from baseline at 3 years, and 24.2% more subjects in this arm had a less than 15 letters improvement but reported at least one an IOP related AE.

6.3 Conclusions and Recommendations

The DEX arms had significantly higher proportion of subjects with a 15 letter or more improvement in BCVA from baseline at 3 years compared to subjects in the Sham arm. However, the difference in the mean change in BCVA from baseline at 3 years was small (approximately 2 letters) and not statistically significant. A substantially higher proportion of subjects in the two DEX arms reported adverse events compared to subjects in the Sham arm. As a result, the net benefit, a BCVA improvement adjusted for risk of adverse event was either negative or close to zero. In conclusion, there is a statistical evidence of efficacy in favor of the two DEX arms, however the substantially higher number of adverse events reported in the two DEX arms cast doubt on the safe use of these treatments. Although the review's risk-benefit analyses suggested that the observed benefit might not outweigh the risk, the final evaluation of the risk-benefit outlook and the subsequent recommendation for approval of this product will have to be done in consultation with the clinical and other review teams.

6.4 Labeling Recommendations

There were five protocol amendments for the two phase 3 studies used in this review. Specifically, in Amendment 4, the primary analysis was changed from Month 24 to Month 36. Additionally, as per the same amendment, patients were allowed to receive a study treatment at Month 36 as needed by retreatment criteria, and a Month 39 visit was added to provide an assessment of efficacy and safety from any month 36 retreatment. Consequently, the applicant defined the primary efficacy endpoint as the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at the patient's final assessment. The final assessment corresponds to Month 39 for those subjects who were retreated at Month 36 and had a Month 39 visit. For the rest, the final measurement would either be Month 36 or an earlier time if they discontinued the study prematurely. According to our review, only 173(16.5%) of the 1048 randomized patients completed the 39-month visit. Consequently, in the applicant's

primary efficacy analysis on the final visit (labeled as 36Month/39Month), the majority of patients (83.5%) did not have BCVA measurements at the 39-month visit. Therefore the reviewer recommends the “Clinical Studies” section related to DME of the final labeling use the results of the primary efficacy endpoint evaluated at Month 36 and be presented as follows.

(b) (4)



7 Appendix

Table 34: Proportion of subjects with ≥ 15 letters gain from baseline (ITT LOCF)

Visit	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Month 1.5	20(12.3%)	18(10.8%)	6(3.6%)	8.6% (2.8%, 14.4%)	7.2% (1.7%, 12.7%)
Month 3	23(14.1%)	23(13.9%)	10(6.1%)	8% (1.6%, 14.5%)	7.8% (1.4%, 14.2%)
Month 4.5	25(15.3%)	21(12.7%)	11(6.7%)	8.7% (2%, 15.4%)	6% (-0.3%, 12.3%)
Month 6	23(14.1%)	17(10.2%)	12(7.3%)	6.8% (0.2%, 13.5%)	3% (-3.1%, 9%)
Month 7.5	26(16%)	26(15.7%)	11(6.7%)	9.3% (2.5%, 16.1%)	9% (2.3%, 15.7%)
Month 9	31(19%)	30(18.1%)	12(7.3%)	11.7% (4.5%, 19%)	10.8% (3.7%, 17.9%)
Month 10.5	26(16%)	29(17.5%)	11(6.7%)	9.3% (2.5%, 16.1%)	10.8% (3.9%, 17.7%)
Month 12	22(13.5%)	25(15.1%)	13(7.9%)	5.6% (-1%, 12.3%)	7.2% (0.4%, 14%)
Month 15	24(14.7%)	27(16.3%)	10(6.1%)	8.7% (2.1%, 15.2%)	10.2% (3.5%, 16.9%)
Month 18	26(16%)	16(9.6%)	15(9.1%)	6.9% (-0.3%, 14%)	0.5% (-5.7%, 6.8%)
Month 21	25(15.3%)	25(15.1%)	12(7.3%)	8.1% (1.3%, 14.9%)	7.8% (1.1%, 14.5%)
Month 24	21(12.9%)	25(15.1%)	15(9.1%)	3.8% (-3%, 10.6%)	6% (-1%, 13%)
Month 27	31(19%)	32(19.3%)	18(10.9%)	8.1% (0.4%, 15.8%)	8.4% (0.7%, 16%)
Month 30	25(15.3%)	33(19.9%)	16(9.7%)	5.6% (-1.5%, 12.8%)	10.2% (2.6%, 17.7%)
Month 33	34(20.9%)	29(17.5%)	16(9.7%)	11.2% (3.5%, 18.9%)	7.8% (0.4%, 15.1%)
Month 36	32(19.6%)	33(19.9%)	18(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
Month 39	34(20.9%)	31(18.7%)	19(11.5%)	9.3% (1.4%, 17.3%)	7.2%(-0.5%, 14.8%)
Study 206207-011					
Month 1.5	21(11.2%)	23(12.7%)	3(1.6%)	9.5% (4.7%, 14.4%)	11.1% (5.9%, 16.3%)
Month 3	22(11.7%)	26(14.4%)	5(2.7%)	9% (3.8%, 14.2%)	11.7% (6%, 17.3%)
Month 4.5	22(11.7%)	23(12.7%)	7(3.8%)	7.9% (2.6%, 13.3%)	8.9% (3.3%, 14.5%)
Month 6	16(8.5%)	11(6.1%)	6(3.2%)	5.3% (0.5%, 10%)	2.8% (-1.5%, 7.2%)
Month 7.5	27(14.4%)	24(13.3%)	14(7.6%)	6.8% (0.5%, 13.1%)	5.7%(-0.5%, 11.9%)
Month 9	29(15.4%)	25(13.8%)	12(6.5%)	8.9% (2.7%, 15.2%)	7.3% (1.2%, 13.5%)
Month 10.5	26(13.8%)	25(13.8%)	15(8.1%)	5.7% (-0.6%, 12%)	5.7% (-0.7%, 12.1%)
Month 12	23(12.2%)	17(9.4%)	17(9.2%)	3%(-3.2%, 9.3%)	0.2% (-5.7%, 6.2%)
Month 15	22(11.7%)	25(13.8%)	17(9.2%)	2.5% (-3.7%, 8.7%)	4.6% (-1.9%, 11.1%)
Month 18	21(11.2%)	18(9.9%)	16(8.6%)	2.5% (-3.5%, 8.6%)	1.3% (-4.7%, 7.2%)
Month 21	26(13.8%)	15(8.3%)	18(9.7%)	4.1%(-2.4%, 10.6%)	-1.4%(-7.3%, 4.4%)
Month 24	31(16.5%)	15(8.3%)	18(9.7%)	6.8%(-0.1%, 13.6%)	-1.4%(-7.3%, 4.4%)
Month 27	28(14.9%)	20(11%)	18(9.7%)	5.2%(-1.5%, 11.8%)	1.3%(-4.9%, 7.6%)
Month 30	31(16.5%)	20(11%)	18(9.7%)	6.8%(-0.1%, 13.6%)	1.3%(-4.9%, 7.6%)

Month 33	31(16.5%)	24(13.3%)	17(9.2%)	7.3% (0.6%, 14%)	4.1%(-2.4%, 10.5%)
Month 36	33(17.6%)	28(15.5%)	19(10.3%)	7.3% (0.3%, 14.3%)	5.2%(-1.6%, 12%)
Month 39	38(20.2%)	31(17.1%)	19(10.3%)	9.9% (2.7%, 17.2%)	6.9%(-0.2%, 13.9%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy on or prior to a given visit were set as treatment failures.

Table 35: Proportion of subjects with ≥15 letters gain from baseline (Complete Cases)

	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Month 1.5	20/156(12.8%)	18/160(11.3%)	6/155(3.9%)	8.9% (2.9%, 15%)	7.4% (1.6%,13.1%)
Month 3	23/156(14.7%)	23/161(14.3%)	10/147(6.8%)	7.9% (1%, 14.8%)	7.5% (0.7%, 14.2%)
Month 4.5	24/151(15.9%)	21/154(13.6%)	11/139(7.9%)	8% (0.6%, 15.3%)	5.7% (-1.3%, 12.8%)
Month 6	21/143(14.7%)	16/154(10.4%)	12/126(9.5%)	5.2%(-2.6%, 12.9%)	0.9% (-6.2%,7.9%)
Month 7.5	21/137(15.3%)	25/145(17.2%)	8/111(7.2%)	8.1% (0.4%, 15.8%)	10%(2.2%,17.8%)
Month 9	29/138(21%)	30/152(19.7%)	10/102(9.8%)	11.2% (2.3%, 20.1%)	9.9%(1.4%,18.5%)
Month 10.5	21/133(15.8%)	27/139(19.4%)	9/102(8.8%)	7% (-1.3%, 15.3%)	10.6%(2%,19.2%)
Month 12	19/137(13.9%)	25/151(16.6%)	11/103(10.7%)	3.2%(-5.1%, 11.5%)	5.9%(-2.5%,14.3%)
Month 15	22/129(17.1%)	27/141(19.1%)	8/90(8.9%)	8.2% (-0.6%,16.9%)	10.3%(1.5%,19%)
Month 18	24/124(19.4%)	16/136(11.8%)	11/81(13.6%)	5.8%(-4.4%,16%)	-1.8%(-11%,7.4%)
Month 21	20/114(17.5%)	25/133(18.8%)	10/79(12.7%)	4.9%(-5.2%,15%)	6.1%(-3.8%,16%)
Month 24	16/116(13.8%)	24/125(19.2%)	11/75(14.7%)	-0.9%(-11%,9.3%)	4.5%(-6%,15.1%)
Month 27	24/107(22.4%)	30/122(24.6%)	14/69(20.3%)	2.1%(-10.2%,14.5%)	4.3%(-7.9%,16.5%)
Month 30	17/102(16.7%)	28/110(25.5%)	12/65(18.5%)	-1.8%(-13.7%,10.1%)	7%(-5.5%,19.5%)
Month 33	27/102(26.5%)	27/112(24.1%)	10/61(16.4%)	10.1%(-2.6%,22.7%)	7.7%(-4.5%,19.9%)
Month 36	25/104(24%)	29/107(27.1%)	13/63(20.6%)	3.4%(-9.5%,16.3%)	6.5%(-6.6%,19.5%)
Month 39	6/30(20%)	8/38(21.1%)	4/18(22.2%)	-2.2%(-26.2%,21.7%)	-1.2%(-24.3%,22%)
Study 206207-011					
Month 1.5	21/183(11.5%)	23/176(13.1%)	3/172(1.7%)	9.7%(4.7%,14.7%)	11.3%(6%,16.7%)
Month 3	22/182(12.1%)	26/173(15%)	5/175(2.9%)	9.2%(3.9%,14.6%)	12.2%(6.3%,18%)
Month 4.5	19/175(10.9%)	22/166(13.3%)	7/159(4.4%)	6.5%(0.8%,12.1%)	8.9%(2.8%,14.9%)
Month 6	15/170(8.8%)	11/164(6.7%)	6/148(4.1%)	4.8%(-0.5%,10.1%)	2.7%(-2.3%,7.6%)
Month 7.5	26/164(15.9%)	23/152(15.1%)	14/130(10.8%)	5.1%(-2.6%,12.8%)	4.4%(-3.4%,12.2%)
Month 9	28/157(17.8%)	23/156(14.7%)	9/126(7.1%)	10.7%(3.2%,18.2%)	7.6%(0.4%,14.8%)
Month 10.5	23/155(14.8%)	25/151(16.6%)	14/114(12.3%)	2.6%(-5.7%,10.8%)	4.3%(-4.2%,12.7%)
Month 12	22/157(14%)	17/148(11.5%)	17/113(15%)	-1%(-9.6%,7.5%)	-3.6%(-11.9%,4.8%)
Month 15	21/148(14.2%)	24/135(17.8%)	16/106(15.1%)	-0.9%(-9.7%,7.9%)	2.7%(-6.7%,12.1%)
Month 18	20/142(14.1%)	18/141(12.8%)	15/98(15.3%)	-1.2%(-10.4%,7.9%)	-2.5%(-11.5%,6.5%)
Month 21	24/132(18.2%)	15/122(12.3%)	17/86(19.8%)	-1.6%(-12.3%,9.1%)	-7.5%(-17.7%,2.8%)
Month 24	24/128(18.8%)	14/117(12%)	16/79(20.3%)	-1.5%(-12.7%,9.6%)	-8.3%(-18.9%,2.3%)
Month 27	23/120(19.2%)	19/113(16.8%)	15/73(20.5%)	-1.4%(-13%,10.3%)	-3.7%(-15.3%,7.8%)
Month 30	25/112(22.3%)	19/109(17.4%)	14/68(20.6%)	1.7%(-10.6%,14.1%)	-3.2%(-15.1%,8.8%)
Month 33	26/108(24.1%)	21/109(19.3%)	14/66(21.2%)	2.9%(-9.9%,15.6%)	-1.9%(-14.3%,10.4%)
Month 36	27/107(25.2%)	25/101(24.8%)	16/68(23.5%)	1.7%(-11.3%, 14.7%)	1.2%(-11.9%,14.4%)
Month 39	10/25(40%)	7/28(25%)	7/22(31.8%)	8.2%(-19.2%, 35.5%)	-6.8%(-32%,18.4%)

Source: Reviewer's Analysis. Subjects with Missing BCVA measurement were excluded from the analysis.

Table 36: Summary of Mean change from Baseline BCVA (ITT LOCF)

	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Month 1.5	5.9(7)	5.8(7.3)	2.8(6.5)	3.1(1.6,4.6)	3(1.5,4.5)
Month 3	5.9(7.7)	6(8.4)	2.4(8.5)	3.5(1.7,5.2)	3.5(1.7,5.3)
Month 4.5	4.5(9.8)	5.6(8.1)	2.4(8.5)	2.1(0.1,4.1)	3.2(1.4,5)
Month 6	4.6(9)	3.7(9.1)	2(9)	2.6(0.7,4.6)	1.8(-0.2,3.7)
Month 7.5	5.8(9)	6.2(9.4)	1.6(9.2)	4.2(2.2,6.1)	4.6(2.6,6.6)
Month 9	5.5(10)	6.2(9.8)	1.4(10.2)	4.1(1.9,6.3)	4.8(2.7,7)
Month 10.5	4.2(11.5)	5.2(10.1)	1.2(9.9)	2.9(0.6,5.3)	4(1.8,6.1)
Month 12	3.3(10.7)	3.7(10.4)	1.2(10.2)	2.1(-0.2,4.4)	2.5(0.3,4.8)
Month 15	4.6(10.8)	4.5(11.3)	0.8(10.5)	3.8(1.5,6.1)	3.7(1.4,6.1)
Month 18	2.3(12.4)	2.1(11.3)	1.1(10.9)	1.1(-1.4,3.7)	0.9(-1.5,3.3)
Month 21	4(11.7)	3.4(12.4)	1(10.7)	3(0.6,5.5)	2.4(-0.1,4.9)
Month 24	1.5(14.4)	2.3(14.7)	1.1(11.1)	0.5(-2.3,3.2)	1.2(-1.6,4.1)
Month 27	3.1(14.5)	2.9(14.3)	1.2(11.4)	1.9(-0.9,4.7)	1.7(-1.1,4.5)
Month 30	2.3(14.8)	2.3(15.2)	1.3(11.7)	1(-1.9,3.9)	1(-1.9,4)
Month 33	3.5(14.3)	4.2(13.4)	1(11.4)	2.5(-0.3,5.3)	3.1(0.4,5.8)
Month 36	3.7(14.1)	5.1(12.3)	1(11.6)	2.7(-0.1,5.5)	4.1(1.5,6.7)
Month 39	4.1(13.9)	5(12)	0.8(11.9)	3.3(0.5,6.1)	4.2(1.7,6.8)
Study 206207-011					
Month 1.5	6.5(7.4)	6.2(8.2)	2.2(5.4)	4.3(3,5.6)	4(2.5,5.4)
Month 3	6.5(8)	6.8(8.3)	2.4(7.1)	4.2(2.6,5.7)	4.4(2.8,6)
Month 4.5	5.2(8.4)	4.9(8.8)	1.3(9.3)	3.9(2.1,5.7)	3.6(1.7,5.4)
Month 6	3.6(8.6)	2.2(10.7)	1.1(10.2)	2.5(0.6,4.4)	1.1(-1,3.3)
Month 7.5	5.6(9.7)	4.7(11.6)	1.4(11.4)	4.3(2.1,6.5)	3.3(1,5.7)
Month 9	4.6(10.9)	4.3(10.7)	0.9(11.9)	3.7(1.3,6)	3.3(1,5.6)
Month 10.5	2.4(12)	3.8(11.4)	0.6(13.5)	1.8(-0.8,4.4)	3.2(0.6,5.7)
Month 12	1.9(12.4)	1.9(11.2)	0.7(12.9)	1.2(-1.4,3.8)	1.3(-1.2,3.7)
Month 15	2.1(12.5)	3.1(12.2)	0.5(13.1)	1.6(-1,4.2)	2.6(0,5.2)
Month 18	-1(14.7)	0.1(13.5)	-0.2(14.1)	-0.8(-3.8,2.1)	0.3(-2.6,3.1)
Month 21	-0.2(15.3)	0.8(12.9)	0.4(14.4)	-0.6(-3.7,2.4)	0.4(-2.4,3.2)
Month 24	-1.2(17.4)	-1.6(14.5)	-0.5(15.3)	-0.7(-4.1,2.6)	-1.1(-4.2,2)
Month 27	0.1(15.9)	-0.1(14.1)	-0.4(15.3)	0.5(-2.6,3.7)	0.4(-2.7,3.4)
Month 30	0.1(16.7)	-0.4(14.6)	-0.1(15.1)	0.2(-3,3.4)	-0.3(-3.3,2.7)
Month 33	1(16.4)	-0.1(15.1)	-0.3(15.1)	1.4(-1.9,4.6)	0.2(-2.9,3.3)
Month 36	0.7(17.2)	0.4(15.6)	-0.1(15.3)	0.9(-2.4,4.2)	0.6(-2.6,3.7)
Month 39	1.3(17)	1.4(15.2)	0(15.4)	1.4(-1.9,4.7)	1.4(-1.7,4.6)

Source: Reviewer's Analysis. LOCF was used for imputing missing data.

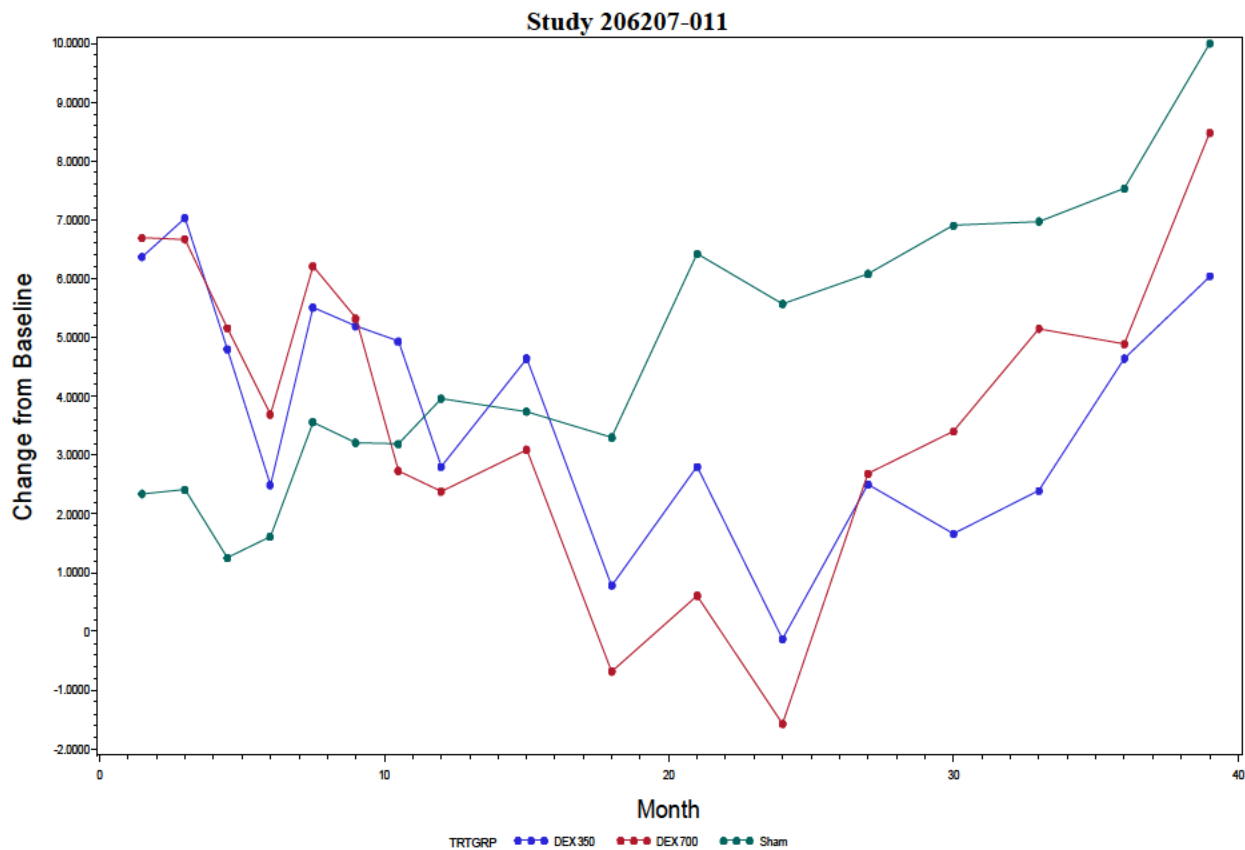
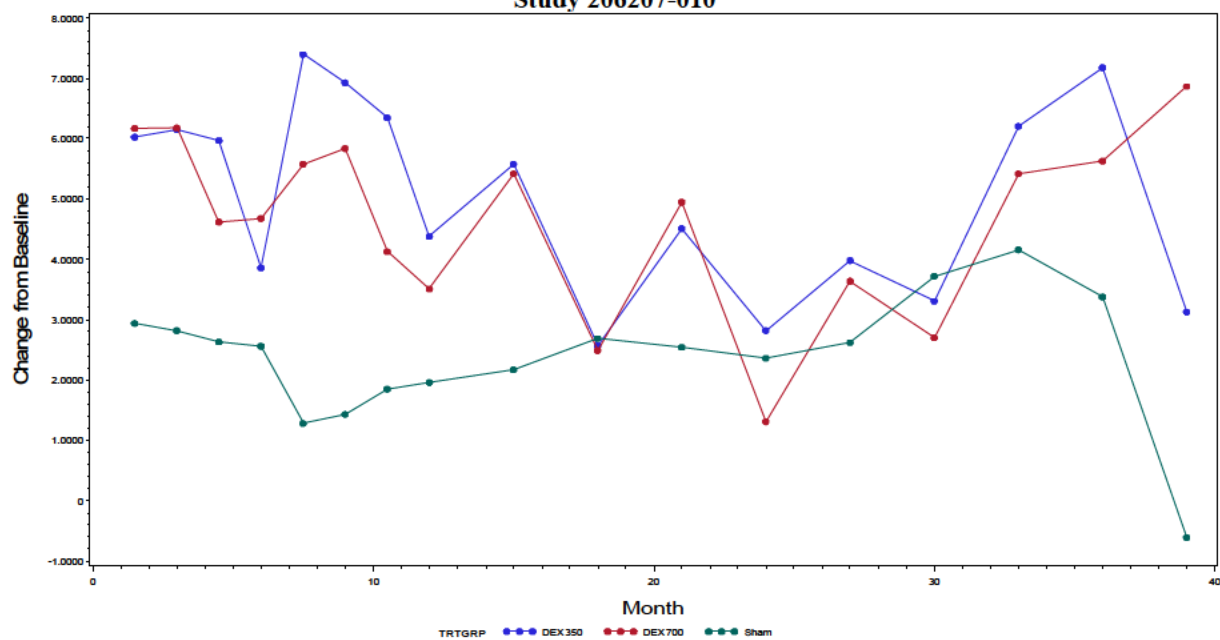
Table 37: Summary of the Mean Change from Baseline BCVA (Complete Cases)

	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010					
Month 1.5	6.2(7)	6(7.4)	2.9(6.6)	3.2(1.7,4.7)	3.1(1.5,4.6)
Month 3	6.2(7.8)	6.1(8.4)	2.8(8.6)	3.4(1.5,5.2)	3.3(1.4,5.2)
Month 4.5	4.6(10.1)	6(8.2)	2.6(8.7)	2(-0.2,4.2)	3.3(1.4,5.3)
Month 6	4.7(9.3)	3.9(9.3)	2.6(9.1)	2.1(-0.1,4.3)	1.3(-0.9,3.5)
Month 7.5	5.6(9.1)	7.4(8.4)	1.3(9)	4.3(2,6.6)	6.1(3.9,8.3)
Month 9	5.8(10.1)	6.9(9.6)	1.4(10.9)	4.4(1.7,7.1)	5.5(2.9,8.1)
Month 10.5	4.1(11.7)	6.4(9.6)	1.9(9.8)	2.3(-0.5,5)	4.5(2,7)

Month 12	3.5(10.6)	4.4(10.3)	2(10.4)	1.5(-1.2,4.2)	2.4(-0.2,5)
Month 15	5.4(10.7)	5.6(11.3)	2.2(10.4)	3.3(0.4,6.1)	3.4(0.6,6.3)
Month 18	2.5(12.7)	2.6(11.8)	2.7(10.2)	-0.2(-3.4,3)	-0.1(-3.1,2.9)
Month 21	4.9(11.6)	4.5(12.6)	2.5(10.5)	2.4(-0.8,5.6)	2(-1.2,5.1)
Month 24	1.3(15.1)	2.8(15.7)	2.4(11.1)	-1(-4.8,2.7)	0.5(-3.3,4.2)
Month 27	3.6(14.9)	4(15)	2.6(11.8)	1(-3,5)	1.4(-2.5,5.2)
Month 30	2.7(14.9)	3.3(16.5)	3.7(12.2)	-1(-5.2,3.1)	-0.4(-4.7,3.9)
Month 33	5.4(13.2)	6.2(14.1)	4.2(9.9)	1.3(-2.4,4.9)	2(-1.6,5.7)
Month 36	5.6(13.4)	7.2(12.3)	3.4(11.3)	2.2(-1.6,6.1)	3.8(0.1,7.5)
Month 39	6.9(10.8)	3.1(14.4)	-0.6(13.9)	7.5(-0.3,15.3)	3.7(-4.4,11.9)
Study 206207-011					
Month 1.5	6.7(7.4)	6.4(8.2)	2.3(5.5)	4.4(3,5.7)	4(2.6,5.5)
Month 3	6.7(8.1)	7(8.3)	2.4(7.2)	4.3(2.7,5.9)	4.6(3,6.3)
Month 4.5	5.2(7.7)	4.8(9)	1.3(9.6)	3.9(2,5.8)	3.5(1.5,5.6)
Month 6	3.7(8.7)	2.5(10.3)	1.6(10.5)	2.1(-0.1,4.2)	0.9(-1.4,3.2)
Month 7.5	6.2(9.3)	5.5(11.4)	3.6(9.3)	2.7(0.5,4.8)	1.9(-0.5,4.4)
Month 9	5.3(10.5)	5.2(10.2)	3.2(9.1)	2.1(-0.2,4.4)	2(-0.3,4.2)
Month 10.5	2.7(11.7)	4.9(10.6)	3.2(12.3)	-0.5(-3.4,2.5)	1.7(-1.1,4.6)
Month 12	2.4(12.4)	2.8(10.9)	4(10.9)	-1.6(-4.4,1.2)	-1.2(-3.8,1.5)
Month 15	3.1(11.9)	4.6(12.1)	3.7(11.6)	-0.6(-3.6,2.3)	0.9(-2.1,3.9)
Month 18	-0.7(15.2)	0.8(13.9)	3.3(13.6)	-4(-7.7,-0.3)	-2.5(-6.1,1)
Month 21	0.6(16.2)	2.8(12.2)	6.4(11.3)	-5.8(-9.5,-2.1)	-3.6(-6.9,-0.4)
Month 24	-1.6(18.6)	-0.1(14.1)	5.6(13.3)	-7.1(-11.5,-2.8)	-5.7(-9.6,-1.8)
Month 27	2.7(14.3)	2.5(12.5)	6.1(12.4)	-3.4(-7.2,0.4)	-3.6(-7.3,0.1)
Month 30	3.4(14.6)	1.7(13.6)	6.9(11.3)	-3.5(-7.3,0.3)	-5.2(-9,-1.5)
Month 33	5.1(13.6)	2.4(14.1)	7(11.4)	-1.8(-5.6,2)	-4.6(-8.4,-0.7)
Month 36	6.2(7)	6(7.4)	2.9(6.6)	3.2(1.7,4.7)	3.1(1.5,4.6)
Month 39	6.2(7.8)	6.1(8.4)	2.8(8.6)	3.4(1.5,5.2)	3.3(1.4,5.2)

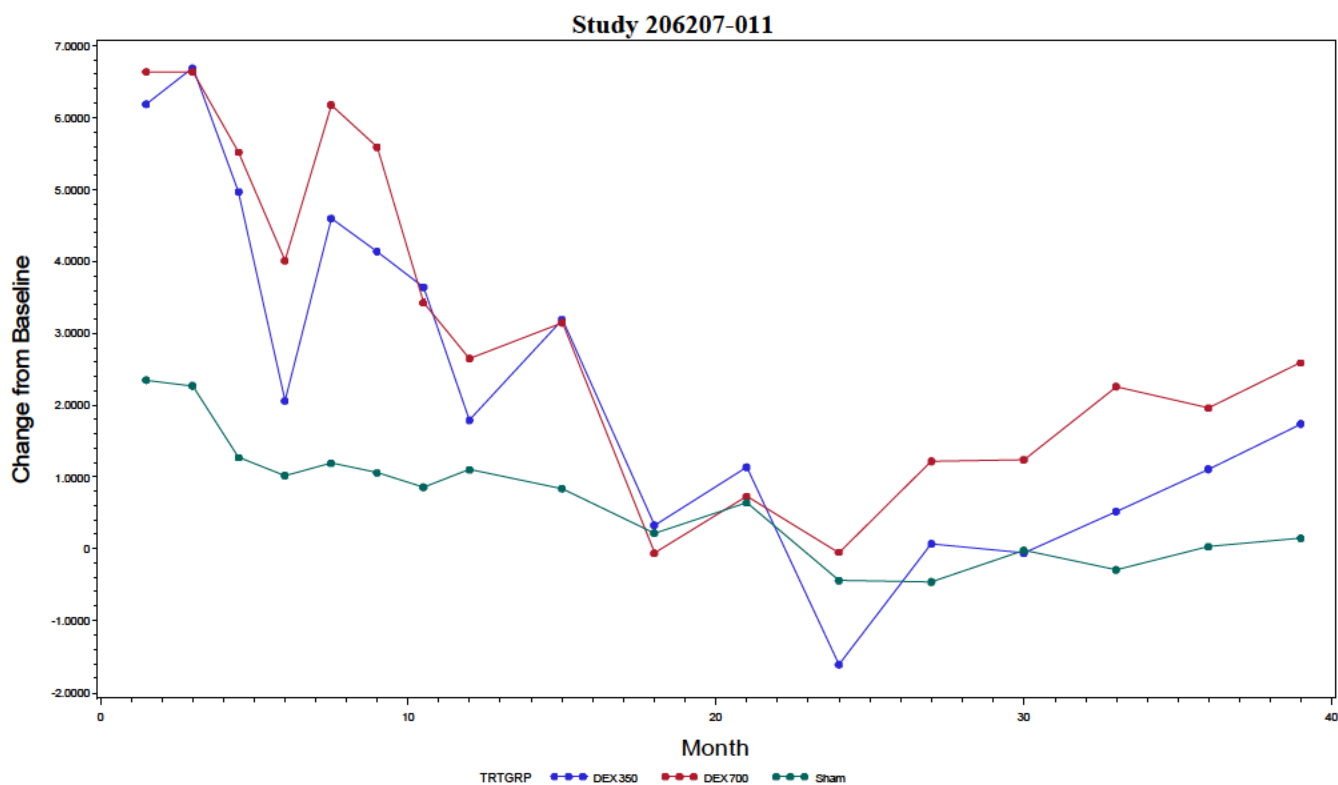
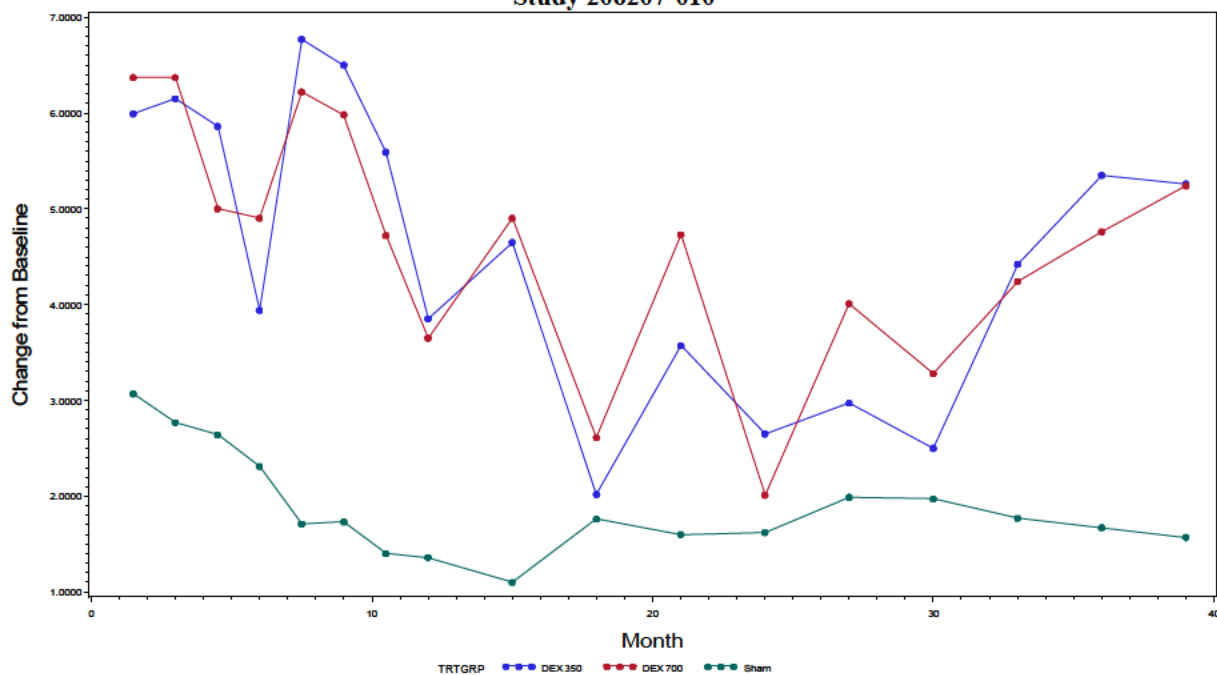
Source: Reviewer's Analysis. Subjects with Missing BCVA measurement were excluded from the analysis.

Figure 13: Plot of Mean change in BCVA from Baseline (Complete Case)
Study 206207-010



Sources: Reviewer's analysis. Subjects who received escape therapies before a given visit were set as treatment failures in that visit.

Figure 14: Plot of Mean change in BCVA from Baseline (Per-Protocol)
Study 206207-010



Sources: Reviewer's analysis. Subjects who received escape therapies before a given visit were set as treatment failures in that visit.

Table 38: Summary of Adverse Events for baseline Pseudophakic subjects

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=85	DEX 350 N=87	Sham N=100	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	81 (95.3%)	86 (98.9%)	86 (86%)	9.3% (1.1%, 17.4%)	12.9% (5.7%, 20%)
Any Ocular AE	63 (74.1%)	73 (83.9%)	61 (61%)	13.1% (-0.2%, 26.5%)	22.9% (10.6%, 35.2%)
Any Serious AE	31 (36.5%)	37 (42.5%)	36 (36%)	0.5% (-13.4%, 14.4%)	6.5% (-7.5%, 20.5%)
Any Ocular Serious AE	2 (2.4%)	0 (0.0%)	0 (0.0%)	2.4% (-0.9%, 5.6%)	
Any Severe AE	38 (44.7%)	40 (46%)	38 (38%)	6.7% (-7.5%, 20.9%)	8% (-6.2%, 22.1%)
Any Ocular Severe AE	11 (12.9%)	15 (17.2%)	8 (8%)	4.9% (-4%, 13.8%)	9.2% (-0.3%, 18.8%)
Any IOP Related AE	25 (29.4%)	29 (33.3%)	9 (9%)	20.4% (9.2%, 31.6%)	24.3% (12.9%, 35.7%)
≥10 mm Hg IOP Change from Baseline at any visit	20 (23.5%)	24 (27.6%)	2 (2%)	21.5% (12.1%, 31%)	25.6% (15.8%, 35.4%)
≥25 mm Hg IOP at any visit	21 (24.7%)	24 (27.6%)	6 (6%)	18.7% (8.4%, 29%)	21.6% (11.1%, 32.1%)
≥35 mm Hg IOP at any visit	6 (7.1%)	4 (4.6%)	1 (1%)	6.1% (0.3%, 11.8%)	3.6% (-1.2%, 8.4%)
Glaucoma	1 (1.2%)	1 (1.1%)	0 (0%)	1.2% (-1.1%, 3.5%)	1.1% (-1.1%, 3.4%)
IOP Lowering Procedures	1 (1.2%)	0 (0.0%)	0 (0.0%)	1.2% (-1.1%, 3.5%)	
≥15 Letters Loss from Baseline	5 (5.9%)	4 (4.6%)	7 (7%)	-1.1% (-8.2%, 6%)	-2.4% (-9.1%, 4.3%)
Death	1 (1.2%)	3 (3.4%)	2 (2.0%)	-0.8% (-4.4%, 2.8%)	1.4% (-3.3%, 6.2%)
Escape Therapy*	7 (8.2%)	9 (10.3%)	12 (12%)	-3.8% (-12.4%, 4.9%)	-1.7% (-10.7%, 7.4%)

Source: Reviewer's Analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye.

Escape therapy refers to any therapy provided for macular edema other than the assigned medication at the discretion of the investigator.

Subjects are analyzed according to the treatment they received not randomized.

Table 39: Summary of Adverse Events Reported in ≥2% of Subjects (All Treated Subjects)

Adverse events	DEX 700 N=347	DEX 350 N=343	Sham N=350
Cataract	131(37.8%)	111(32.4%)	34(9.7%)
Intraocular pressure increased	107(30.8%)	103(30%)	12(3.4%)
Conjunctival haemorrhage	73(21%)	89(25.9%)	45(12.9%)
Cataract subcapsular	41(11.8%)	41(12%)	12(3.4%)
Visual acuity reduced	29(8.4%)	28(8.2%)	14(4%)
Vitreous haemorrhage	24(6.9%)	45(13.1%)	25(7.1%)
Dry eye	21(6.1%)	19(5.5%)	9(2.6%)
Ocular hypertension	21(6.1%)	17(5%)	5(1.4%)
Conjunctival hyperaemia	20(5.8%)	30(8.7%)	19(5.4%)
Macular fibrosis	20(5.8%)	37(10.8%)	10(2.9%)
Conjunctivitis	19(5.5%)	15(4.4%)	8(2.3%)
Cataract nuclear	18(5.2%)	15(4.4%)	8(2.3%)
Eye pain	18(5.2%)	24(7%)	13(3.7%)
Macular oedema	18(5.2%)	13(3.8%)	19(5.4%)
Vitreous detachment	17(4.9%)	23(6.7%)	8(2.3%)
Vitreous floaters	17(4.9%)	9(2.6%)	7(2%)
Lenticular opacities	16(4.6%)	11(3.2%)	4(1.1%)
Conjunctival oedema	15(4.3%)	17(5%)	4(1.1%)
Retinal exudates	14(4%)	14(4.1%)	15(4.3%)
Retinal haemorrhage	14(4%)	20(5.8%)	15(4.3%)

Posterior capsule opacification	13(3.7%)	13(3.8%)	7(2%)
Diabetic retinopathy	12(3.5%)	8(2.3%)	7(2%)
Punctate keratitis	12(3.5%)	11(3.2%)	9(2.6%)
Vitreous opacities	11(3.2%)	5(1.5%)	3(0.9%)
Blepharitis	10(2.9%)	5(1.5%)	16(4.6%)
Corneal abrasion	10(2.9%)	10(2.9%)	6(1.7%)
Retinal aneurysm	10(2.9%)	11(3.2%)	6(1.7%)
Lacrimation increased	8(2.3%)	10(2.9%)	9(2.6%)
Cataract cortical	7(2%)	13(3.8%)	9(2.6%)
Corneal erosion	7(2%)	4(1.2%)	3(0.9%)
Diabetic retinal oedema	7(2%)	7(2%)	5(1.4%)
Foreign body sensation in eyes	7(2%)	6(1.7%)	5(1.4%)
Eye irritation	5(1.4%)	4(1.2%)	7(2%)
Retinal neovascularisation	4(1.2%)	14(4.1%)	18(5.1%)
Eye pruritus	3(0.9%)	4(1.2%)	7(2%)
Anterior chamber cell	1(0.3%)	7(2%)	1(0.3%)

Source: Table 12-6 of the Applicant's study report.

Table 40: Summary of Treatment-Related Ocular AE in the Study Eye Reported in $\geq 2\%$ of Subjects (All Treated Subjects)

Adverse events	DEX 700 N=347	DEX 350 N=343	Sham N=350
Cataract	101(29.1%)	83(24.2%)	21(6%)
Intraocular pressure increased	96(27.7%)	86(25.1%)	8(2.3%)
Conjunctival haemorrhage	57(16.4%)	77(22.4%)	34(9.7%)
Cataract subcapsular	34(9.8%)	30(8.7%)	11(3.1%)
Ocular hypertension	20(5.8%)	17(5%)	4(1.1%)
Cataract nuclear	15(4.3%)	11(3.2%)	7(2%)
Conjunctival hyperaemia	13(3.7%)	22(6.4%)	10(2.9%)
Conjunctival oedema	13(3.7%)	13(3.8%)	4(1.1%)
Eye pain	13(3.7%)	15(4.4%)	9(2.6%)
Vitreous floaters	10(2.9%)	3(0.9%)	1(0.3%)
Cataract cortical	6(1.7%)	10(2.9%)	7(2%)

Source: Table 12-9 of the Applicant's study report.

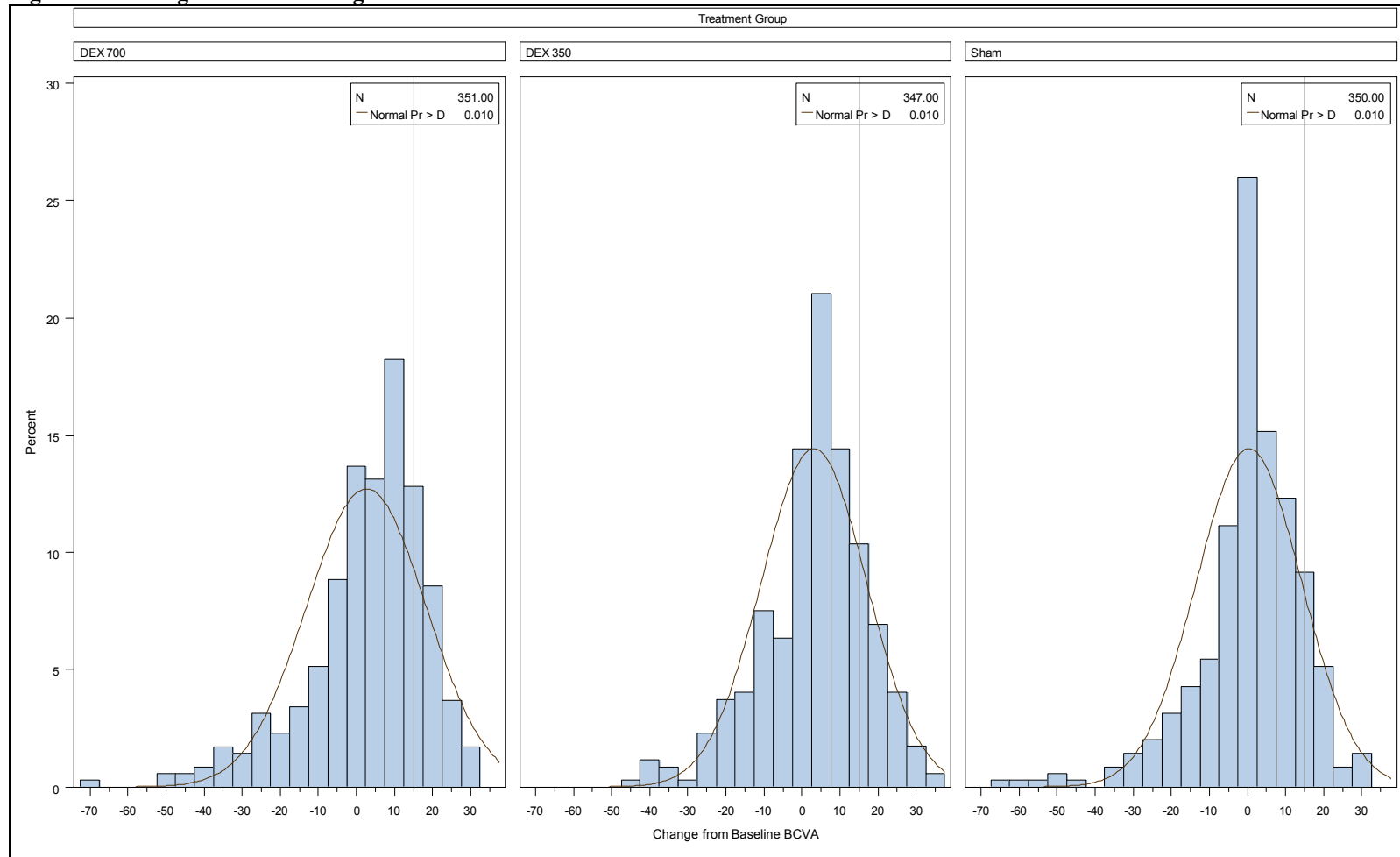
Table 41: Summary of Serious adverse Events Reported in ≥ 1 Subject (All Treated Subjects)

Adverse events	DEX 700 N=347	DEX 350 N=343	Sham N=350
Cataract	10(2.9%)	9(2.6%)	3(0.9%)
Vitreous haemorrhage	10(2.9%)	5(1.5%)	5(1.4%)
Cellulitis	5(1.4%)	5(1.5%)	1(0.3%)
Cerebrovascular accident	4(1.2%)	3(0.9%)	4(1.1%)
Renal failure acute	4(1.2%)	4(1.2%)	2(0.6%)
Cardiac failure congestive	3(0.9%)	9(2.6%)	2(0.6%)
Coronary artery disease	3(0.9%)	4(1.2%)	3(0.9%)
Osteoarthritis	3(0.9%)	2(0.6%)	2(0.6%)
Syncope	3(0.9%)	3(0.9%)	2(0.6%)

Transient ischaemic attack	3(0.9%)	3(0.9%)	1(0.3%)
Acute myocardial infarction	2(0.6%)	1(0.3%)	3(0.9%)
Atrioventricular block complete	2(0.6%)	1(0.3%)	2(0.6%)
Colon cancer	2(0.6%)	1(0.3%)	1(0.3%)
Macular fibrosis	2(0.6%)	1(0.3%)	2(0.6%)
Renal failure	2(0.6%)	2(0.6%)	1(0.3%)
Arrhythmia	1(0.3%)	1(0.3%)	1(0.3%)
Cardiac arrest	1(0.3%)	3(0.9%)	2(0.6%)
Carotid artery stenosis	1(0.3%)	2(0.6%)	1(0.3%)
Diabetes mellitus inadequate control	1(0.3%)	2(0.6%)	1(0.3%)
Dyspnoea	1(0.3%)	1(0.3%)	1(0.3%)
Myocardial infarction	1(0.3%)	9(2.6%)	4(1.1%)
Myocardial ischaemia	1(0.3%)	2(0.6%)	3(0.9%)
Osteomyelitis	1(0.3%)	2(0.6%)	2(0.6%)
Prostate cancer	1(0.3%)	5(1.5%)	3(0.9%)
Vitreous adhesions	1(0.3%)	1(0.3%)	1(0.3%)

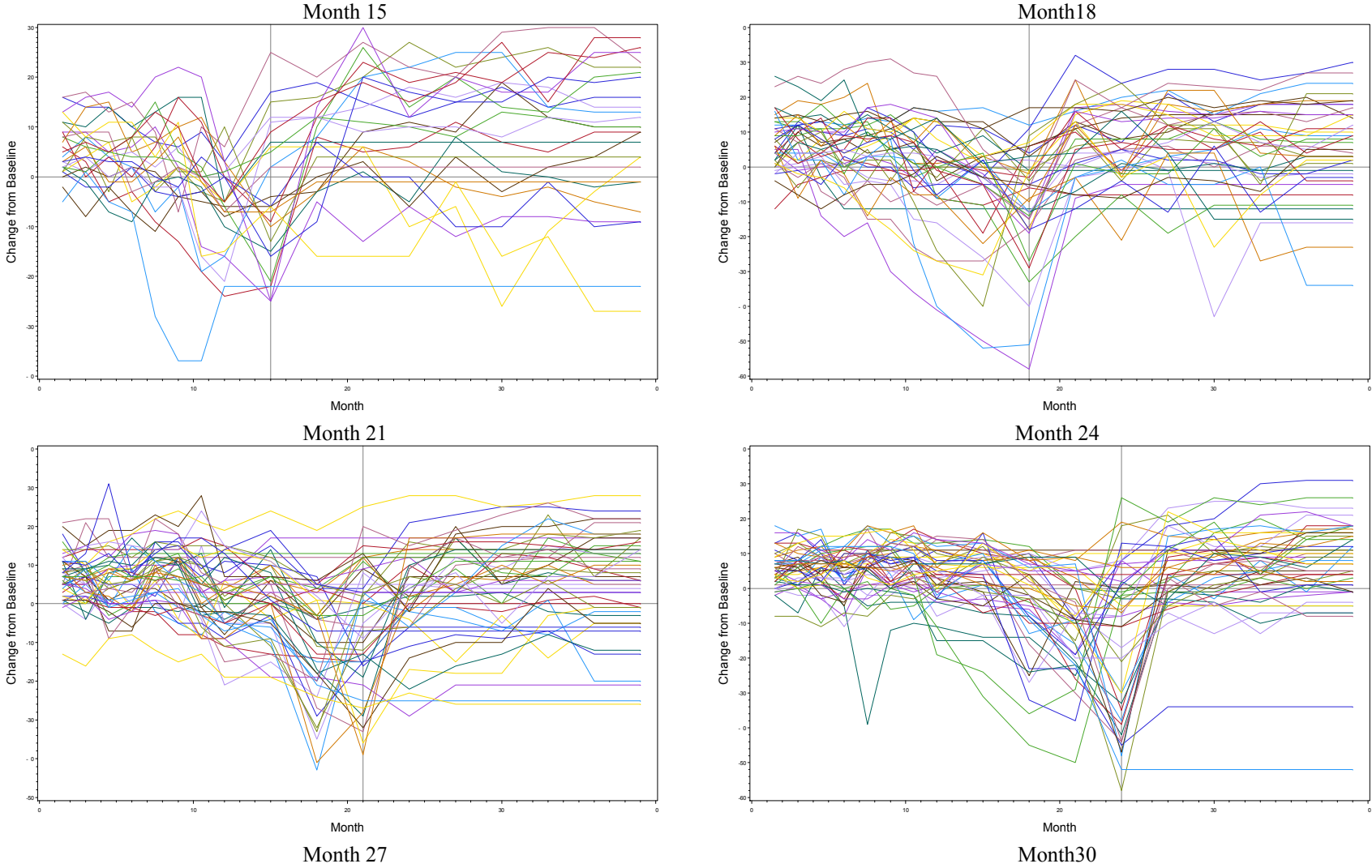
Source: Table 12-12 of the Applicant's study report.

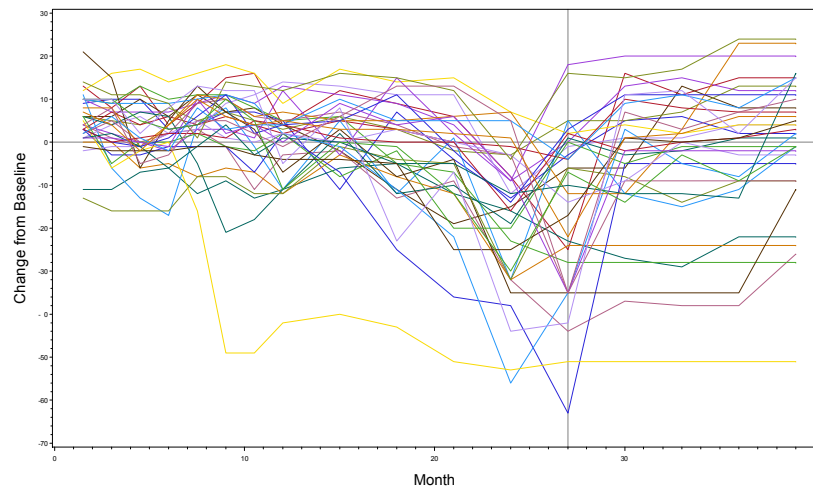
Figure 15 : Histogram of the Change from Baseline BCVA at 3 Years



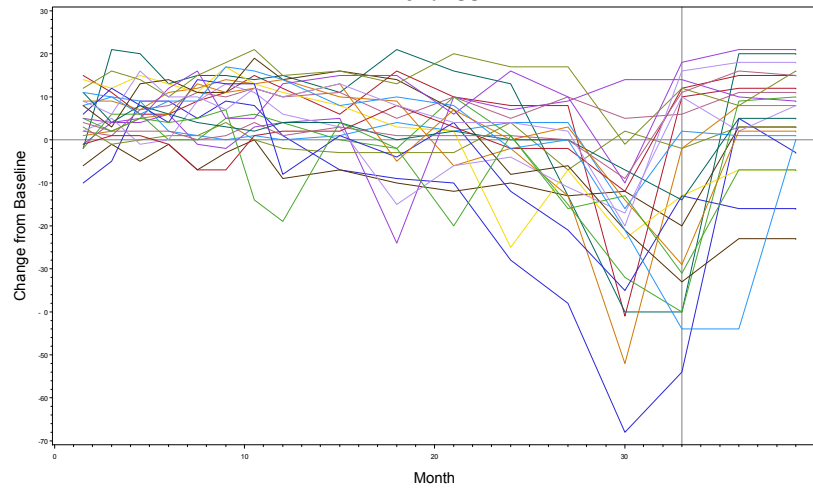
Source: Reviewer's Analysis. Vertical line corresponds to a BCVA change from baseline of 15 letters. P-value is from a Kolmogorov-Smirnov D test for normality.

Figure 16: Plot of Change from Baseline BCVA over time for Subjects who had Cataract Surgery by Month of Surgery

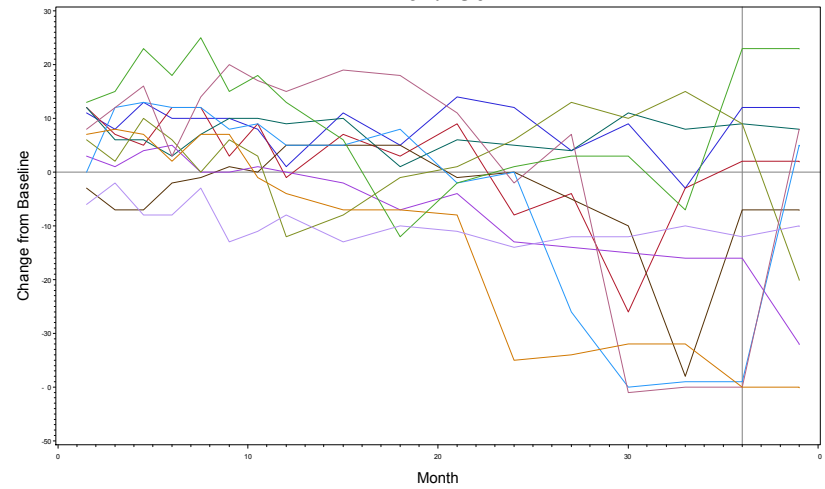
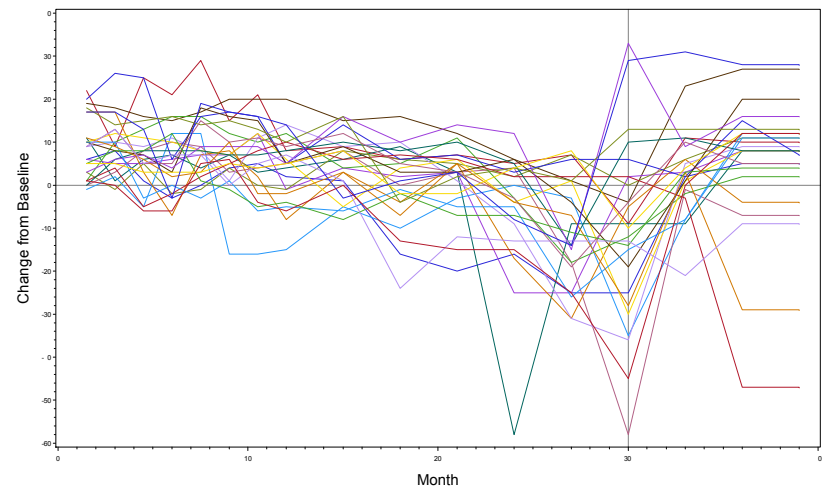




Month 33

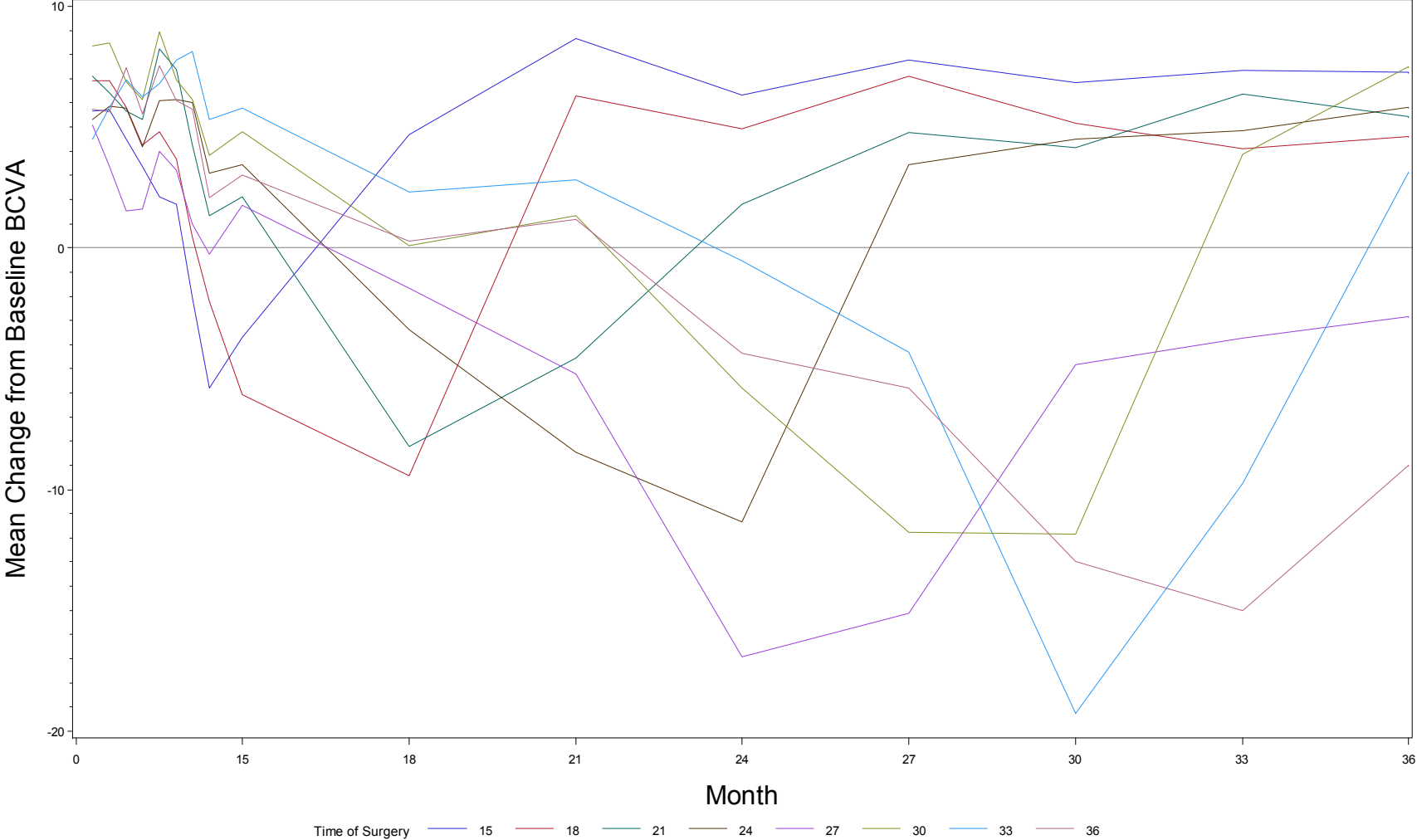


Month 36



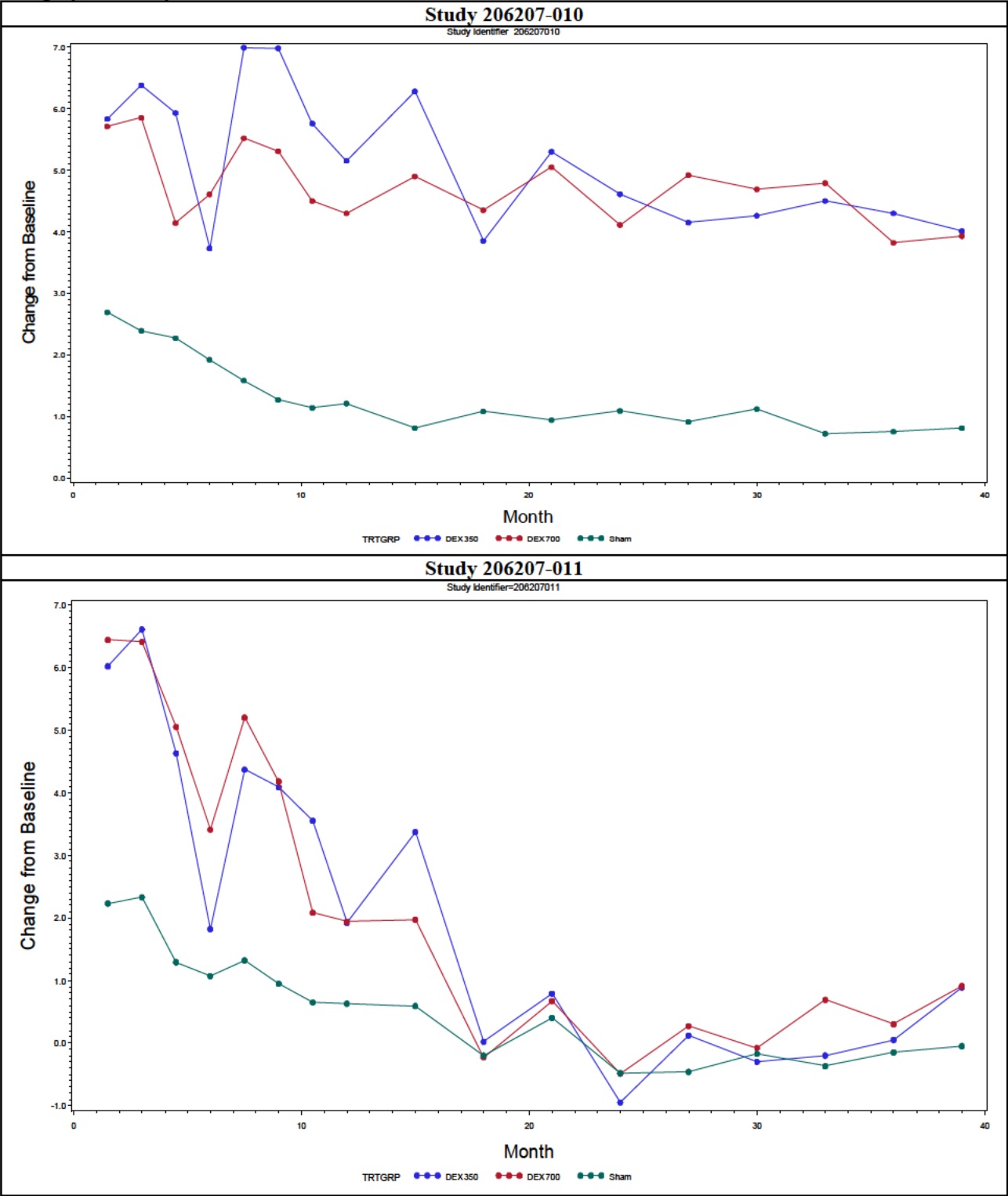
Source: Reviewer's Analysis. Vertical lines refer to the reported Month of surgery.

Figure 17: Mean Change BCVA plot over time for Subjects who Underwent Cataract Surgery



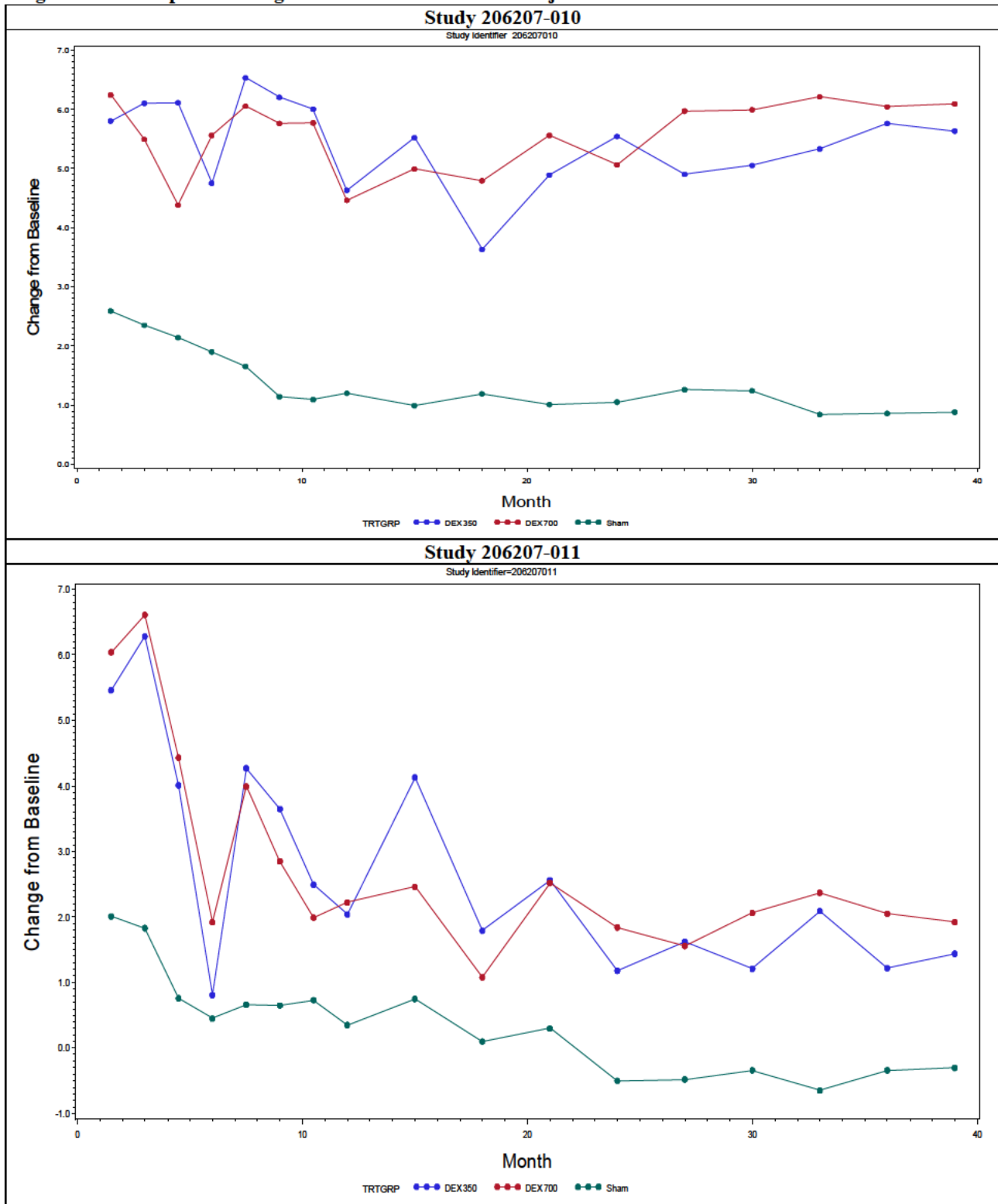
Source: Reviewer's analysis.

Figure 18: Mean plot of change from baseline BCVA for subjects who had no surgery or had cataract surgery within a year after randomization



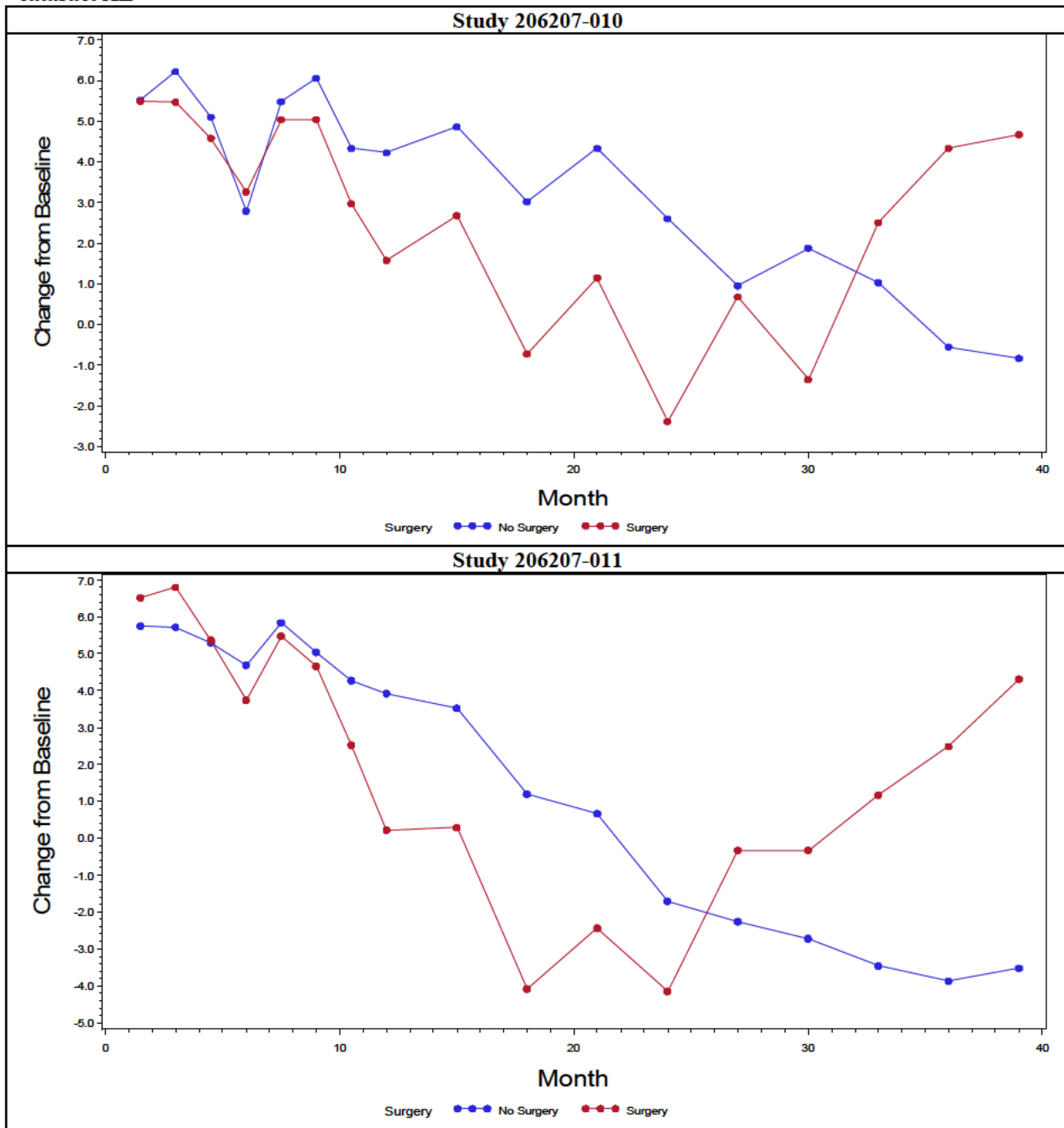
Source: Reviewer's analysis.

Figure 19: Mean plot of change from baseline BCVA for subjects Without Cataract AE



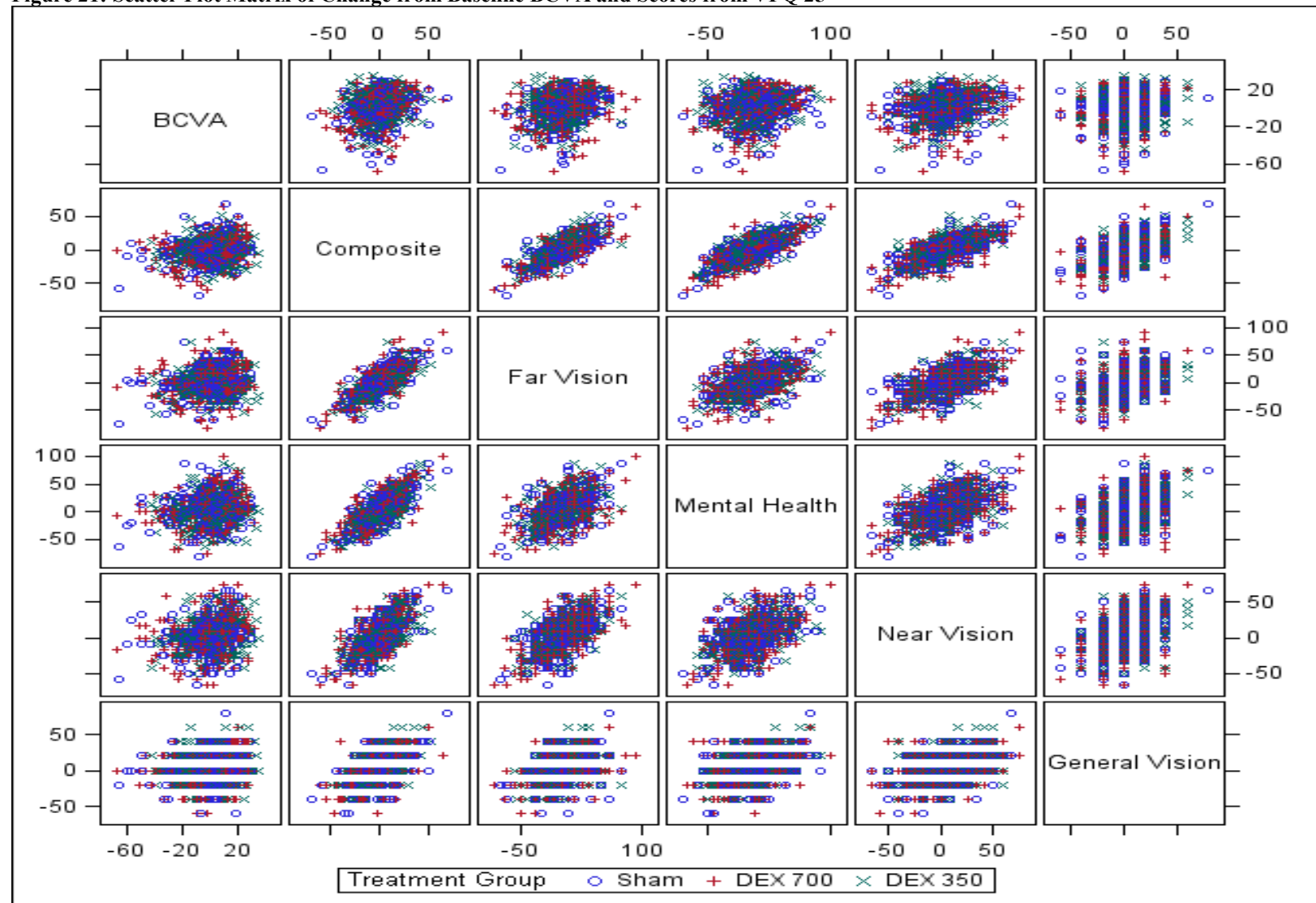
Source: Reviewer's analysis.

Figure 20: Mean plot of change from baseline BCVA by Surgery Status among Subjects who reported cataract AE



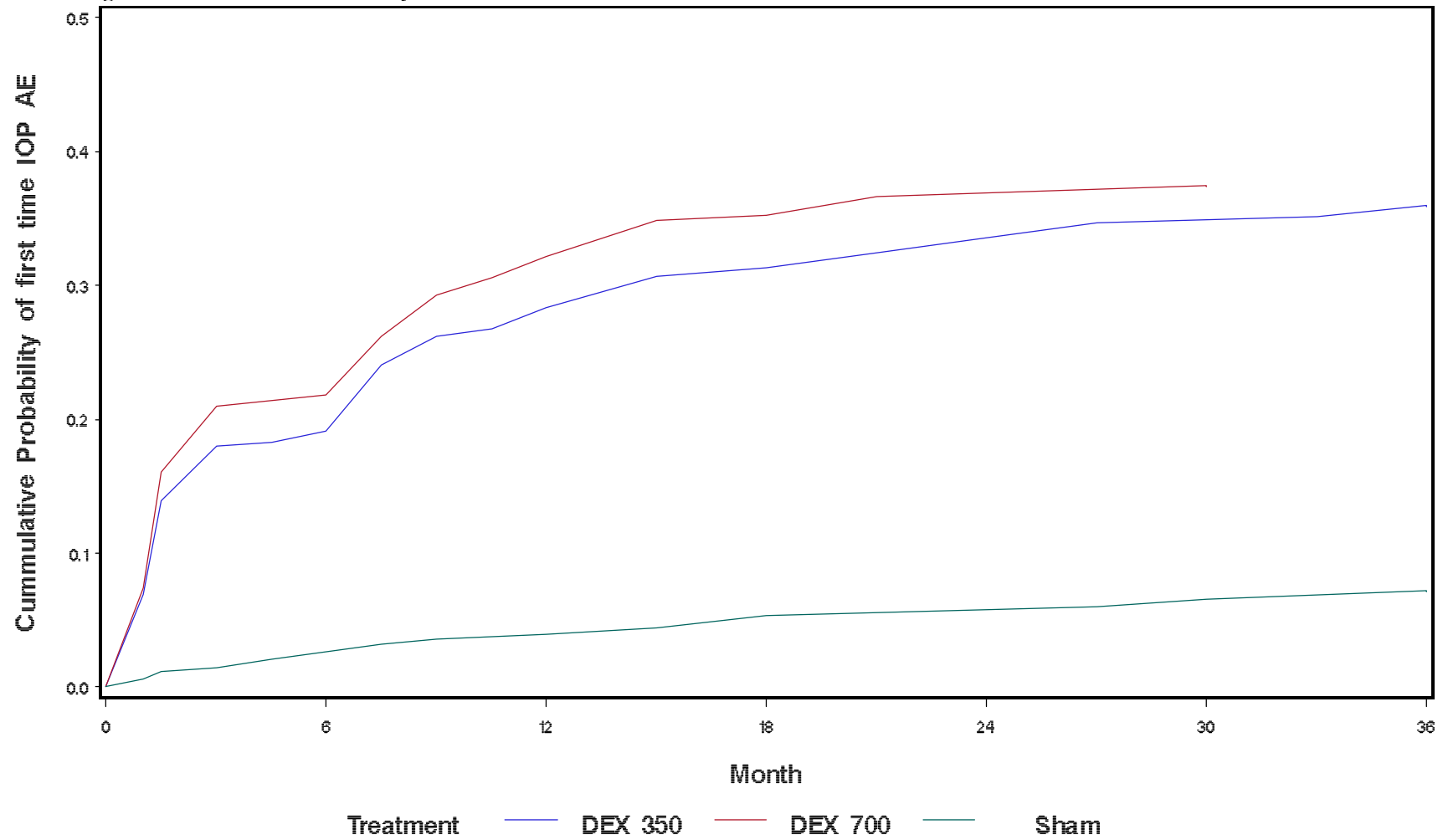
Source: Reviewer's analysis.

Figure 21: Scatter Plot Matrix of Change from Baseline BCVA and Scores from VFQ 25



Source: Reviewer's Analysis.

Figure 22: Cumulative Probability of first time elevated IOP AE



Source: Reviewer's analysis.

Table 42: Formula for Computing Area under the Curve

Let t_{ij} be the visit time (in days) for the patient i at visit j , and y_{ij} be the corresponding observed BCVA, where $i = 1, 2, \dots, N$, $j = 0, 1, 2, \dots, n_i$, where n_i is the number of visits with non-missing BCVA for patient i , $j = 0$ corresponds to baseline visit.

Define BCVA change from baseline at visit j for the patient i

$$\Delta y_{ij} = y_{ij} - y_{i0} \quad j > 0$$

$$AUC_i = \sum_{j=1}^{n_i} (\Delta y_{ij} + \Delta y_{i(j-1)}) \times \left(\frac{t_{ij} - t_{i(j-1)}}{2} \right), \quad j = 1, \dots, n_i, \quad \Delta y_{i0} = 0$$

Average change from baseline in BCVA for patient $i = AUC_i / (t_{in_i} - t_{i0})$.

Source: Applicant's Statistical analysis plan.

8 References

1. Cook RJ, Sackett DL. (1995). The number needed to treat: a clinically useful measure of treatment effect. British Medical Journal: 310:452-4.
2. Altman, D G. (1998). Confidence intervals for the number needed to treat. British Medical Journal: 317(7168): 1309-1312.
3. M. Buyse, G. Molenberghs, T. Burzykowski, D. Renard, H. Geys (2000). The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 1(1): 49-67.

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

/s/

ABEL T ESHETE
03/10/2014

YAN WANG
03/10/2014
I concur.

Statistics Filing Checklist for NDA022315

NDA Number: 022315

Applicant:
Allergan, Inc.

Stamp Date:
June 12, 2013

Drug Name:
DEX PS DDS

NDA Type:
Standard Review

Indication:
Treatment of Diabetic Macular
Edema

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		✓		#1 #2
4	Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? **Yes**

The NDA is fileable from the statistical perspective. However, the following issues were noted during the preliminary review.

1. The applicant did not conduct subgroup analysis for gender, racial, and geriatric subgroups for the individual studies.
2. Three of the reasons for study discontinuation are listed as protocol violation, “other” and “personal reason”. No further detail was provided with respect to what constitutes a personal reason and other reasons.
3. The applicant used different window definitions for different datasets. This makes it difficult to merge datasets for further analysis.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			

Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA.	✓			#1 #2
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

We have the following information request for the applicant:

1. Please conduct safety and efficacy analysis for gender, racial, and geriatric subgroups for study 206207-010 and study 206207-011 in the same manner as you did for ISE and ISS reports.
2. Please include the list of reasons for discontinuation specified under “Others”, personal reasons and protocol violations in the patient disposition table.
3. Three variables “WINDOW” (window name), “ADT” (analysis date) and “ADY” (analysis day) appear to be derived differently for different datasets and it is not clear to us how these variables were defined. For examples, the following table presents your definition for “WINDOW” and “ADT” in some of the datasets in the ISE folder:

“WINDOW”	Source/Computational Method
va.xpt	No definition was provided.
cp.xpt	Derived from WINDNUM: use window definition 1b, see Timing Variables worksheet for details.
io.xpt	Derived using window definition 1d, see Timing Variables worksheet for details.
“ADT”	
va.xpt	No definition was provided.
cp.xpt	Derived from conprocs.cpdvnc: convert to a SAS date.
io.xpt	Derived from iop.iovdt: rename.

Please provide a detailed definition of these variables in all the datasets that included these variables. Please also include a variable in the dataset “cp.xpt” to indicate the exact date of each procedure.

4. Please prepare the summary of the proportion of subjects with ≥ 15 -letter BCVA improvement and the mean change in BCVA from baseline at each time point grouped by the number of injections they received.

Brief summary of controlled clinical trials

This application provides data from two phase 3 studies (206207-010 and 206207-011) to support the safety and efficacy of DEX PS DDS in the treatment of Diabetic Macular Edema. The following tables contain information on the relevant trials contained in the submission.

Study number	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
206207-010	A Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema	<ul style="list-style-type: none"> – DEX 700: N=163 – DEX 350: N=166 – Sham : N=165 <p>Note: Study drug containing an extruded dosage form of 700 µg or 350 µg dexamethasone in an inactive biodegradable polymer matrix of poly [lactic-glycolic] acid (PLGA) was administered into the vitreous through the pars plana into the study eye only using the DEX PS DDS Applicator System.</p>	<p>Primary: The proportion of subjects with ≥ 15-letter BCVA improvement at year 3/final</p> <p>The primary analysis was a statistical evaluation of superiority of the two dose groups to sham with respect to the primary efficacy variable. A gate-keeping procedure was used to control the overall type I error at 5%. The comparison of DEX 700 versus Sham was considered significant if the p-value was ≤ 0.05. Only if the comparison of DEX 700 versus Sham was significant, was the comparison of DEX 350 versus Sham to be performed at a significance level of 0.05. A Pearson's chi-square test was used to compare the groups.</p>	<p>The primary endpoint of proportion of patients with ≥ 15-letter BCVA improvement at year 3/final was significantly higher with DEX 700 (22.1%) compared with Sham (13.3%), $p = 0.038$. Following the gate-keeping procedure, the comparison of DEX 350 (18.7%) versus Sham (13.3%) was not statistically significant ($p = 0.185$).</p>
206207-011	A Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700	<ul style="list-style-type: none"> – DEX 700: N=188 – DEX 350: N=181 – Sham : N=185 <p>Note: Study drug containing an extruded dosage form of 700 µg or 350 µg dexamethasone in an inactive biodegradable polymer matrix of poly</p>	<p>Primary: The proportion of subjects with ≥ 15-letter BCVA improvement at year 3/final</p> <p>The primary analysis was a statistical evaluation of superiority of the two dose groups to sham with respect to the primary efficacy variable. A</p>	<p>The primary endpoint of proportion of patients with ≥ 15-letter BCVA improvement at year 3/final statistically significantly higher with DEX 700 (22.3%) compared with Sham (10.8%), $p = 0.003$. Following the gate-keeping</p>

Study number	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
	µg and 350 µg Dexamethasone Posterior segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema	[lactic-glycolic] acid (PLGA) was administered into the vitreous through the pars plana into the study eye only using the DEX PS DDS Applicator System.	gate-keeping procedure was used to control the overall type I error at 5%. The comparison of DEX 700 versus Sham was considered significant if the p-value was ≤ 0.05 . Only if the comparison of DEX 700 versus Sham was significant, was the comparison of DEX 350 versus Sham to be performed at a significance level of 0.05. A Pearson's chi-square test was used to compare the groups.	procedure, the comparison of DEX 350 versus Sham was statistically significant (18.2% versus 10.8%, $p = 0.044$).

Table 1: Patient Disposition (ITT Population)

	Studies					
	206207-010			206207-011		
	DEX 700 n (%)	DEX 350 n (%)	Sham n (%)	DEX 700 n (%)	DEX 350 n (%)	Sham n (%)
Number of Subjects Randomized	163 (32.9%)	166 (33.6%)	165 (33.4%)	188 (33.9%)	181 (32.7%)	185 (33.4%)
Subjects who completed the study	107/163 (65.6%)	118/166 (71.1%)	70/165 (42.4%)	118/188 (62.8%)	112/181 (61.9%)	82/185 (44.3%)
Primary Reason for Early Termination						
Adverse Events	20/56 (35.7%)	18/48 (37.5%)	16/95 (16.8%)	25/70 (35.7%)	30/69 (43.5%)	23/103 (22.3%)
Lack of Efficacy	9/56 (16.1%)	14/48 (29.2%)	37/95 (38.9%)	14/70 (20.0%)	11/69 (15.9%)	47/103 (45.6%)
Lost-to-Follow-up	5/56 (8.9%)	5/48 (10.4%)	10/95 (10.5%)	6/70 (8.5%)	7/69 (10.1%)	8/103 (7.7%)
Personal Reason	7/56 (12.5%)	4/48 (8.3%)	16/95 (16.8%)	7/70 (10.0%)	6/69 (8.7%)	10/103 (9.7%)
Protocol Violations	2/56 (3.6%)	0/48 (0.0%)	0/95 (0.0%)	1/70 (1.4%)	3/69 (4.3%)	1/102 (0.9%)
Other ¹	13/56 (23.2%)	7/48 (14.6%)	16/95 (16.8%)	17/70 (24.3%)	12/69 (17.4%)	14/103 (13.6%)

Source: Figure 10-1 and Tables 14-1-2.1 of Applicant's submitted Study Reports

¹ Other reasons for early discontinuation of the study obtained from listing 16.2.1-2 include: Site closed, switched to alternative therapy, required escape therapy, consent withdrawal, unscheduled visit, poor compliance from patient, sponsor request, patient relocation, patient participation in other trial, etc

Table 2: Baseline and Demographics: Study 206207-010 (ITT population)

	DEX 700 (N=163)	DEX 350 (N=166)	Sham (N=165)	Total (N=494)	P-value
Age(years)					
Mean (SD)	63.1 (8.01)	63.3 (9.01)	62.6 (9.10)	63.0 (8.71)	0.696
Range	33-84	27-82	26-83	26-84	
<45	4 (2.5%)	5(3.0%)	7(4.2%)	16 (3.2%)	
45-65	89 (54.6%)	97 (58.4%)	95 (57.6%)	281 (56.9%)	
>65	70 (42.9%)	64 (38.6%)	63 (38.2%)	197 (39.9%)	
Sex					
Male	102 (62.6%)	100 (60.2%)	102 (61.8%)	304 (61.5%)	0.906
Female	61 (37.4%)	66 (39.8%)	63 (38.2%)	190 (38.5%)	
Race					
Caucasian	138 (84.7%)	140 (84.3%)	134 (81.2%)	412 (83.4%)	0.649
Non-Caucasian	25 (15.3%)	26 (15.7%)	31 (18.8%)	82 (16.6%)	
Black	7 (4.3%)	7 (4.2%)	13 (7.9%)	27 (5.5%)	
Asian ^a	12 (7.4%)	14 (8.4%)	13 (7.9%)	39 (7.9%)	
Hispanic	1 (0.6%)	2 (1.2%)	2 (1.2%)	5 (1.0%)	
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	5 (3.1%)	3 (1.8%)	3 (1.8%)	11 (2.2%)	
Iris Color					
Light	69 (42.3%)	74 (44.6%)	73 (44.2%)	216 (43.7%)	0.907
Dark	94 (57.7%)	92 (55.4%)	92 (55.8%)	278 (56.3%)	
Baseline Lens Status					
Phakic	119 (73.0%)	119 (71.7%)	115 (69.7%)	353 (71.5%)	0.799
Pseudophakic	47 (28.3%)	47 (28.3%)	50 (30.3%)	141 (28.5%)	
Weight (Kg)					
Mean (SD)	84.3 (17.8)	85.1 (20.4)	82.2 (16.9)	83.8 (18.5)	0.337
Range	48 -144	43 - 155	50 - 150	43 - 155	
Height (cm)					
Mean (SD)	167.2 (9.3)	167.3 (10.1)	167.0 (8.8)	167.1 (9.4)	0.957
Range	146 -188	139 -191	142- 188	139- 191	

Source: Tables 10.1 of Applicant's submitted Study Reports. SD = standard deviation. P-values for continuous variables of age, height, and weight are from a 1-way analysis of variance (ANOVA). P-values for categorical values of sex, race (Caucasian versus non-Caucasian), and iris color (light versus dark) are from Pearson's chi-square test. ^aAsian race excludes Japanese

Table 3: Baseline and Demographics: Study 206207-011 (ITT population)

	DEX 700 (N=188)	DEX 350 (N=181)	Sham (N=185)	Total (N=554)	P-value
Age(years)					
Mean (SD)	61.9 (8.57)	61.3 (9.34)	62.4 (9.85)	61.9 (9.26)	0.558
Range	40-85	25-84	29-88	25-88	
<45	2 (1.1%)	8 (4.4%)	6(3.2%)	16(2.9%)	
45-65	116 (61.7%)	109 (60.2%)	108 (58.4%)	333 (60.1%)	
>65	70 (37.2%)	64 (35.4%)	71 (38.4%)	205 (37.0%)	
Sex					
Male	111 (59.0%)	106 (58.6%)	115 (62.2%)	332 (59.9%)	0.746
Female	77 (41.0%)	75 (41.4%)	70 (37.8%)	222 (40.1%)	
Race					
Caucasian	96 (51.1%)	94 (51.9%)	99 (53.5%)	289 (52.2%)	0.891
Non-Caucasian	92 (48.9%)	87 (48.1%)	86 (46.5%)	265 (47.8%)	
Black	9 (4.8%)	9 (5.0%)	7 (3.8%)	25 (4.5%)	
Asian ^a	42 (22.3%)	42 (23.2%)	40 (21.6%)	124 (22.4%)	
Hispanic	34 (18.1%)	32 (17.7%)	31 (16.8%)	97 (17.5%)	
Japanese	1 (0.5%)	2 (1.1%)	1 (0.5%)	4 (0.7%)	
Other	6 (3.2%)	2 (1.1%)	7 (3.8%)	15 (2.7%)	
Iris Color					
Light	58 (30.9%)	47 (26.0%)	53 (28.6%)	158 (28.5%)	0.582
Dark	130 (69.1%)	134 (74.0%)	132 (71.4%)	396 (71.5%)	
Baseline Lens Status					
Phakic	146 (77.7%)	140 (77.3%)	134 (72.4%)	420 (75.8%)	0.420
Pseudophakic	42 (22.3%)	41 (22.6%)	51 (38.1%)	134 (24.2%)	
Weight (Kg)					
Mean (SD)	81.2 (22.6)	79.0 (20.1)	78.9 (18.1)	79.7 (20.4)	0.483
Range	41 -204	43 - 160	45 - 135	41 - 204	
Height (cm)					
Mean (SD)	163.8 (9.4)	164.5 (9.7)	165.0 (9.51)	164.4 (9.5)	0.502
Range	137 -196	135 -186	133- 190	133- 196	

Source: Tables 10.1 of Applicant's submitted Study Reports. SD = standard deviation. P-values for continuous variables of age, height, and weight are from a 1-way analysis of variance (ANOVA). P-values for categorical values of sex, race (Caucasian versus non-Caucasian), and iris color (light versus dark) are from Pearson's chi-square test. ^aAsian race excludes Japanese

Table 4: Proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at year 3 (Primary Efficacy Endpoint)

Studies	Treatment			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010	36/163 (22.1%)	31/ 166 (18.7%)	22/165 (13.3%)	8.7% (0.5%, 17.0%)	5.3% (-2.5%, 13.2%)
Study 206207-011	42/188 (22.3%)	33/181 (18.2%)	20/185 (10.8%)	11.5% (4.1%, 19.0%)	7.4% (0.2%, 14.6%)
Pooled	78/351 (22.2%)	64/347 (18.4%)	42/350 (12.0%)	10.2% (4.7%, 15.7%)	6.4% (1.1%, 11.8%)

Source: Applicant's submitted Study Reports. LOCF is used for imputing missing Data.

Table 5: Summary of the Primary Efficacy Endpoint by Region (USA and Non-USA)

Studies	Region	Treatment			% Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010	USA	8/29 (27.6%)	2/ 28 (7.1%)	7/31 (22.6%)	5.0% (-16.9%, 26.9%)	-15.4% (-33.0, 2.1%)
	Non-USA	28/134 (20.9%)	29/138 (21.0%)	15/134 (11.2%)	9.7% (0.09%, 18.4%)	9.8% (1.2%, 18.5%)
Study 206207-011	USA	18/71 (25.3%)	13/67 (19.4%)	6/69 (8.7%)	16.7% (4.5%, 28.8%)	10.7% (-0.8%, 22.3%)
	Non-USA	24/117 (20.5%)	20/114 (17.5%)	14/116 (12.1%)	8.4% (-0.9%, 17.9%)	5.5% (-3.7%, 14.6%)
Pooled	USA	26/100 (26.0%)	15/95 (15.8%)	13/100 (13.0%)	13.0% (2.2%, 23.8%)	2.8% (-7.1%, 12.6%)
	Non-USA	52/251 (20.7%)	49/252 (19.4%)	29/250 (11.6%)	9.1% (2.7%, 15.5%)	7.8 % (1.5%, 14.1%)

Source: Reviewer's Analysis. LOCF is used for imputing missing Data.

Table 6: Summary of the Primary Efficacy Endpoint by Baseline Lens Status

Studies	Lens Status	Treatment			% Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010	Pseudophakic	15/44 (34.1%)	7/47 (14.9%)	8/50 (16.0%)	18.1% (0.8%, 35.4%)	-1.1% (-15.5%, 13.3%)
	Phakic	5/47 (20.9%)	9/47 (19.1%)	12/107 (11.2%)	-0.6% (-11.2, 10.1%)	7.9% (-4.8%, 20.7%)
	Phakic +Surgery ¹	16/72 (22.2%)	15/72 (20.8%)	2/8 (25.0%)	-2.9% (-34.3%, 28.7%)	-4.2% (-36.6%, 27.3%)
Study 206207-011	Pseudophakic	5/42 (11.9%)	7/41 (17.1%)	3/51 (5.9%)	6.0% (5.7%, 17.7%)	11.2% (-2.0%, 24.4%)
	Phakic	12/63 (19.0%)	7/78 (9.0%)	15/124 (12.1%)	6.9% (-4.3%, 18.2%)	-3.1% (-11.7%, 5.4%)
	Phakic +Surgery ¹	25/83 (30.1%)	19/62 (30.6%)	2/10 (20.0%)	10.1% (-16.6%, 36.8%)	10.6% (-16.7%, 38.0%)
Pooled	Pseudophakic	20/86 (23.3%)	14/88 (15.9%)	11/101 (10.9%)	12.4% (1.6%, 23.2%)	5.0% (-4.7%, 14.8%)
	Phakic	17/110 (15.4%)	16/125 (12.8%)	27/231 (11.7%)	3.8% (-4.2%, 11.7%)	1.1% (-6.1%, 8.3%)
	Phakic +Surgery ¹	41/155 (26.4%)	34/134 (25.4%)	4/18 (22.2%)	4.2% (-16.2%, 24.6%)	3.1% (-17.4%, 23.7%)

Source: Reviewer's Analysis. LOCF is used for imputing missing Data.

Phakic: Phakic subjects who did not require cataract surgery during the study.

Phakic plus surgery¹: Phakic subjects who required cataract surgery sometime during the study.

Table 7: Summary of the Mean Baseline and Change from Baseline in BCVA in the Study Eye

Studies	Visit	Treatment			Mean Diff (95% CI)	
		DEX 700 Mean (SD)	DEX 350 Mean (SD)	Sham Mean (SD)	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 206207-010	Baseline	56.24 (10.05)	55.87 (9.64)	56.76 (8.66)	-0.51 (-2.55, 1.52)	-0.89 (-2.87, 1.09)
	Month 6	4.60 (9.03)	3.73 (9.12)	1.95 (9.05)	2.63 (0.63, 4.60)	1.70 (-0.19, 3.74)
	Month 12	3.30 (10.71)	3.70 (10.37)	1.18 (10.24)	2.12 (-0.17, 4.38)	2.50 (0.29, 4.75)
	Month 24	1.51 (14.36)	2.29 (14.73)	1.05 (11.09)	0.46 (-2.34, 3.25)	1.23 (-1.60, 4.05)
	Month 39/Final	4.13 (13.89)	5.04 (11.97)	0.81 (11.89)	3.31 (0.51, 6.13)	4.20 (1.66, 6.82)
Study 206207-011	Baseline	55.88 (9.82)	55.20 (9.68)	57.03 (8.76)	-1.15 (-3.04, 0.74)	-1.83 (-3.73, 0.06)
	Month 6	3.63 (8.56)	2.23 (0.67)	1.11 (10.21)	2.50 (0.63, 4.44)	1.12 (-1.02, 3.27)
	Month 12	1.88 (12.38)	1.94 (11.24)	0.68 (12.87)	1.19 (-1.37, 3.77)	1.25 (-1.22, 3.74)
	Month 24	-1.17 (17.36)	-1.55 (14.48)	-0.45 (15.29)	-0.72 (-4.05, 2.60)	-1.10 (-4.16, 1.96)
	Month 39/Final	1.33 (17.03)	1.42 (15.17)	-0.02 (15.40)	1.35 (-1.95, 4.66)	1.40 (-1.70, 4.60)

Source: Reviewer's Analysis. LOCF is used for imputing missing Data.

Figure 1: Plot of mean change from baseline in BCVA

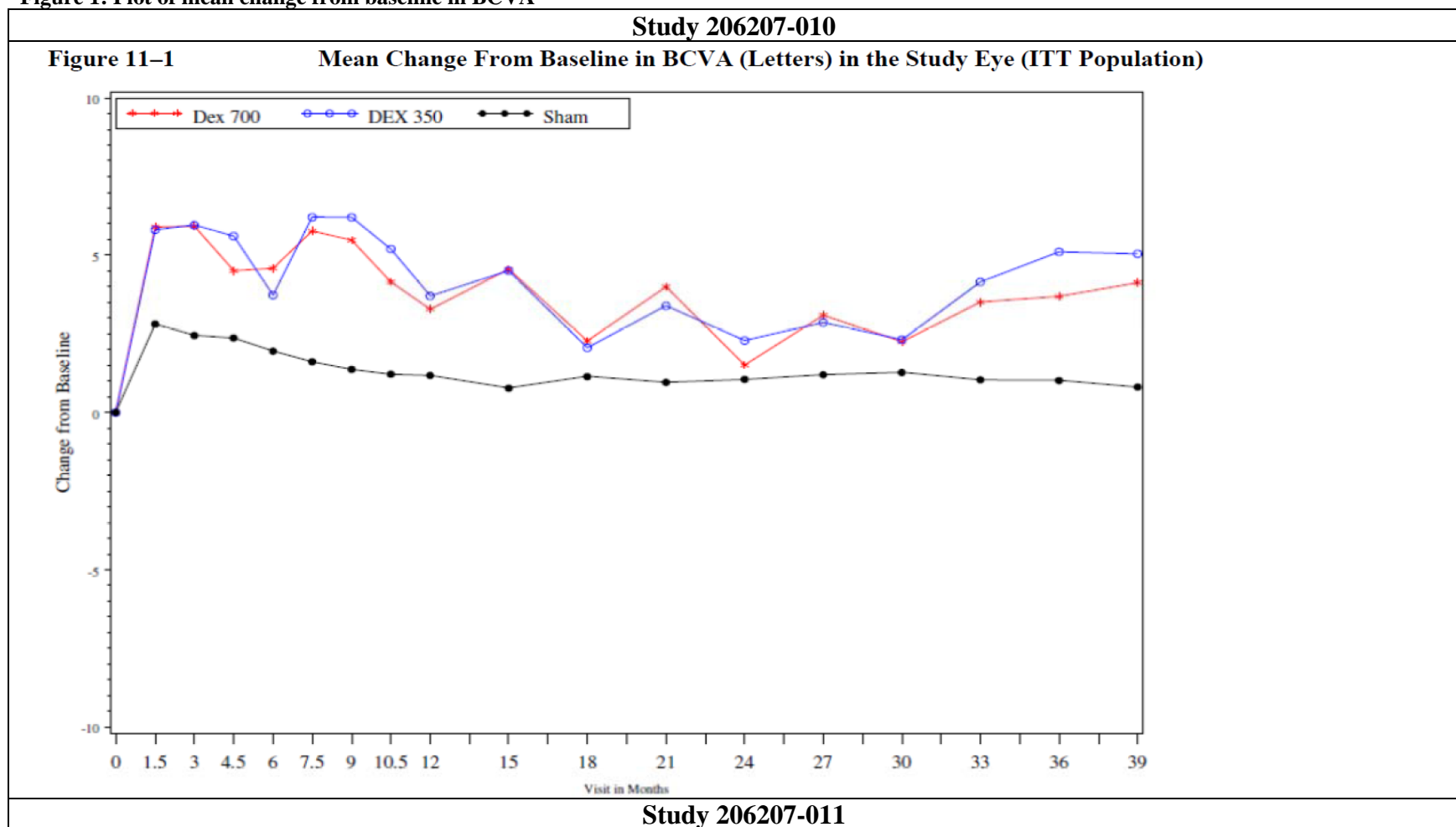
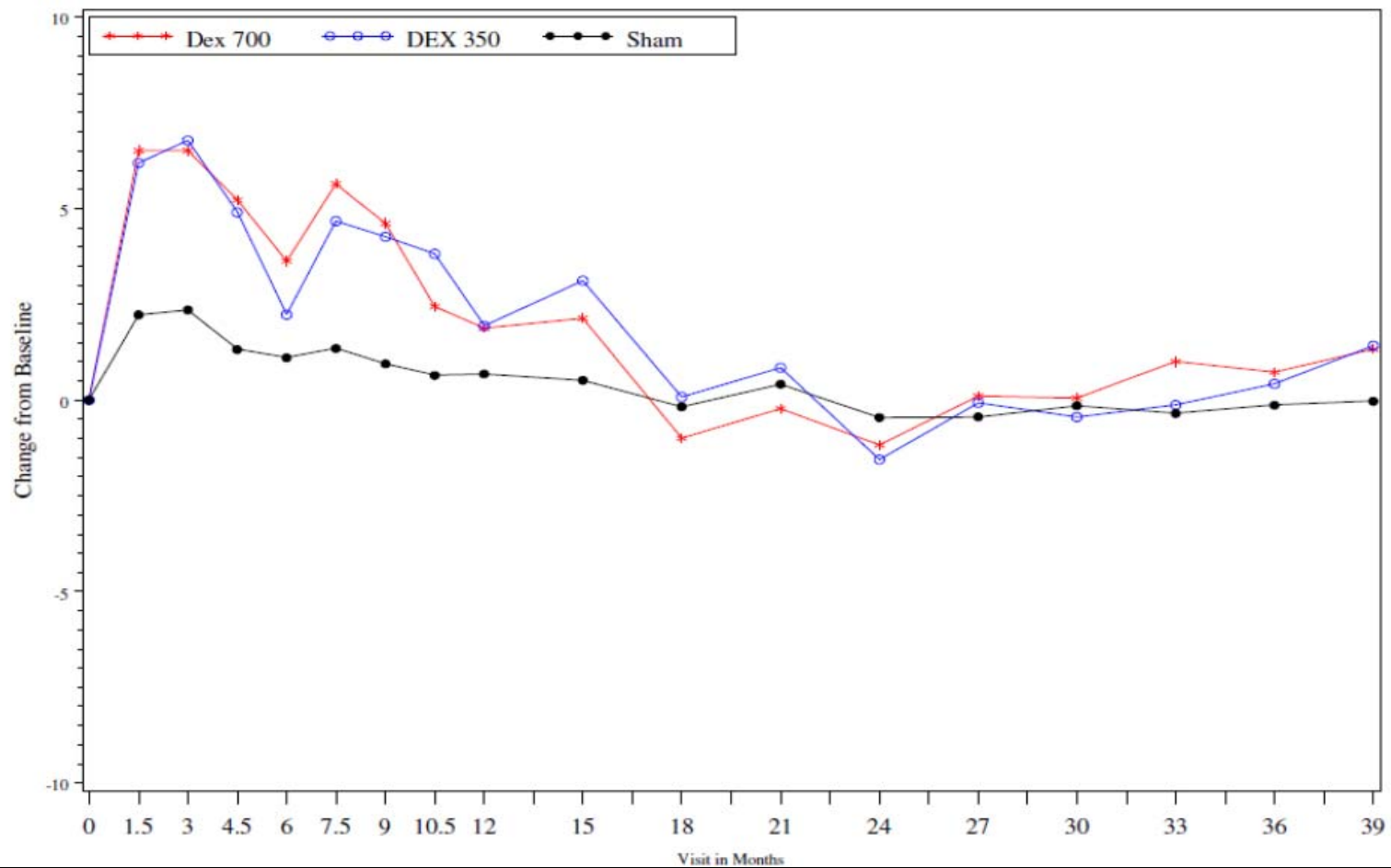


Figure 11-1 Mean Change from Baseline in BCVA (Letters) in the Study Eye (ITT Population)



Source: Figure 11-1 of the Applicant's submitted Study Reports. LOCF is used for imputing missing Data.

Reviewing Statistician	Date
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Supervisor/Team Leader	Date
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABEL T ESHETE
08/20/2013

YAN WANG
08/20/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			Office of Clinical Pharmacology Review	
Reviewer: Gerlie Gieser, PhD			Team Leader: Philip M. Colangelo, PharmD, PhD	
IND No.:	NDA No.: 22-315	SN/SDN: SE-009 (SDN-211)	DATE OF REVIEW: 16 July 2013	DATE OF SUBMISSION: 13 June 2013
NAME OF DRUG/FORMULATION: Ozurdex® (dexamethasone intravitreal implant)			ROUTE OF ADMINISTRATION: For injection into the posterior segment of the eye (b) (4) using a specially designed applicator	
INDICATION: for the treatment of diabetic macular edema (DME)			DOSE (proposed): one intravitreal implant (containing 700 mcg dexamethasone); (b) (4)	
SPONSOR: Allergan				
TYPE OF SUBMISSION				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PHASE I PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED </div> <div style="width: 33%;"> <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) </div> <div style="width: 33%;"> <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>) <div style="border: 1px solid black; height: 15px; width: 100%;"></div> </div> </div>				
REVIEW ACTION				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail) </div> <div style="width: 33%;"> <input type="checkbox"/> Oral communication with Name: [] <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: [] </div> <div style="width: 33%;"> <input type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): <div style="border: 1px solid black; height: 15px; width: 100%;"></div> </div> </div>				
REVIEW COMMENT(S)				
<input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR				
<p>Ozurdex® (dexamethasone intravitreal implant, 700 mcg) is approved for the treatment of macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), and non-infectious uveitis affecting the posterior segment of the eye. The sponsor submitted this efficacy supplement to seek approval of Ozurdex® 700 mcg for the treatment of diabetic macular edema (DME), based mainly on the clinical efficacy and safety findings of two multicenter, blinded, randomized, sham-controlled Phase 3 trials involving 1,048 DME patients who received up to 7 Ozurdex® intravitreal injections during the 3-year study period. In a subset of DME patients in these two trials, plasma dexamethasone concentrations were measured up to 90 days following the administration of the first Ozurdex® intravitreal injection. The sponsor proposes to update (b) (4) of the Ozurdex® USPI with plasma PK data obtained from DME patients, as follows. See Part II of this action sheet for the Clinical Pharmacology reviewer's labeling recommendations.</p> <div style="background-color: #cccccc; height: 150px; width: 100%; margin-top: 10px;">(b) (4)</div>				

A total of 21 DME patients were included in the PK substudies of Phase 3 Studies 206207-010 and 206207-011; 10 patients received Ozurdex® 700 mcg and 11 patients received 350 mcg. Plasma dexamethasone concentrations were measured at baseline (prior to dosing) and on days 1, 7, 21, 45, and 90 following the first Ozurdex® intravitreal injection. Ninety percent (47/52) of the samples obtained from those who received 700 mcg and 100% (60/60) of the samples obtained from those who received 350 mcg had plasma dexamethasone concentrations that were below the lower limit of quantitation (LLOQ = 50 pg/mL) of the HPLC/MS/MS assay. The highest plasma concentration was 120 pg/mL, observed on day 7 following one intravitreal injection of Ozurdex® 700 mcg. [As per the sponsor, this particular plasma dexamethasone concentration is 1.13% of the plasma dexamethasone concentration following multiple ocular application of 1 drop of dexamethasone disodium phosphate (0.1%) to one eye every 1.5 hours (Weijtens et al, 2002).] At 90 days post-injection (the last collection timepoint), all plasma samples of DME patients had dexamethasone concentrations below LLOQ. Note that the HPLC/MS/MS assay used to measure plasma dexamethasone concentrations following Ozurdex® injection in DME patients was the same validated PK assay as that used previously in RVO patients. The plasma dexamethasone exposures in DME patients were similar to those observed in BRVO/CRVO patients following the first Ozurdex® injection.

Note also that the reported overall rates of non-ocular adverse events in DME patients in the pooled Phase 3 trials was not different between Ozurdex® 700 mcg and 350 mcg patients (70% and 69%, respectively), suggesting the lack of an apparent relationship between Ozurdex® dose and systemic toxicity.

II. LABELING RECOMMENDATIONS:

The Clinical Pharmacology reviewer’s deleted text is marked with a strikethrough; added text is marked with an underscore.

(b) (4)



SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC: <reviewer>, <team leader>, <dep dir>, <dir>, <MO>, <MO TL>, <PM>	

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

/s/

GERLIE GIESER
07/22/2013

PHILIP M COLANGELO
07/22/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 22-315	Brand Name	OZURDEX®
OCP Division (I, II, III, IV, V)	DCPIV	Generic Name	dexamethasone
Medical Division	DTOP	Drug Class	corticosteroid
OCP Reviewer	Gerlie Gieser, Ph.D.	Indication(s)	Treatment of diabetic macular edema (DME)
OCP Team Leader	Philip Colangelo, PharmD, PhD	Dosage Form	Injection/implant
Pharmacometrics Reviewer	-	Dosing Regimen	0.7 mg (b) (4)
Date of Submission	13 June 2013	Route of Administration	For injection into the posterior segment of the eye (b) (4) using a specially designed applicator
Estimated Due Date of OCP Review	09 March 2014	Sponsor	Allergan
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	13 April 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-	DME patients			
single dose:	X			PK substudies of primary Phase 3 trials 206207-010 (n=15) and 206207-011 (n=15)
multiple dose:				
Dose proportionality -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	2			

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical	X			same PK assay as that used for RVO studies (crossreference to GSRev SN-003 New NDA, 12/24/2008)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	assay?				
5	Has a rationale for dose selection been submitted?	X			Per sponsor: Both 0.700 mg and 0.350 mg effective but higher dose showed greater and more consistent response/efficacy; no significant dose-dependence of AEs. Thus, choose 0.700 mg to maximize therapeutic benefit.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	Majority of PK samples BLOQ; summary tables for individual patient concentration data provided as CSR appendices
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	No diff. between high dose and low dose groups in terms of non-ocular AE rates; plasma PK data limited to first 3 months after first OZURDEX injection
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Sites of action and administration are local thus, plasma PK not relevant for efficacy determination
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Full waiver of ped. research studies requested since DME is not common in children
16	Did the applicant submit all the pediatric			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	exclusivity data, as described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Gerlie Gieser, PhD

28 June 2013

Reviewing Clinical Pharmacologist

Date

Philip Colangelo, PharmD, PhD

11 July 2013

Team Leader/Supervisor

Date

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

/s/

GERLIE GIESER
07/12/2013

PHILIP M COLANGELO
07/12/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022315Orig1s009

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff – Maternal Health Memorandum

Date: June 27, 2014

Date Consulted: March 27, 2014

From: Melissa S Tassinari, PhD, DABT, Senior Clinical Advisor
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader- Maternal Health
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Transplant and Ophthalmology Products (DTOP)

NDA: 22315/S-009

Drug: Ozurdex (dexamethasone intravitreal implant)

Sponsor: Allergan, Inc.

Materials Reviewed: Proposed labeling, nonclinical review (3/12/14), efficacy supplement (6/12/13), and selected literature

Consult Request: We would like some advice regarding how best to address dose/exposure multiples and communicate risk in section 8.1 of the label.

Introduction

Ozurdex (dexamethasone intravitreal implant, NDA 22315), was approved on June 17, 2009, for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Subsequently, Ozurdex was approved on September 24, 2010, for the treatment of non-infectious uveitis affecting the posterior segment of the eye (NDA 22-315/S-003). This efficacy supplement is for an indication of diabetic macular edema (NDA 22315/S009).

The Division of Transplant and Ophthalmology Products (DTOP) consulted the Pediatric and Maternal Health Staff- Maternal Health Team (PMHS-MHT) to review the Pregnancy and Nursing Mothers subsections of labeling and provide recommendations on how best to address dose/exposure multiples and communicate risk for Ozurdex.

This PMHS-MHT consult includes recommendations and suggested revisions for the labeling based on review of the proposed labeling, nonclinical review (3/12/14), efficacy supplement (6/12/13), and selected literature.

Background

Ozurdex (dexamethasone intravitreal implant) is an intraocular drug delivery system. The active ingredient is dexamethasone. Dexamethasone is combined with biodegradable polymers as a small implant for delivery into the posterior segment of the eye through a specifically designed applicator.

Dexamethasone is a synthetic corticosteroid used to treat inflammatory disorders. Corticosteroids have been shown to be teratogenic in animal species, particularly mice, when given during organogenesis (first trimester) with the principal birth defect being cleft palate. Epidemiological studies have shown some association with oral clefting with human exposure to corticosteroids. However, small epidemiology studies looking at maternal dexamethasone use in the first trimester have not shown an increased incidence of birth defects.¹

¹ TERIS

http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidenceexpert/CS/4BC247/ND_AppProduct/evidenceexpert/DUPLICATIONSHIELDSYNC/236B80/ND_PG/evidenceexpert/ND_B/evidenceexpert/ND_P/evidenceexpert/PFActionId/evidenceexpert.IntermediateToDocumentLink?docId=1643&contentSetId=3&title=DEXAMETHASONE&servicesTitle=DEXAMETHASONE&topicId=null Accessed 6/27/2014

REPROTOX

http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidenceexpert/CS/31456A/ND_AppProduct/evidenceexpert/DUPLICATIONSHIELDSYNC/1D6DAF/ND_PG/evidenceexpert/ND_B/evidenceexpert/ND_P/evidenceexpert/PFActionId/evidenceexpert.IntermediateToDocumentLink?docId=1381&contentSetId=35&title=DEXAMETHASONE&servicesTitle=DEXAMETHASONE&topicId=null Accessed 6/27/2014

Discussion

No additional non-clinical studies were submitted with this application. The studies reported in the pregnancy subsection of the labeling are found in other FDA approved labeling for dexamethasone. These studies were conducted via a topical route that is different than the proposed route of administration for Ozurdex. According to the Pharmacology/ Toxicology NDA Review, these studies have not been formally reviewed by the FDA. However, published reports of the studies were reviewed by the DTOP staff. Adequate animal exposure data are not available; consequently the human dose equivalents were determined based on a mg/m^2 basis. The resulting calculations, based on BSA scaling and assumptions of average animal (rabbit and mouse) resulted in values of 4 and 3 times, respectively, the human dose from the intravitreal injection of dexamethasone (0.7 mg). The human systemic concentration of dexamethasone following intravitreal treatment with OZURDEX[®] is low. As noted in section 12.3, Clinical Pharmacology, the majority of systemic dexamethasone concentrations after the intravitreal implants were below the limits of quantitation (LLOQ = 50 pg/mL).

The limited systemic availability of dexamethasone via ophthalmic applications are not expected cause adverse reactions in a breast fed infant.²

Reviewer Comment:

We generally expect that the exposures for the animal studies are noted in terms of human exposure equivalents. Systemic exposures are preferred but dose exposure comparisons may be used when systemic exposure data are not available. In this case, however, the animal data are from studies using an alternate route making the dose exposure calculations less relevant and there no available systemic exposures that could be compared to the information we had on this particular product. For that reason, the human dose equivalents will not be included in the Risk Summary. A more complete description of the animal data, including the human dose equivalent should be included in the animal data section. In the Nursing Mother's subsection,

(b) (4)

Conclusions

The intravitreal implant releases local concentrations of dexamethasone that acts on the inflammation in the eye during the condition of diabetic macular edema. Given the evidence of low systemic availability of dexamethasone from the implant, the likelihood of systemic exposure from Ozurdex treatment leading to the potential for teratogenic risk appears low.

Recommendations

PMHS- MHT discussed the labeling with DTOP Pharmacology Toxicology. Final labeling is subject to negotiations with the applicant and may not fully reflect changes suggested here. See the final approved labeling in DARRTS, which will be appended to

² LACTMED. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?/.temp/~budOrc:2> Accessed 6/27/2014

the approval letter. The following are the PMHS-MHT's recommendations for Ozurdex Pregnancy and Nursing Mothers labeling.

(b) (4)



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

/s/

MELISSA S TASSINARI
06/27/2014

JEANINE A BEST
06/27/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 22315 BLA#	NDA Supplement #:S- 009 BLA Supplement #	Efficacy Supplement Type SE- 1
Proprietary Name: Ozurdex Established/Proper Name: dexamethasone Dosage Form: intravitreal implant Strengths: 0.7 mg		
Applicant: Allergan, Inc. Agent for Applicant (if applicable):		
Date of Application: 6/12/13 Date of Receipt: 6/13/13 Date clock started after UN:		
PDUFA Goal Date: 4/13/14		Action Goal Date (if different):
Filing Date: 8/12/13		Date of Filing Meeting: 7/19/13
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): treatment of diabetic macular edema		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 58663				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p> <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required </p>
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p> <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears </p>

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm </p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 9/8/03	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

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

/s/

MICHAEL J PUGLISI
03/25/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 20, 2014

To: Michael Puglisi, Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA #022135
Ozurdex[®] (dexamethasone intravitreal implant)

As requested in your consult dated July 30, 2013, the Office of Prescription Drug Promotion (OPDP) has reviewed the proposed draft labeling (PI) for Ozurdex[®] (dexamethasone intravitreal implant).

OPDP's comments on the PI are based on the substantially complete version of the PI titled, "NDA 22315S009.docx" which was received via email from DTOP on March 19, 2014.

OPDP's comments on the PI are attached in the clean substantially complete version of the labeling.

If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or at christine.corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this proposed labeling.

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

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/s/

CHRISTINE G CORSER
03/20/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 10, 2014

TO: Lucious Lim, Medical Officer
William Boyd, Clinical Safety Reviewer
Michael Puglisi, Regulatory Project Manager
Division of Transplant and Ophthalmology Products

FROM: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-315/SE1-009

APPLICANT: Allergan Inc.

DRUG: Ozurdex (dexamethasone intravitreal implant)
NME: No
THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of diabetic macular edema

CONSULTATION REQUEST DATE: July 15, 2013
INSPECTION SUMMARY GOAL DATE: February 13, 2014
DIVISION ACTION GOAL DATE: March 13, 2014
PDUFA DATE: April 13, 2014

I. BACKGROUND:

Macular edema is a nonspecific response of the retina which involves breakdown of the inner blood-retinal barrier at the level of the capillary endothelium, resulting in abnormal retinal vascular permeability and leakage into the adjacent tissues. The macula becomes thickened due to fluid accumulation resulting in significant disturbances in visual acuity. Prolonged edema can cause irreversible damage, resulting in permanent visual loss. Macular edema may occur in diseases causing cumulative injury over many years, such as diabetic retinopathy. Focal/grid laser photocoagulation has been shown to be efficacious in the prevention of mild to moderate vision loss from macular edema due to diabetic retinopathy. The sponsor claims that there is evidence supporting the efficacy of intraocular steroids for the treatment of macular edema. However, topical use of steroids has yielded limited success in treating retinal disorders including macular edema, largely due to inability to deliver and maintain adequate quantities of the drug to the posterior segment.

The DEX PS DDS Applicator System contains dexamethasone that is released over time to provide a total dose of approximately 350 µg or 700 µg. The DEX PS DDS is injected into the posterior segment of the eye using a specially designed applicator. The polymer gradually degrades over time so that there is no need to remove the implant. Systemic routes of administration require much higher daily doses of dexamethasone to obtain equivalent levels of drug into the posterior segment of the eye. The present application contains the results of two phase 3 studies to support the indication of treatment of diabetic macular edema (DME).

A brief synopsis of the protocols, for which the review division has requested clinical investigator inspections, is given below.

Protocol 206207-010: A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

This was a randomized, masked trial of DEX PS DDS efficacy compared with sham in the treatment of diabetic macular edema which was conducted at 59 study centers in 10 countries. The primary objective of the study was to evaluate the efficacy and safety of the 700 µg DEX PS DDS Applicator System and 350 µg EEX PS DDS Applicator System compared with a sham DEX PS DDS Applicator System in patients with DME.

Included in the study were male or female subjects, at least 18 years of age, with a diagnosis of diabetes mellitus (type 1 or type 2), clinically observable macular edema involving the center of the macula (fovea) associated with diabetic retinopathy, best-corrected visual acuity (BCVA) score between 34 and 68 letters in the study eye, and retinal thickness of > 300 µm by optical coherence tomography (OCT). After the qualification/baseline visit, the randomization (Day 0) visit, at which patients received the first treatment, occurred within 4 to 14 days. Retreatment criteria were assessed every 3 months at a study-scheduled visit from month 6 through month 36. Patients were eligible for retreatment if retinal thickness in the 1 mm central macular subfield by OCT was >175 µm (determined by the site) or upon investigator interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the center subfield). The duration of treatment was three years. Starting from the month six visit, patients were evaluated for retreatment eligibility every three months and could have received up to six additional retreatments of the same assigned study medication, but the study treatment procedure was not to be performed more often than approximately every 6 months. The primary efficacy variable was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at the final assessment with missing values imputed by last observation carried forward. Safety measurements included adverse events, BCVA, IOP, biomicroscopic and ophthalmoscopic findings, systolic and diastolic blood pressure, pulse rate, pregnancy test, residual DEX PS DDS assessment, HbA1c level, glomerular filtration rate (GFR), and endothelial cell density.

Brief Summary of Results

A total of 494 patients were randomized and enrolled into the study; of these, 65.6% (107/163), 71.1% (118/166), and 42.4% (70/165) of patients in the DEX 700 group, DEX 350 group, and sham group, respectively, completed the 3-year study. By year 3/exit, 40.3% (199/494) of patients discontinued the study: 34.4% (56/163) in the DEX 700 group, 28.9% (48/166) in the DEX 350 group, and 57.6% (95/165) in the sham group.

The proportion of patients with 15 or more letters BCVA improvement from baseline was significantly higher with DEX 700 (22.1%) compared with sham (13.3%) at year 3. The mean BCVA average change from baseline during the study was also significantly greater with DEX 700 compared with sham. According to the sponsor, the DEX PS DDS Applicator System was well tolerated with an acceptable 3-year safety profile with DEX 700 for up to 7 treatments; the safety profiles were similar between the DEX 700 and DEX 350 groups. Approximately 40% of patients in the DEX groups used IOP-lowering agents and only 2 patients required trabeculectomy to control elevated IOP.

Protocol 206207-011: A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

This was a randomized, masked, sham-controlled trial of DEX PS DDS efficacy compared with sham in the treatment of diabetic macular edema which was conducted at 72 study centers in 14 countries. The primary objective of the study was to evaluate the efficacy and safety of the 700 µg DEX PS DDS Applicator System and 350 µg EEX PS DDS Applicator System compared with a sham DEX PS DDS Applicator System in patients with diabetic macular edema (DME).

Inclusion, exclusion, and retreatment criteria were identical to Study 206207-010. Also identical to Study 206207-010 were treatment duration, primary efficacy variable, and safety measurements.

Brief Summary of Results

A total of 554 patients were randomized and enrolled into the study; of these, 62.68 (118/188), 61.9% (112/181), and 44.3% (82/185) of patients in the DEX 700 group, DEX 350 group, and sham group, respectively, completed the 3-year study. By year 3/exit, 43.7% (242/554) of patients discontinued the study: 37.2% (70/188) in the DEX 700 group, 38.1% (69/181) in the DEX 350 group, and 55.7% (103/185) in the sham group.

The proportion of patients with 15 or more letters BCVA improvement from baseline was significantly higher with DEX 700 (22.3%) compared with sham (10.8%) at year 3. The mean BCVA average change from baseline during the study was greater with DEX 700 compared with sham, but was not statistically significant. According to the sponsor, the DEX PS DDS Applicator System was well tolerated with an acceptable 3-year safety profile with DEX 700 for up to 7 treatments; the safety profiles were similar between the DEX 700 and DEX 350 groups. Less than 40% of patients in the DEX groups used IOP-lowering agents, and no subjects required surgical procedures to control elevated IOP.

II. RESULTS (by Site):

Name of CI	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
Glenn L. Wing, M.D. National Ophthalmic Research Institute 6901 International Center Blvd. Ft. Myers, FL 33912	Protocol # 206207-010 Site #10024 14 subjects	August 26 – September 12, 2013	NAI
Kenneth Sall, M.D. Sall Research Medical Center 11423 187 th Street, Suite 200 Artesia, CA 90701	Protocol #206207-011 Site #10022 68 subjects	September 3 – 11, 2013	VAI
Steven Rose MD Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618	Protocol #206207-011 Site #10021 15 subjects	October 15 – 21, 2013	NAI
Allergan, Inc. 2525 Dupont Drive Irvine, CA 92612-1599	Protocols # 206207-010 and 206207-011	December 12 – 23, 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

The sites of Dr. Sell and Wing were chosen for inspection because they were the highest domestic enrollers in each of the two pivotal studies. Dr. Rose's site is the second site chosen for inspection for Protocol 206207-011. Dr. Sell's site was selected for inspection enrolled the largest number of subjects at a domestic site. It was decided to inspect a second site for this protocol because there was an employee at the initial site who had previously been accused of inappropriately enrolling subjects, without definitive evidence that such events occurred again. An inspection of the sponsor Allergan is requested because this entity has never been inspected and due to the serious nature of Dr. Sall's employee's regulatory violations. Although the employee is no longer at the site and the allegations have been previously investigated by the Los Angeles District Office and the IRB, it is important to ensure that monitoring for these two studies were adequate.

- a. Glenn L. Wing, M.D.**
National Ophthalmic Research Institute
6901 International Center Blvd.

Ft. Myers, FL 33912

- a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. This inspection was performed as a data audit for NDA 22-315 SE1-009. This site has not been previously inspected. At this site, 18 subjects were screened, 14 subjects were enrolled in the study, and 10 subjects completed the study. Of the 14 subjects enrolled, 4 did not complete the study due to personal reasons, debilitating diabetic retinopathy/lack of efficacy, or pregnancy.
- b. General observations/commentary: An audit of 14 subjects' records was conducted. All 14 subjects signed the informed consent document; however 7 of the 14 enrolled subjects did not sign the latest IRB approved version of the Informed Consent Form on the next immediate visit. The amended protocol did not contain any notable treatment changes which would put the study subjects' health or safety at risk. No other significant regulatory violations were noted.
- c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Kenneth Sall, M.D.**
Sall Research Medical Center
11423 187th Street, Suite 200
Artesia, CA 90701

- a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. This inspection was performed as a data audit for NDA 22-315/SE1-009. There have been three previous inspections at this site: two classified as NAI and one as VAI for failure to adhere to the protocol. At this site, 100 subjects were screened, 68 subjects were randomized, and 31 subjects completed the study. Included in the investigation were IRB record review, 100% Subject Informed Consent review, comparison of source records with data listings, concomitant medications and procedures, test drug accountability, and monitoring records.

During a previous for cause inspection at this site, falsification of study records occurred, allegedly by an employee at the site whose employment has since been terminated. This site was chosen for inspection for the current study because Dr. Sall was the highest domestic enroller. Upon initiation of the inspection, Dr. Sall informed the inspector of these facts, and noted that the same employee had been involved in enrolling subjects into the current study. At the time of the previous inspection, Dr. Sall reviewed his research, and reported the findings reported to the Sponsor, the IRB, and the FDA.

- b. General observations/commentary: An audit of 22 subjects' records was conducted; these were the subjects that Dr. Sall had previously identified as containing fraudulent or potentially data. Inspection revealed failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, there were several discrepancies in source documentation, which were also noted by the Principal Investigator during the course of the study.
- i. The protocol requires that there be retinal thickness of ≥ 300 μm by OCT (Optical Coherence Tomography) scan in the 1 mm central macular subfield of the study eye at qualification/baseline as determined the by the investigator. The following randomized subjects' printed baseline OCT scans have been substituted for another individual's scan that does not resemble the same subject. The investigator based this on the difference in appearance of the blood vessel patterns present that can be visualized on some of the OCT scans compared to the same subject's fundus pictures that were also performed at baseline:

Subject #	Eye (OD, OS)	Study Arm (DEX 350, DEX 700, Sham)
7105	OD	DEX 350
7106	OD	DEX 350
7123	OS	SHAM
7144	OS	DEX 700
7146	OS	SHAM
7147	OS	DEX 350
7622	OS	SHAM
7819	OD	DEX 700

In addition, there were 11 additional subjects who had Baseline OCT scans that could not clearly reveal a blood vessel pattern for comparison, although the scans did reveal macular edema. These OCT scans were considered by Dr. Sall to be unconfirmed. These subjects are 7118, 7121, 7143, 7359, 7360, 7362, 7620, 7621, 7625, 7818, and 7920.

- ii. The following BCVA (Best Corrected Visual Acuity) record were observed and suspected to be falsified according to Dr. Sall: Subject 7622 and 7819. In addition, the suspected employee conducted virtually all the BCVA scores until the point of her termination, which is up to 20 individual BCVA evaluations per subject for 68 subjects.

There were no other regulatory findings identified during this inspection. Dr. Sall adequately responded to the inspection findings most recently in a letter dated

September 22, 2013. He described his investigations of the fraudulent activities, subsequent actions and communications with FDA, and noted that this was the last study that this employee was involved with at this site.

- c. Assessment of data integrity: Because there is demonstrated fraud at this site involving an individual no longer employed with Dr. Sall, the reliability of the data at this site cannot be verified. OSI recommends that the data from this site be excluded from safety and efficacy analysis. Of note, Dr. Sall has already taken measures to address the issues described.

3. **Steven Rose MD**
Rochester Ophthalmological Group, PC
2100 South Clinton Avenue
Rochester, NY 14618

- a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. This inspection was performed as a data audit for NDA 22-315 SE1-009. There were no previous INDs associated with the inspected entity in CDER's database, and there were no previous inspections. At this site, 27 subjects were screened, and 15 of these were randomized and enrolled in the study. One additional subject was transferred from another site. Eleven subjects completed the study and 5 subjects discontinued early, primarily because the treating investigator thought that the subject would benefit from alternative treatment(s).
- b. General observations/commentary: An audit of all 16 subjects' records was conducted. No significant regulatory violations were noted. Minor protocol violations noted were enrollment of a subject with an excluded glomerular filtration rate due to a sponsor miscalculation; this was reported to the IRB and a waiver was granted for continuing in the study. Also, one study subject received the study drug outside the protocol timeframe for retreatment: the protocol required that the study drugs should be administered no more often than every six months. Study Subject #7070 received study drug 166 days apart. Both of these regulatory violations are minor, isolated, and unlikely to impact study outcome.
- c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. **Allergan, Inc.**
2525 Dupont Drive
Irvine, CA 92612

- a. What was inspected: This sponsor inspection was issued to review the conduct of clinical studies performed in support of NDA 22-315 SE1 009 Ozurdex. The purpose of the inspection, which was conducted in accordance with the Sponsor/Monitor/Contract

Research Organization (CRO) compliance program, was to evaluate sponsor conduct, especially monitoring, of clinical study conduct.

The inspection audited Protocols 206207-010 and 206207-011, and focused on the following clinical investigators: Dr. Glenn Wing (Florida, Protocol 010), Dr. Kenneth Sall, (California, Protocol 011) and Dr. Steven Rose (New York, Protocol 011).

Evaluated during the inspection were selection and monitoring of clinical investigators. The inspection reviewed the following quality assurance and clinical operations, study monitoring procedures, records and reports, data safety monitoring board documentation, informed consents, participating clinical investigators, IRB documentation, data collection, and study drug accountability.

- b. General observations/commentary: No significant observations of noncompliance were noted. A Form FDA 483, Inspectional Observations, was not issued at the end of inspection. In particular, no issues with monitoring were noted. There were two discussion items.
 - i. The inspector thought that the sponsor demonstrated inadequate investigation of Dr. Sall's reporting of substituted records. However, after initial discovery, Dr. Sall exhaustively examined records which may have been altered by the employee in question. He subsequently provided to FDA and Allergan the results of his analysis.
 - ii. Incomplete records of test article disposition. There were no records of return and destruction for all test articles except for what was returned to Allergan in Irvine. Allergan stated that all records exist; however they were maintained globally. The firm agreed to provide an accurate reconciliation to the inspector within 15 days. Allergan submitted their response in writing on January 9, 2014. In this response was provided confirmation that the investigational product not dosed during the course of these studies has been removed from investigational sites. However, available records were not able to provide the necessary detail to confirm destruction of all investigational returns from all regions.
- c. Assessment of data integrity: The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of NDA 22-315 SE1-009, as well as the sponsor Allergan. There were no significant regulatory violations at the sites of Drs. Wing and Rose. At Dr. Sall's site, which was chosen because the most domestic subjects were enrolled in Study 011, evidence of fraud was described. Substitution of OCT scans to ensure that subjects met inclusion criteria was noted, as well as falsification of BCVA values by an employee was observed during a previous inspection, and this

employee also participated in Study 011. The employee has since left the firm, and Dr. Sall has taken corrective action to prevent such occurrences in the future. However, OSI cannot endorse data integrity and subject safety at Dr. Sall's site. Inspection of the sponsor did not reveal significant regulatory violations. In particular, monitoring appeared to be adequate. The data from the two sites inspected as well as from the sponsor may be considered reliable.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN D THOMPSON
02/10/2014

KASSA AYALEW
02/10/2014

DSI CONSULT: Request for Clinical Inspections

Date: July 15, 2013

To: Susan Thompson, M.D., Acting Branch Chief, GCP
Kassa Ayalew, Medical Officer, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Lucious Lim, MD, Medical Officer, 301-796-0749
Division of Transplant and Ophthalmology Products

From: Michael Puglisi, Regulatory Health Project Manager, 301-796-0791
Division of Transplant and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#:	NDA 22-315/SE1-009
Applicant/ Applicant contact information:	Allergan, Inc. 2525 Dupont Drive Irvine, CA 9261 2-1599 Contact: James McAllister, MBA Manager, Global Regulatory Development Tel 1-714-216-2343
Drug:	Ozurdex (dexamethasone intravitreal implant)
NME:	No
Review Priority:	No
Study Population includes < 17 years of age:	No
Is this for Pediatric Exclusivity:	No
Proposed Indication:	treatment of diabetic macular edema
PDUFA:	April 13, 2014
Action Goal Date:	March 13, 2014
Inspection Summary Goal Date:	February 13, 2014

II. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Randomized	Indication
DSI Choice	206207-010	494	treatment of diabetic macular edema
DSI Choice	206207-011	554	treatment of diabetic macular edema

III. Site Selection/Rationale

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

An inspection is requested for at least one site for each of these clinical trials only as your resources permit.

Note that the highest DOMESTIC enrollers in Study 206207-010 are: Raj Maturi, MD (11), and Glenn Wing, MD (14).

Note that the highest DOMESTIC enrollers in Study 206207-011 are: Kenneth Sall, MD (68), Bernard Doft, MD (18), and Steven Rose, MD (15).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ☐ Enrollment of large numbers of study subjects
- ☐ High treatment responders (specify):
- ☐ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☒ Other (specify): Routine Inspections

International Inspections:

Reasons for inspections (please check all that apply):

- ☐ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☐ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Goal Date for Completion:

We request that the inspections be performed and that the Inspection Summary Results be provided by February 13, 2014. We intend to issue an action letter on this application by March 13, 2014. The PDUFA due date for this application is **April 13, 2013**.

Should you require any additional information, please contact Michael Puglisi at 301-796-0791 or Lucious Lim, MD at 301-796-0749.

Additional Information:

This is an electronic NDA. The List and Description of Investigators for the previously identified studies are provided below.

Study 206207-010: A 3-Year, Phase 3, Multicenter, Masked, Randomized,

Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Juan Orellana, MD (10017/ 0448) Department of Ophthalmology Virginia Commonwealth University 401 North 11th Street Nelson Clinic, 4th Floor, Room 437 Richmond, VA 23219 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4085, 4086
Itamar Klemperer, MD (13302/ 2341) Soroka University Medical Center Outpatient Eye Clinic POB 151 Beer Sheva, 84101 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	9	4343, 4344, 4346, 4345, 4347, 4348, 4349, 4350, 4351
Petrus Gous, MD (15207/ 3084) Pretoria Eye Institute 630 Schoeman Street Arcadia Pretoria, 0007 SOUTH AFRICA	(b) (6) (subinvestigator) (b) (6) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	12	5012, 5013, 5014, 5015, 5016, 5017, 5018, 5019, 5020, 5045, 5046, 5047
Stefanie Schmickler, MD (12513/ 3193) Augenarzte Gemeinschaftspraxis Domhof 15 D-48683 Ahaus GERMANY	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	5261, 5262, 5263, 5264, 5265, 5266, 5282
Stewart Lake, MD (10705/ 6354) Department of Ophthalmology Flinders Medical Centre Flinders Drive Bedford Park, SA 5042 AUSTRALIA <i>replaced Russell Phillips, MD, FRCOphth (10705/ 3395) who was investigator from 29Aug2005 to 05Jul2007 at the same address</i>	(b) (6) (subinvestigator) (b) (6) (subinvestigator under R. Phillips, MD, FRCOphth) (b) (6) (subinvestigator)	0	

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Gil Sartani, MD (13301/ 3983) HaEmek Medical Center Ophthalmology Department Afula, 18101 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	10	4289, 4290, 4291, 4292, 4293, 4294, 4295, 4296, 4297, 4298
Joel Corwin, MD (10004/ 4082) Miramar Eye Specialists Medical Group 3085 Loma Vista Road Ventura, CA 93003 USA	(b) (6) (subinvestigator)	2	4025, 4026
Andrew Antoszyk, MD (10001/ 4221) Charlotte Eye Ear Nose & Throat Associates, PA 6035 Fairview Road Charlotte, NC 28210 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	4019, 4020, 4021, 4022, 4023, 4024, 4103
David M. Brown, MD (10003/ 4231) Vitreoretinal Consultants 6560 Fannin Street, Suite 750 Houston, TX 77030 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4001, 4002
Robert G. Devenyi, MD (11302/ 4241) The University Health Network Toronto Western Hospital 399 Bathurst Street New East Wing, 6th Floor, Room 438 Toronto, ONT M5T 2S8 CANADA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	4184
Richard Dreyer, MD (10005/ 4243) Retina Northwest PC 2525 NW Lovejoy Suites 300, 305, 100 Portland, OR 97210 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	4124

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Gregory M. Fox, MD (10007/ 4250) Retina Associates PA 9301 West 74th Street, Suite 210 Shawnee Mission, KS 66204 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	4061, 4062, 4063, 4064, 4065, 4066, 4193
David Glaser, MD (10008/ 4252) Retina Associates of St. Louis 1224 Graham Road, Suite 3011 Florissant, MO 63031 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	4112, 4113, 4114, 4115
Lawrence Halperin, MD (10010/ 4256) Retina Group of Florida 5601 North Dixie Highway, Suite 307 Ft. Lauderdale, FL 33334 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	5	4067, 4068, 4070, 4071, 4072
Dennis Han, MD (10011/ 4258) Eye Institute/Medical College of Wisconsin 925 North 87th Street Milwaukee, WI 53226 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	4007, 4008, 4009, 4010
Raj K. Maturi, MD (10014/ 4277) Midwest Eye Institute 200 West 103rd Street, Suite 1060 Indianapolis, IN 46290 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	11	4013, 4014, 4015, 4017, 4018, 4130, 4131, 4132, 4169, 4170, 4171

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
James Miller, Jr., MD (10015/ 4280) Southeastern Retina Associates, PC 20202 Kay Street Knoxville, TN 37920 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	4037, 4038, 4040
James Peace, MD (10019/ 4288) United Medical Research Institute 431 North Prairie Avenue Inglewood, CA 90301 USA	(b) (6) (subinvestigator)	7	4106, 4107, 4109, 4108, 4110, 4111, 4157
Glenn L. Wing, MD (10024/ 4311) National Ophthalmic Research Institute 6901 International Center Boulevard Fort Myers, FL 33912 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	14	4073, 4074, 4075, 4076, 4077, 4078, 4535, 4536, 4537, 4556, 4557, 4558, 4628, 4629
Ingrid E. Zimmer-Galler, MD (10025/ 4314) Wilmer Eye Institute John Hopkins University 600 North Wolfe Street Maumenee 749 Baltimore, MD 21287 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	4421

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
<p>Patrick L. Tsai, MD (10018/ 4316) University of Arizona Department of Ophthalmology and Vision Science 707 North Alvernon Way, 3rd Floor Tucson, AZ 85711 USA</p> <p><i>replaced John Nichols, MD (10018/ 4316) who was investigator from 10Jun2010 to 11Jun2010 at the same address</i></p> <p><i>J Nichols, MD replaced Robert Park, MD (10018/ 4316) who was investigator from 30Apr2010 to 10Jun2010 at the same address</i></p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator under P. Tsai, MD and R. Park, MD)</p>	2	4163, 4164
<p>Alan Cruess, MD (11301/ 4341) Capital Health 1276 South Park Street Suite 2035, Victoria West Building Halifax, NS B3H 2Y9 CANADA</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	9	4044, 4043, 4045, 4046, 4047, 4048, 4469, 4470, 4471
<p>Albert J. Augustin, MD, PhD (12507/ 4353) Staetisches Klinikum Department of Ophthalmology Moltkestrasse 90 D-76133 Karlsruhe GERMANY</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	11	4742, 4743, 4744, 4745, 4746, 4747, 5036, 5037, 5038, 5192, 5193
<p>Mark Daniell, MD (10707/ 4368) Ophthalmology Clinic Royal Melbourne Hospital Melbourne Health 1 South Grattan Street Parkville, VIC 3052 AUSTRALIA</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	7	4781, 4782, 4783, 4784, 4785, 4786, 4796

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Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Prof. Karl Ulrich Bartz-Schmidt (12508/ 4391) University Eye Hospital Tuebingen Schleichstrasse 12 72076 Tuebingen GERMANY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	4724, 4725, 4726
Jose Maria Ruiz Moreno, MD (12202/ 4396) Instituto Oftalmologico de Alicante- Vissum C/Cabanal, 1 03016 Alicante SPAIN	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	10	4580, 4581, 4582, 4583, 4584, 4585, 4763, 4764, 4765, 4793
Alvaro Fernandez-Vega Sanz, MD (12205/ 4397) Instituto Oftalmologico Fernandez- Vega Avenida Doctores Fernandez-Vega 114 33012 Oviedo SPAIN	(b) (6) (subinvestigator)	17	4829, 4830, 4831, 4832, 4833, 4834, 4964, 4965, 4966, 4994, 4995, 4996, 5021, 5022, 5023, 5027, 5028
Ramakrishna Ratnakaram, MD (10020/ 4411) University of Florida Department of Ophthalmology 1600 SW Archer Road Gainesville, FL 32610 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	4049
Marta Suarez-Figueroa, MD (12204/ 4416) Hospital Oftalmologico de Madrid- Vissum C/ Santa Hortensia, N°58 28002 Madrid SPAIN	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4586, 4588

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Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Judianne Kellaway, MD (10012/ 4431) Clinical Trials Unit 6400 Fannin Street, Suite 1910 Houston, TX 77030 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4097, 4098
Adiel Barak, MD (13303/ 4447) Department of Ophthalmology The Tel-Aviv Medical Center 6 Weizmann Street Tel Aviv, 64239 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	31	4307, 4308, 4309, 4310, 4311, 4312, 4313, 4316, 4314, 4315, 4317, 4318, 4319, 4320, 4321, 4322, 4323, 4324, 4952, 4953, 4954, 4955, 4956, 4957, 4958, 4959, 4960, 4961, 4962, 4963, 4973
Joseph R. Ferencz, MD (13304/ 4449) Meir Medical Center Eye Clinic 59 Tsharnichovsky Street Kfar-Saba, 44281 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	42	4253, 4254, 4255, 4256, 4257, 4258, 4259, 4260, 4261, 4262, 4263, 4264, 4265, 4266, 4267, 4268, 4269, 4270, 4373, 4374, 4375, 4405, 4403, 4404, 4631, 4632, 4633, 4658, 4659, 4660, 4685, 4686, 4687, 4757, 4758, 4759, 4769, 4770, 4771, 4838, 4839, 4840

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Joseph Moisseiev, MD (13306/ 4450) The Goldschleger Eye Institute The Sheba Medical Center Tel-Hashomer, 52621 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	4235, 4236, 4237, 4238
Prof. Ayala Pollack (13305/ 4451) Kaplan Medical Center Department of Ophthalmology PO Box 1 Rehovot, 76100 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	31	4271, 4272, 4273, 4274, 4275, 4276, 4277, 4278, 4279, 4280, 4281, 4282, 4283, 4284, 4285, 4286, 4287, 4288, 4442, 4443, 4444, 4571, 4572, 4573, 4616, 4617, 4618, 4625, 4626, 4627, 4739

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Dov Weinberger, MD (13307/ 4452) Eye Clinic Rabin Medical Center Campus Belinson Petach - Tikva, 49100 ISRAEL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	20	4325, 4326, 4327, 4328, 4329, 4330, 4331, 4332, 4333, 4334, 4335, 4336, 4337, 4338, 4339, 4340, 4341, 4342, 4614, 4615
Jiong Yan, MD (10030/ 4458) Emory University Eye Center 1365 B Clifton Road, NE Atlanta, GA 30322 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4367, 4368
John R. Gonder, MD (11304/ 4474) Ivey Eye Institute 268 Grosvenor Street London, ONT N6A 4V2 CANADA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	12	4118, 4119, 4120, 4121, 4122, 4123, 4142, 4143, 4144, 4181, 4182, 4183
Paul McCartney, MD (10703/ 4496) Department of Ophthalmology Hobart Eye Surgeons 182 Argyle Street Hobart, TAS AUSTRALIA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	4463

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
<p>Susanna Park, MD, PhD (10031/ 4514) UC Davis Medical Center Department of Ophthalmology 4860 Y Street, Suite 2400 Sacramento, CA 95817 USA</p> <p><i>replaced Lawrence Morse, MD, PhD (10031/ 4514) who was investigator from 15Mar2005 to 01Jul2005 at the same address</i></p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator under S. Park, MD, PhD) (b) (6) (subinvestigator under L. Morse, MD, PhD) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	6	4379, 4380, 4381, 4383, 4382, 4384
<p>Henry Newland, MD (10704/ 4520) Royal Adelaide Hospital Department of Ophthalmology North Terrace Adelaide, SA 5000 AUSTRALIA</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	2	4445, 4446
<p>Richard B. Rosen, MD (10026/ 4539) New York Eye and Ear Infirmary 310 East 14th Street, Suite 319 South Building New York, NY 10003 USA</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	3	4385, 4386, 4387
<p>Oliver Zeitz, MD (12511/ 5295) Universitätsklinikum Hamburg-Eppendorf Klinik und Poliklinik für Augenheilkunde Martinistrasse 52 20246 Hamburg GERMANY</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	0	

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Ivan Fiser, MD (11704/ 6413) Cornea Lexum Eye Clinic Visnova 25/1957 140 00 Prague 4 CZECH REPUBLIC	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	4475, 4476, 4477
Jiri Rehak, MD, CSc (11702/ 6415) University Hospital Olomouc Department of Ophthalmology I.P. Pavlova 6 775 20 Olomouc CZECH REPUBLIC	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	12	4481, 4482, 4483, 4484, 4485, 4486, 4688, 4689, 4690, 4826, 4827, 4828
Jan Studnicka, MD, PhD (11705/ 6417) Fakultni nemocnice Hradec Kralove Ocni klinika Sokolska 581 500 05 Hradec Kralove CZECH REPUBLIC	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	8	4493, 4494, 4495, 4496, 4497, 4498, 4844, 4845
Igor Vicha, MD (11703/ 6418) Fakultni nemocnice Brno Ocni klinika Jihlavská 20 625 00 Brno CZECH REPUBLIC	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	25	4499, 4500, 4501, 4502, 4503, 4504, 4670, 4671, 4672, 4736, 4737, 4835, 4836, 4837, 4853, 4854, 4855, 4883, 4884, 4885, 4738, 4886, 4887, 4888, 4889
Bohdana Kalvodova, MD, PhD (11701/ 6652) General Teaching Hospital, Ophthalmology Clinic U nemocnice 2 128 08 Prague 2 CZECH REPUBLIC	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	4505, 4506, 4507, 4508
James Acton, MD (15201/ 6653) 7A Oosterzee Street Belville Cape Town, 7530 SOUTH AFRICA	(b) (6) (subinvestigator)	7	4652, 4653, 4654, 4655, 4656, 4657, 4697

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Linda Visser, MD (15206/ 6654) Department of Ophthalmology Nelson R Mandela School of Medicine University of Kwazulu Natal Durban, 4001 SOUTH AFRICA <i><u>Patients were seen and treated at:</u></i> Inkosi Albert Luthuli Central Hospital 800 Bellair Road Cato Manor Durban, 4058 SOUTH AFRICA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	4982, 4983, 4984
Trevor Carmichael, MD (15202/ 6655) Wits Donald Gordon Medical Centre Eton Road, Parktown Johannesburg, 2157 SOUTH AFRICA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	12	4664, 4665, 4666, 4667, 4668, 4669, 4679, 4680, 4681, 4748, 4749, 4750
Joao Figueira, MD (14501/ 6685) AIBILI Azinhaga de Santa Comba-Celas 3000-548 Coimbra, PORTUGAL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	18	4691, 4692, 4693, 4694, 4695, 4696, 4790, 4791, 4792, 4799, 4800, 4801, 4865, 4866, 4867, 4967, 4968, 4969
Rafael Navarro, MD (12203/ 7605) Instituto de Microcirugia Ocular Josep Maria Llado N°3 08035 Barcelona SPAIN	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4598, 4599
Harvey Uy, MD (14301/ 7871) Asian Eye Institute 9F Phinma Plaza Building Rockwell Center Makati, 1200 PHILIPPINES	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	28	4802, 4803, 4804, 4805, 4806, 4807, 4850, 4851, 4852, 4862, 4863, 4864, 4895, 4896, 4897, 4898, 4899, 4900, 4925, 4926, 4927, 4970, 4971, 4972, 5024, 5025, 5084, 5026

Principal Investigator (PI) Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Dirk Sandner, MD (12509/ 8092) University Eye Clinic Dresden Fetscherstrasse 74 01307 Dresden GERMANY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	4718, 4719
Miroslav Veith, MD (11707/ 31120) The Eye Department University Hospital Kralovske Vinohrady Srobarova 50 100 34 Prague 10 CZECH REPUBLIC <i>replaced Petr Soucek, MD, PhD (11707/ 8093) who was investigator from 11May2007 to 22Nov2010 at the same address</i>	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	10	4712, 4713, 4714, 4715, 4716, 4717, 4733, 4734, 4735, 4766
Jan Ernest, MD, PhD (11706/ 8907) Ocni klinika Ustredni vojenska nemocnice U vojenske nemocnice 1200 169 02 Praha CZECH REPUBLIC	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	4727, 4728, 4729, 4730, 4731, 4732, 4979

^a Bolded PI numbers are those under which patients were screened or enrolled.

Study 206207-011: A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

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Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
<p>Srinivas Sadda, MD (10036/ 6236) University of Southern California Keck School of Medicine Department of Ophthalmology Doheny Eye Institute 1450 San Pablo Street Los Angeles, CA 90033 USA</p> <p><i>replaced Dean Elliott, MD (10036/ 2680) who was investigator from 30Apr2009 to 02Feb2011 at the same address</i></p> <p><i>D. Elliott, MD (10036/ 2680) replaced Lawrence P. Chong, MD (10036/ 1671) who was investigator from 08Nov2005 to 30Apr2009 at the same address</i></p> <p><i>L. P. Chong, MD (10036/1671) replaced Tom Chang, MD(10036/ 4335) who was investigator from 04Apr2005 to 08Nov2005 at the same address</i></p>	<p>(b) (6) (subinvestigator under D. Elliott, MD; subinvestigator under L. Chong; subinvestigator under T. Chang, MD)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p>	13	7325, 7326, 7327, 7328, 7329, 7330, 7394, 7395, 7396, 7637, 7638, 7639, 7763
<p>Kenneth Sall, MD (10022/ 2707) Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701 USA</p>	<p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p> <p>(b) (6) (subinvestigator)</p>	68	7103, 7104, 7105, 7106, 7107, 7108, 7118, 7119, 7120, 7121, 7122, 7123, 7142, 7143, 7144, 7145, 7146, 7147, 7181, 7182, 7183, 7187, 7188, 7189, 7199, 7200, 7201, 7217, 7218, 7219, 7358, 7359, 7360, 7361, 7362, 7363, 7385, 7386, 7387, 7577, 7578, 7579, 7592, 7593, 7594, 7619, 7620, 7621, 7622, 7623, 7624, 7625, 7626, 7627, 7817, 7818, 7819, 7889, 7890, 7891, 7916, 7917, 7918, 7919, 7920, 7921, 7922, 7923

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Prof. Jean-Paul Romanet (12406/ 2793) Centre Hospitalier Universitaire de Grenoble Hopital Michallon Service d'Ophtalmologie Boulevard de la Chantourne BP 217 38043 Grenoble Cedex 09 FRANCE	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	8429, 8430, 8431, 8432
Prof. Eric Souied (12401/ 28409) Centre Hospitalier Intercommunal de Cretail Departement d'ophtalmologie 40 avenue de verdun Cretail, 94010 FRANCE <i>replaced Prof. Gisele Soubrane (12401/ 3059) who was investigator from 01Feb2007 to 31Aug2011 at the same address</i>	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	6	7457, 7458, 7459, 7460, 7461, 7462
Prof. Catherine Creuzot-Garcher (12404/ 3361) Hopital de Dijon Service Ophtalmologie 3 rue Faubourg Raines – BP 519 21033 Dijon FRANCE	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	8129, 8130, 8131
Kim Ramaswamy, MD (13005/ 4019) Aravind Eye Hospital 1 Anna nagar Madurai-625020, Tamilnadu INDIA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	8411, 8412, 8413

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Prof. Ugo Menchini (13403/ 4044) Azienda Ospedaliero -Universitaria Careggi Clinica Oculistica – Dipartimento di Scienze Chirurgiche Specialistiche Largo Brambilla, 3 50134 Firenze ITALY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	12	7475, 7476, 7477, 7478, 7479, 7480, 7604, 7605, 7606, 7685, 7686, 7687
David S. Boyer, MD (10003/ 4207) Retina Vitreous Associates Medical Group 8641 Wilshire Boulevard, Suite 210 Beverly Hills, CA 90211 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	7013, 7014, 7015

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Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Caroline Bauml, MD (10030/ 4224) Tufts Medical Center 800 Washington Street, Box 450 Boston, MA 02111 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	5	7256, 7257, 7258, 7259, 7260
Isaac Loose, MD (10031/ 4227) Retina Research Center 3705 Medical Parkway, Suite 410 and 420 Austin, TX 78705 USA	(b) (6) (subinvestigator)	7	7049, 7050, 7051, 7052, 7053, 7054, 7148
William Z. Bridges, Jr., MD (10004/ 4230) Western Carolina Retinal Associates 21 Medical Park Drive Asheville, NC 28803 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	7001, 7002, 7003, 7004
Ken Carnevale, MD (10005/ 4234) Ophthalmic Consultants of Long Island 360 Merrick Road, 3rd Floor Lynbrook, NY 11563 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	7190, 7191, 7192

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Bernard H. Doft, MD (10006/ 4242) Retina Vitreous Consultants 3501 Forbes Avenue, Suite 500 Pittsburgh, PA 15213 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	18	7007, 7008, 7009, 7010, 7011, 7012, 7154, 7155, 7156, 7355, 7356, 7357, 7676, 7677, 7678, 7709, 7710, 7711
Sharon Fekrat, MD (10032/ 4247) Duke University Eye Center Erwin Road, Wadsworth Building Box 3802 Durham, NC 27710 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	7343, 7344, 7345
Steven D. Schwartz, MD (10010/ 4255) Doris Stein Eye Research Center 200 Stein Plaza Los Angeles, CA 90095 USA <i>replaced Anurag Gupta, MD (10010/ 4255) who was investigator from 05May2005 to 02Jan2008 at the same address</i>	(b) (6) (subinvestigator under A. Gupta, MD) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	7136, 7137

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Peter Kaiser, MD (10033/ 4265) Cleveland Clinic Foundation 9500 Euclid Avenue Cleveland, OH 44195 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	7427, 7428
Jose A. Martinez, MD (10015/ 4276) Austin Retina Associates 801 West 38th Street, Suite 200 Austin, TX 78705 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	6	7061, 7062, 7063, 7064, 7065, 7066
Peter R. Pavan, MD (10009/ 4287) University of South Florida Ophthalmology Department 2020 Laurel Drive Tampa, FL 33612 USA <i>replaced Burton G. Goldstein, MD (10009/ 4409) who was investigator from 21Apr2005 to 22Jan2006 at the same address</i>	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator under B. Goldstein, MD) (b) (6) (subinvestigator)	6	7073, 7074, 7075, 7076, 7077, 7078
Don J. Perez-Ortiz, MD (10018/ 4289) International Eye Center 4506 Wishart Boulevard Tampa, FL 33603 USA	(b) (6) (subinvestigator)	1	7038

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
<p>Seenu M. Hariprasad, MD (10019/ 5099) University of Chicago Department of Ophthalmology and Visual Science 5758 S. Maryland Avenue Chicago, IL 60637 USA</p> <p><i>replaced Kourous Rezaei, MD (10019/ 4292) who was investigator from 07Dec2004 to 20Mar2006 at the same address</i></p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	9	7079, 7080, 7081, 7082, 7083, 7084, 7160, 7161, 7162
<p>Daniel Rosberger, MD, PhD (10020/ 4294) MaculaCare 52 E. 72nd Street New York, NY 10021 USA</p>	<p>(b) (6) (subinvestigator)</p>	0	
<p>Michael Singer, MD (10023/ 4298) Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240 USA</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	6	7025, 7026, 7027, 7028, 7029, 7030

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Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Steven Rose, MD (10021/ 4338) Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	15	7067, 7068, 7069, 7070, 7071, 7072, 7166, 7167, 7168, 7382, 7383, 7384, 7628, 7629, 7630
Prof. Pascale Massin (12402/ 4348) CHNO des Quinze-Vingts Service IV (Pr Sahel) 28 rue de Charenton 75571 Paris Cedex 12 FRANCE	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	7463, 7464, 7465, 7466
Prof. Edoardo Midena (13406/ 4355) Dipartimento di Oftalmologia Azienda Ospedaliero-Universitaria di Padova Via Giustiniani, 2 35128 Padova ITALY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	11	7481, 7482, 7483, 7484, 7485, 7486, 7904, 7905, 7906, 7949, 7950
William R. Freeman, MD (10008/ 4361) University of California, San Diego Jacobs Retina Center 9415 Campus Point Drive La Jolla, CA 92093 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	7442

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Carl C. Awh, MD (10001/ 4364) Tennessee Retina, PC 345 23rd Avenue North, Suite 350 Nashville, TN 37203 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	7031, 7032, 7033, 7034
Mark Donaldson, MD (14101/ 4379) Department of Ophthalmology Greenlane Clinical Centre Greenlane Road West Epsom, Auckland NEW ZEALAND	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	7541, 7542, 7543, 7544, 7545, 7546, 8006
Monique Leys, MD (10014/ 4380) West Virginia University Eye Institute One Stadium Drive Morgantown, WV 26506 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	7097, 7098, 7099, 7100, 7101, 7102, 7403

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
<p>Prof. Andrew Lotery (10502/ 5271) Southampton General Hospital Eye Unit Tremona Road Southampton, S016 6YD UNITED KINGDOM</p> <p><i>replaced Richard Newsom, MD (10502/ 4393) who was investigator from 18May2007 to 28Jan2009 at the same address</i></p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator under Richard Newsom, MD) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	2	7808, 7809
<p>Rosangela Lattanzio, MD (13402/ 4401) Dipartimento di Oftalmologia e Scienze della Visione Fondazione Centro S. Raffaele del Monte Tabor Via Olgettina, 60 20132 Milano ITALY</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	11	7376, 7377, 7378, 7379, 7380, 7381, 7409, 7410, 7411, 7694, 7695
<p>Mark Michels, MD (10016/ 4406) Retina Care Specialists 3399 PGA Boulevard, Suite 350 Palm Beach Gardens, FL 33410 USA</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	6	7055, 7056, 7057, 7058, 7059, 7060
<p>Prof. Giovanni Staurenghi (13407/ 4408) Clinica Oculistica “Ospedale Luigi Sacco” Via Giovani Battista Grassi, 74 20157 Milano ITALY</p>	<p>(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)</p>	7	7493, 7494, 7495, 7496, 7497, 7498, 8042

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Antonio M. Casella, MD (11206/ 4453) Ambulatorio do Hospital de Clinicas da Universidade Estadual de Londrina Rodovia Celso Garcia Cid, S/Nº PR 445 - Km 380 Campus Universitario Londrina - PR – 86051-990 BRAZIL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	7736, 7737, 7738
Joao L. Ferreira, MD (11207/ 4454) Vista Medicina dos Olhos Rua Deputado Leoberto Leal 14 - Centro Florianopolis - SC - 88015-080 BRAZIL	(b) (6) (subinvestigator)	2	7988, 7989
Randy S. Katz, MD (10012/ 4456) Florida Eye Microsurgical Institute, Inc. 1717 Woolbright Road Boynton Beach, FL 33426 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	7112
Fareed Ali, MD, FRCSC (11304/ 4473) Canadian Centre for Advanced Eye Therapeutics 1880 Sismet Road Mississauga, ON L4W 1W9 CANADA	(b) (6) (subinvestigator)	1	7349
Prof. Daniele Tognetto (13408/ 32070) Clinica Oculistica Azienda Ospedaliero Universitaria “Ospedali Riuniti” Ospedale Maggiore Piazza Ospitale, 1 34129 Trieste ITALY <i>replaced Prof. Giuseppe Ravalico (13408/ 0471) who was investigator from 16Jan2009 to 28Oct2011 at the same address</i> <i>Prof. G. Ravalico (13408/ 0471) replaced Maurizio Battaglia Parodi, MD (13416/ 4498) who was investigator from 25Jul2007 to 16Jan2009 at the same address</i>	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	11	7511, 7512, 7513, 7514, 7515, 7516, 7982, 7983, 7984, 7985, 7986

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Lawrence J. Ulanski, II, MD (10035/ 4523) University of Illinois at Chicago 1905 West Taylor Street, MC648 Chicago, IL 60612 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	3	7319, 7320, 7321
Thomas F. Essman, MD (10007/ 4529) Mercy Clinic Eye Specialists- Ophthalmology-Surgery Center 1229 East Seminole, Suite 430 Springfield, MO 65804 USA	(b) (6) (subinvestigator)	1	7124
Edmund Wong, MD (15601/ 4531) Singapore National Eye Centre 11 Third Hospital Avenue Singapore 168751 SINGAPORE	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	5	7553, 7554, 7555, 7556, 7557
Muna Bhende, MD (13001/ 4614) Sankara Nethralaya No. 18 College Road Nungambakkam Chennai-600 006, Tamil Nadu INDIA <i>replaced Lingam Gopal, MD (13001/ 4533) who was investigator from 26Apr2006 to 31Mar2011 at the same address</i>	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	19	7301, 7302, 7303, 7304, 7305, 7306, 7307, 7308, 7309, 7310, 7311, 7312, 7313, 7314, 7315, 7316, 7317, 7318, 7598

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
John Lehr, MD (10029/ 4569) Magruder Eye Institute 1911 North Mills Avenue Orlando, FL 32803 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	7331
Ajit B. Majji, MD (13002/ 4571) L V Prasad Eye Institute L V Prasad Marg, Banjara Hills Hyderabad, Andhra Pradesh 500 034 INDIA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	4	7283, 7284, 7285, 7286
Francisco J. Rodriguez Alvira, MD (15801/ 4580) Fundacion Oftalmologica Nacional - FUNDONAL Calle 50 # 13 - 50, 6th Floor Bogota COLOMBIA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	9	7517, 7518, 7519, 7520, 7521, 7522, 7523, 7524, 7525
Augusto Paranhos, Jr., MD (11209/ 4582) Hospital Israelita Albert Einstein – CPC - IIEP Av. Albert Einstein 627/701 - 2° Subsolo Sao Paulo - SP - 05651-901 BRAZIL	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	5	7680, 7681, 7682, 7683, 7684
Philip M. Falcone, MD (10028/ 4583) Connecticut Retina Consultants, LLC 4920 Main Street, Suite 309 Bridgeport, CT 06606 USA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	7226

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Prof. Young Hee Yoon (15901/ 4618) Department of Ophthalmology Asan Medical Center 388-1 Pungnap2-dong, Songpa-gu Seoul 138-736 SOUTH KOREA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	39	7220, 7221, 7222, 7223, 7224, 7225, 7244, 7245, 7246, 7253, 7254, 7255, 7262, 7263, 7264, 7265, 7266, 7267, 7268, 7269, 7270, 7271, 7272, 7273, 7274, 7275, 7276, 7277, 7278, 7279, 7280, 7281, 7282, 7340, 7341, 7342, 7400, 7401, 7402
Bradley Foster, MD (10027/ 5020) New England Retina Consultants, PC 3640 Main Street, Suite 201 Springfield, MA 01107 USA	(b) (6) (subinvestigator)	5	7211, 7212, 7213, 7214, 7215

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Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Prof. Dariusz Kecik (14402/ 6425) Szpital Kliniczny Dzieciatka Jezus Centrum Leczenia Obrazen Klinika Okulistyki 4, Lindley'a Street 02-005 Warszawa POLAND	(b) (6) (subinvestigator) (b) (6) (subinvestigator & treating investigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	2	7730, 7731
Ass. Prof. Edward Wylegala (14405/ 6682) Okregowy Szpital Kolejowy w Katowicach 65, Panewnicka Street 40-760 Katowice POLAND	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	10	7688, 7689, 7690, 7691, 7692, 7693, 7862, 7863, 7864, 7958
Francesco Viola, MD (13409/ 6683) Clinica Oculistica Ospedale Maggiore Policlinico Mangiagalli e Regina Elena Via Manfredo Fanti, 6 20122 Milano ITALY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	12	7865, 7866, 7867, 7868, 7869, 7870, 7874, 7875, 7876, 8003, 8004, 8005
Janos Nemeth, MD (12902/ 6684) Semmelweis University Department of Ophthalmology Tomo u. 25-29 Budapest 1083 HUNGARY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	7	7802, 7803, 7804, 7805, 7806, 7807, 7877

Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Da-Wen Lu, MD (14902/ 6687) Department of Ophthalmology Tri-Service General Hospital 325, Section 2, Cheng-Kun Road Neihu District Taipei 114 TAIWAN	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	7925
San-Ni Chen, MD (14903/ 6689) Department of Ophthalmology Changhua Christian Hospital 135, Nan-Hsia Street Changhua 500 TAIWAN	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	8090
Shwu-Jiuan Sheu, MD (14904/ 6690) Department of Ophthalmology Veterans General Hospital-Kaohsiung 386, Ta-Chung 1st Road Kaohsiung 813 TAIWAN	(b) (6) (subinvestigator) (b) (6) (subinvestigator)	10	7937, 7938, 7939, 7940, 7941, 7942, 7943, 7944, 7945, 7947
Stanislao Rizzo, MD (13410/ 7412) U.O. Chirurgia Oftalmica Dipartimento Organi di Senso Azienda Ospedaliero-Universitaria Pisana- Presidio Ospedaliero di Cisanello Via Paradisa, 2 56124 Pisa ITALY	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	8423
Prof. Won-Ki Lee (15902/ 7873) Department of Ophthalmology The Catholic University of Korea St Mary's Hospital #505 Banpo-dong, Seocho-gu, Seoul 137-040 SOUTH KOREA	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	5	8108, 8109, 8110, 8111, 8112

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Principal Investigator Name (Site/ PI Number ^a), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Geeta Menon, MD, MBBS, MS (Ophth), FRCS (Ophth) (10505/ 9132) Department of Ophthalmology Frimley Park Hospital Portsmouth Road Camberley Surrey, GU16 7UJ UNITED KINGDOM	(b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator) (b) (6) (subinvestigator)	1	8438

^a Bolded PI numbers are those under which patients were screened or enrolled.

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/s/

MICHAEL J PUGLISI
07/15/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022315Orig1s009

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22315

SUPPL # 009

HFD #

Trade Name **Ozurdex**

Generic Name **dexamethasone intravitreal implant, 0.7 mg**

Applicant Name **Allergan, Inc.**

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒

NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒

NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA# 11664

Decadron

NDA# 13422

Maxidex

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 206207-010

Study 206207-011

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 **Study 206207-010** YES ☐ NO ☒

Investigation #2 **Study 206207-011** YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 **Study 206207-010** YES ☐ NO ☒

Investigation #2

Study 206207-011

YES ☐

NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 206207-010

Study 206207-011

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

!

IND # 58663

YES ☒

! NO ☐

! Explain:

Investigation #2

!

!

IND # 58663

YES ☒

! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

!

!

YES ☐

! NO ☐

Explain:

! Explain:

Investigation #2

!

!

YES ☐

! NO ☐

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☒

If yes, explain:

=====

Name of person completing form: Michael Puglisi

Title: Regulatory Project Manager

Date: June 27, 2014

Name of Office/Division Director signing form: Renata Albrecht, MD

Title: Director, Division of Transplant and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MICHAEL J PUGLISI
06/27/2014

RENATA ALBRECHT
06/28/2014



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

COMMUNICATION TRANSMITTAL SHEET

DATE: June 19, 2014

To: Libette Luce, MA, Senior Manager, US Regulatory Affairs	From: Jacquelyn Smith, M.A., Senior Project Manager
Company: Allergan	Division of Transplant and Ophthalmology Products
Phone Number: 908-203-2645	Phone Number: 301-796-1600
Email: luce_libette@allergan.com	Email: jacquelyn.smith@fda.hhs.gov

NDA 22315/S-009 Ozurdex

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. Luce:

Please refer to NDA 22315/S-009, Ozurdex (dexamethasone intravitreal implant) 0.7 mg.

Attached is the Ozurdex labeling for the Pregnancy section. Please review. We can discuss further during tomorrow's teleconference.

We are providing this information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,
Jacquelyn Smith, M.A. (for Michael Puglisi)
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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

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

/s/

JACQUELYN E SMITH
06/19/2014



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

COMMUNICATION TRANSMITTAL SHEET

DATE: June 18, 2014

To: Libette Luce, MA, Senior Manager, US Regulatory Affairs	From: Jacquelyn Smith, M.A., Senior Project Manager
Company: Allergan	Division of Transplant and Ophthalmology Products
Phone Number: 908-203-2645	Phone Number: 301-796-1600
Email: luce_libette@allergan.com	Email: jacquelyn.smith@fda.hhs.gov

NDA 22315/S-009 Ozurdex

Total no. of pages including cover: 14

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. Luce:

Please refer to NDA 22315/S-009, Ozurdex (dexamethasone intravitreal implant) 0.7 mg.

Attached is the proposed text for the package insert. Please review. If you agree with the proposed text, please send confirmation, including the revised package insert incorporating the agreed upon revisions. If further discussion is needed, please contact me or Michael Puglisi.

We are providing this information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,
Jacquelyn Smith, M.A. (for Michael Puglisi)
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

Enclosure:
Package Insert

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

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/s/

JACQUELYN E SMITH
06/18/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Transplant and Ophthalmology
Products

Review Comments Transmittal

DATE: 4/29/14

To: Allergan, Inc.	From: Michael Puglisi, Regulatory Project Manager
Attn: Libette Luce, MA	e-mail: Michael.puglisi@fda.hhs.gov
e-mail: luce_libette@allergan.com	Phone Number: 301-796-0791
Phone: 908-203-2645	

Subject: NDA 22315/S-009

Total no. of pages including cover: 12

Comments:

Dear Ms. Luce,

Attached please find Clinical/Stats comments concerning the Ozurdex (dexamethasone intravitreal implant) DME efficacy supplement. Please provide a response in 3 - 4 weeks. Please confirm you have received these comments and let me know if you have any clarifying questions about them.
Thanks.

Mike

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Information Request:

- 1) Please generate updated tables for section 5.3.5.3, ISS-Tables, excluding data from site 2707
 - a) Table 2-2.1: All adverse reactions by SOC
 - b) Table 2-4: All treatment-related ocular adverse events (descending incidence)
 - c) Table 4-2: All treatment-related adverse events leading to discontinuation (descending incidence)
 - d) Table 6-19.15 : BCVA 30 or more letters from baseline (Phakic)
 - e) Table 6-19.18 : BCVA 30 or more letters from baseline (Pseudophakic)
- 2) Please generate a table of treatment-emergent adverse reactions, or clarify which tables represent treatment-emergent adverse reactions; e.g., adverse event tables or treatment-related adverse event tables.
- 3) Revise the Proposed Package Insert (b) (4) .
 - a) Update the denominators after excluding site 2707
 - b) Include all treatment-emergent adverse reactions reported $\geq 1\%$ of patients, where the rate associated with DEX treatment is approximately twice that seen with sham control. (see Guidance to Industry, Adverse Reaction Section of Labeling
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>)
 - c) Based on the information presented in the April 7, 2014 submission, Table 3833, it appears the following adverse reactions occur more frequently in the DEX treatment arms compared to the sham control and should be included in the table (some of these are currently already included in the table):
 - i. EYE: cataracts (collectively with footnote or individually by type and opacification in phakic patients); cataract surgery; increased intraocular pressure, ocular hypertension, glaucoma, open angle glaucoma, optic nerve cupping; macular edema; vitreous hemorrhage; reduced visual acuity; macular fibrosis; conjunctivitis; retinal hemorrhage; eye pain; conjunctival edema; dry eye; vitreous detachment, vitreous floaters; retinal aneurysm; foreign body sensation in eyes, foreign body in eye; corneal abrasion, corneal erosion; keratitis; ptosis, anterior chamber inflammation, eyelid edema; retinal tear; macular hole; cystoid macular edema
 - ii. SYSTEMIC by SOC: hypertension, increased blood pressure; bronchitis, sinusitis, cellulitis, pneumonia, cystitis; osteoarthritis, arthritis, back pain, ligament sprain carpal tunnel, gout, foot fracture; nausea, diarrhea, vomiting, gastritis, abdominal pain; headache, insomnia, TIA, syncope, paresthesia; renal impairment, renal failure;
 - d) In the text, report on discontinuation due to treatment-emergent adverse reactions (ISS Table 4.2)
- 4) Summary of additional requests
 - a) Patient disposition summary: Please provide the following:
 - The number of subjects who had BCVA measures at each visit (see Mock-up Table 1)
 - The number of subjects who remained in the study at each study visit (see Mock-up Table 2)
 - b) Site 2707: Please provide the following :
 - The number of subjects who remained in the study at each study visit (see Mock-up Table 1)
 - The number of subjects who had BCVA measures at each visit (see Mock-up Table 2)

- Mean change from baseline by treatment arm over time
 - The % of subjects with a ≥ 15 letter gain from baseline at both Month 36 and 39
 - Individual change from baseline BCVA plots
 - The above summaries for the top 5 sites (sites which enrolled at least 10 subjects per treatment arm)
- c) Confounding effect of cataract AE and Surgery
- Please produce the results summarized in the mock-up tables (Table 3 and Table 4) for both Month 36 and Month 39/final visits
 - Please provide the mean BCVA change from baseline plots for the different subgroups by treatment arm
- d) Safety:
- Please produce the safety summary for all subjects and Pseudophakic subjects only (see Mock-up Table 5 and 6). Please also provide the same summaries for each study separately
 - Please produce the number of subjects who had surgery, subjects who reported at least one cataract related AE and subjects who reported at least one IOP related AE at each study visit (see Mock-up Tables 7-9) (Note: Please use the visit window used to define the BCVA measures for all summaries)
 - Please confirm and reproduce the descriptive of the study duration (time from randomization to last study visit on CRF) by the number of injections received (Table 10)
 - Please produce the summary of selected adverse events by number of injection (please also include the number of cataract related AEs in the table (see Mock-up Table 11)
- e) Provide the listing of subjects who received escape therapy – sorted by study, and by treatment group for the study eye (see following for Mock-up listing below)

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
SUBJID	Treatment Group	Day When Escape Therapy Was Given (Relative To Randomization)	Day of last observed BCVA relative to randomization	Difference between column 3 and column 4	Escape Therapy	Reason for Escape Therapy Indication/ Procedure	Last Observed BCVA	Baseline BCVA	Change from baseline BCVA
206207010-4082-4025	Sham	231	200	31		neovascularization	83	66	17
206207011-4234-7191	DEX 700	894	694	200		Worsening DME	78	58	16
ETC									

- f) Provide the listing of subjects who received anti-VEGF therapy prior to study enrollment, include information on what anti-VEGF therapy was received, for what duration, what was the response to anti-VEGF therapy and when anti-VEGF therapy was discontinued relative to study enrollment, by study, and by treatment group for the study eye (see following for Mock-up listing below)

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
SUBJID	Treatment Group	Anti-VEGF used	Indication	Total number of injections/doses	BCVA before start of anti-VEGF	BCVA after completing anti-VEGF	Response to Anti-VEGF (success or failure)	Baseline BCVA at enrollment	Change from column 9 and 7 BCVA
ETC									

- g) Regarding subjects who had BCVA measurements at Month 39 and subjects who were retreated at Month 36, we observed the following:
- We have identified 155 subjects whose last re-treatment was at month 36. Of these, 103 had 7 injections while the remaining had 6 or less injections
 - Of the 155 subjects whose last re-treatment was at month 36, 139 had a complete BCVA measurement at Month 39 while the remaining 16 did not have.
 - The total number of subjects who had a complete BCVA measurement at Month 39 is 161. Of these 161 subjects, 139 were re-treated at Month 36 while the remaining 22 received their last re-treatment prior to Month 36.
 - Per Amendment 4, only subjects who were re-treated at Month 36 should have a BCVA evaluation at Month 39.
 - o Please explain how the 22 subjects (among the 161 subjects who had a BCVA at Month 39) had BCVA measurements at Month 39 without being re-treated at Month 36 (see the list of the 22 subjects on Table 15 in the appendix)
 - o Please produce the following :
 - Descriptive summary of the change from baseline BCVA for the 22 subjects at both Month 36 and 39 (see Mock-up Table 12)
 - Efficacy summary at Month 39/final visit with the BCVA at month 36 carried forward for the 22 subjects who had BCVA measurements at Month 39 without being retreated at Month 36 (See Mock-up Table 13 and Table 14)
 - o Please also explain why the 16 subjects who were re-treated at Month 36 did not have a BCVA evaluation at Month 39 (see the list of the 16 subjects in Table 16 in the appendix).

List of Mock-up tables

Table 1: Number of subjects with observed BCVA measurement by Visit (Not carried forward)

Visit	Study 206207-010			Study 206207-011			Pooled		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163	DEX 700 N=328	DEX 350 N=324	Sham N=328
1.5	156(95.7%)	160(96.4%)	155(93.9%)	162(98.2%)	153(96.8%)	151(92.6%)	318(97%)	313(96.6%)	306(93.3%)
3.0	156(95.7%)	161(97%)	147(89.1%)	159(96.4%)	150(94.9%)	153(93.9%)	315(96%)	311(96%)	300(91.5%)
4.5	151(92.6%)	154(92.8%)	139(84.2%)	153(92.7%)	144(91.1%)	139(85.3%)	304(92.7%)	298(92%)	278(84.8%)
6.0	143(87.7%)	154(92.8%)	126(76.4%)	150(90.9%)	143(90.5%)	132(81%)	293(89.3%)	297(91.7%)	258(78.7%)
7.5	137(84%)	145(87.3%)	111(67.3%)	145(87.9%)	133(84.2%)	115(70.6%)	282(86%)	278(85.8%)	226(68.9%)
9.0	138(84.7%)	152(91.6%)	102(61.8%)	139(84.2%)	135(85.4%)	110(67.5%)	277(84.5%)	287(88.6%)	212(64.6%)
10.5	133(81.6%)	139(83.7%)	102(61.8%)	138(83.6%)	130(82.3%)	98(60.1%)	271(82.6%)	269(83%)	200(61%)
12.0	137(84%)	151(91%)	103(62.4%)	140(84.8%)	126(79.7%)	99(60.7%)	277(84.5%)	277(85.5%)	202(61.6%)
15.0	129(79.1%)	141(84.9%)	90(54.5%)	132(80%)	113(71.5%)	96(58.9%)	261(79.6%)	254(78.4%)	186(56.7%)
18.0	124(76.1%)	136(81.9%)	81(49.1%)	127(77%)	122(77.2%)	89(54.6%)	251(76.5%)	258(79.6%)	170(51.8%)
21.0	114(69.9%)	133(80.1%)	79(47.9%)	116(70.3%)	103(65.2%)	79(48.5%)	230(70.1%)	236(72.8%)	158(48.2%)
24.0	116(71.2%)	125(75.3%)	75(45.5%)	113(68.5%)	98(62%)	73(44.8%)	229(69.8%)	223(68.8%)	148(45.1%)
27.0	107(65.6%)	122(73.5%)	69(41.8%)	106(64.2%)	95(60.1%)	70(42.9%)	213(64.9%)	217(67%)	139(42.4%)
30.0	102(62.6%)	110(66.3%)	65(39.4%)	99(60%)	92(58.2%)	64(39.3%)	201(61.3%)	202(62.3%)	129(39.3%)
33.0	102(62.6%)	112(67.5%)	61(37%)	96(58.2%)	91(57.6%)	62(38%)	198(60.4%)	203(62.7%)	123(37.5%)
36.0	104(63.8%)	107(64.5%)	63(38.2%)	95(57.6%)	84(53.2%)	64(39.3%)	199(60.7%)	191(59%)	127(38.7%)
39.0	30(18.4%)	38(22.9%)	18(10.9%)	25(15.2%)	25(15.8%)	22(13.5%)	55(16.8%)	63(19.4%)	40(12.2%)

Table 2: Number of subjects who remained in the study by visit

Visit	Study 206207-010			Study 206207-011			Pooled		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163	DEX 700 N=328	DEX 350 N=324	Sham N=328
1.0	163(100%)	166(100%)	165(100%)	165(100%)	158(100%)	163(100%)	328(100%)	324(100%)	328(100%)
1.5	160(98.2%)	164(98.8%)	160(97%)	164(99.4%)	156(98.7%)	160(98.2%)	324(98.8%)	320(98.8%)	320(97.6%)
3.0	160(98.2%)	164(98.8%)	154(93.3%)	162(98.2%)	156(98.7%)	157(96.3%)	322(98.2%)	320(98.8%)	311(94.8%)
4.5	158(96.9%)	163(98.2%)	148(89.7%)	161(97.6%)	154(97.5%)	153(93.9%)	319(97.3%)	317(97.8%)	301(91.8%)
6.0	156(95.7%)	162(97.6%)	137(83%)	160(97%)	153(96.8%)	149(91.4%)	317(96.6%)	315(97.2%)	286(87.2%)
7.5	151(92.6%)	159(95.8%)	122(73.9%)	154(93.3%)	148(93.7%)	129(79.1%)	306(93.3%)	307(94.8%)	251(76.5%)
9.0	147(90.2%)	158(95.2%)	118(71.5%)	150(90.9%)	145(91.8%)	124(76.1%)	298(90.9%)	303(93.5%)	242(73.8%)
10.5	145(89%)	157(94.6%)	115(69.7%)	145(87.9%)	142(89.9%)	118(72.4%)	291(88.7%)	299(92.3%)	233(71%)
12.0	144(88.3%)	156(94%)	112(67.9%)	143(86.7%)	138(87.3%)	114(69.9%)	288(87.8%)	294(90.7%)	226(68.9%)
15.0	134(82.2%)	148(89.2%)	100(60.6%)	136(82.4%)	131(82.9%)	105(64.4%)	271(82.6%)	279(86.1%)	205(62.5%)
18.0	128(78.5%)	146(88%)	93(56.4%)	134(81.2%)	129(81.6%)	100(61.3%)	263(80.2%)	275(84.9%)	193(58.8%)

21.0	123(75.5%)	142(85.5%)	86(52.1%)	126(76.4%)	119(75.3%)	92(56.4%)	250(76.2%)	261(80.6%)	178(54.3%)
24.0	122(74.8%)	137(82.5%)	82(49.7%)	123(74.5%)	113(71.5%)	87(53.4%)	246(75%)	250(77.2%)	169(51.5%)
27.0	119(73%)	131(78.9%)	79(47.9%)	115(69.7%)	105(66.5%)	85(52.1%)	235(71.6%)	236(72.8%)	164(50%)
30.0	114(69.9%)	127(76.5%)	76(46.1%)	112(67.9%)	104(65.8%)	80(49.1%)	227(69.2%)	231(71.3%)	156(47.6%)
33.0	111(68.1%)	123(74.1%)	74(44.8%)	108(65.5%)	100(63.3%)	80(49.1%)	220(67.1%)	223(68.8%)	154(47%)
36.0	110(67.5%)	120(72.3%)	73(44.2%)	105(63.6%)	96(60.8%)	79(48.5%)	216(65.9%)	216(66.7%)	152(46.3%)
39.0	30(18.4%)	41(24.7%)	22(13.3%)	26(15.8%)	26(16.5%)	26(16%)	57(17.4%)	67(20.7%)	48(14.6%)

Source: Reviewer's Analysis. The number of subjects who completed a given visit = Total number of subjects randomized to that treatment arm – total number of subjects who discontinued the study prior to that visit (based on the last visit date on the CRF).

Table 3: Proportion of subjects with >=15 letters from baseline at 3 Years for subgroups based on baseline lens status and status of cataract AE after randomization

Subgroup	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 010				
Phakic (0)	18/119(15.1%)	25/119(21%)	10/115(8.7%)	6.4%(-1.8%, 14.7%)	12.3% (3.4%, 21.3%)
Pseudophakic (1)	14/44(31.8%)	8/47(17%)	8/50(16%)	15.8%(-1.3%,32.9%)	1%(-13.8%,15.8%)
Phakic Subjects who had Cataract surgery (2)	13/72(18.1%)	16/72(22.2%)	2/8(25%)	-6.9%(-38.2%,24.3%)	-2.8%(-34.3%,28.7%)
(1)+ (2)	27/116(23.3%)	24/119(20.2%)	10/58(17.2%)	6%(-6.4%,18.4%)	2.9%(-9.2%,15%)
Phakic subjects with No Cataract related AE (3)	6/39(15.4%)	8/37(21.6%)	7/98(7.1%)	8.2%(-4.2%,20.7%)	14.5%(0.3%,28.7%)
(1)+ (3)	20/83(24.1%)	16/84(19%)	15/148(10.1%)	14%(3.6%,24.4%)	8.9%(-0.8%,18.6%)
Study 011					
Phakic (0)	22/127(17.3%)	17/120(14.2%)	13/114(11.4%)	5.9%(-2.9%, 14.7%)	2.8% (-5.8%, 11.3%)
Pseudophakic (1)	3/38(7.9%)	4/38(10.5%)	3/49(6.1%)	1.8%(-9.1%,12.7%)	4.4%(-7.4%,16.2%)
Phakic Subjects who had Cataract surgery (2)	14/76(18.4%)	13/53(24.5%)	1/10(10%)	8.4%(-12.1%,29%)	14.5%(-7.4%,36.4%)
(1)+ (2)	17/114(14.9%)	17/91(18.7%)	4/59(6.8%)	8.1%(-1%,17.3%)	11.9%(1.6%,22.2%)
Phakic subjects with No Cataract related AE (3)	8/41(19.5%)	4/52(7.7%)	10/83(12%)	7.5%(-6.5%,21.5%)	-4.4%(-14.4%,5.7%)
(1)+ (3)	11/79(13.9%)	8/90(8.9%)	13/132(9.8%)	4.1%(-5.1%,13.2%)	-1%(-8.7%,6.8%)
Pooled					
Phakic (0)	40/246(16.3%)	42/239(17.6%)	23/229(10%)	6.2% (0.2%, 12.3%)	7.5% (1.3%,13.7%)
Pseudophakic (1)	17/82(20.7%)	12/85(14.1%)	11/99(11.1%)	9.6%(-1.1%,20.4%)	3%(-6.6%,12.7%)
Phakic Subjects who had Cataract surgery (2)	27/148(18.2%)	29/125(23.2%)	3/18(16.7%)	1.6%(-16.7%,19.9%)	6.5%(-12.2%,25.3%)
(1)+ (2)	44/230(19.1%)	41/210(19.5%)	14/117(12%)	7.2%(-0.6%,14.9%)	7.6%(-0.4%,15.5%)
Phakic subjects with No Cataract related AE (3)	14/80(17.5%)	12/89(13.5%)	17/181(9.4%)	8.1%(-1.2%,17.5%)	4.1%(-4.2%,12.4%)
(1)+ (3)	31/162(19.1%)	24/174(13.8%)	28/280(10%)	9.1%(2.1%,16.1%)	3.8%(-2.4%,10%)

Source: Reviewer's analysis. All subjects who received a rescue therapy are treated as treatment failures

Table 4: Mean BCVA change from baseline at 3 Years for subgroups based on baseline lens status and status of cataract AE after randomization

Subgroup	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
	Study 010				
Phakic (0)	1.6(14.7)	4.6(13)	0.3(12)	1.3(-2.1,4.8)	4.2(1,7.5)
Pseudophakic (1)	9.3(10.8)	6.5(10.2)	2.6(10.4)	6.7(2.3,11)	3.8(-0.3,8)
Phakic Subjects who had Cataract surgery (2)	3.4(14.7)	6.1(12.5)	3.1(16.8)	0.2(-13.9,14.4)	2.9(-11.2,17)
(1)+ (2)	5.6(13.6)	6.2(11.6)	2.7(11.3)	2.9(-0.9,6.7)	3.5(-0.1,7.1)
Phakic subjects with No Cataract related AE (3)	3(12)	4.9(11.9)	0.2(12)	2.8(-1.7,7.3)	4.8(0.2,9.4)
(1)+ (3)	6.3(11.7)	5.8(10.9)	1(11.5)	5.3(2.2,8.5)	4.8(1.8,7.8)
Study 011					
Phakic (0)	-0.9(18.9)	-1.6(16.8)	1(13.2)	-1.8(-6.2,3)	-2.6(-6.5,1.3)
Pseudophakic (1)	1.5(11.9)	5(10.7)	0.1(13.9)	1.4(-4.1,6.9)	4.9(-0.3,10.2)
Phakic Subjects who had Cataract surgery (2)	1.4(17.6)	2.8(16.3)	2.7(12.1)	-1.3(-10.5,8)	0.1(-9.4,9.5)
(1)+ (2)	1.5(15.9)	3.7(14.2)	0.5(13.6)	0.9(-3.6,5.5)	3.2(-1.4,7.8)
Phakic subjects with No Cataract related AE (3)	0.7(16)	-1.4(15.4)	0.2(14.5)	0.6(-5.3,6.4)	-1.6(-6.9,3.7)
(1)+ (3)	1.1(14.1)	1.3(13.9)	0.1(14.2)	1(-3,4.9)	1.2(-2.6,4.9)
Pooled					
Phakic	0.3(17)	1.5(15.3)	0.6(12.6)	-0.3(-3,2.4)	0.8(-1.7,3.4)
Pseudophakic (1)	5.7(11.9)	5.8(10.4)	1.4(12.2)	4.3(0.8,7.9)	4.5(1.2,7.7)
Phakic Subjects who had Cataract surgery (2)	2.4(16.2)	4.7(14.2)	2.9(13.9)	-0.5(-7.8,6.8)	1.8(-5.5,9.1)
(1)+ (2)	3.6(14.9)	5.1(12.8)	1.6(12.5)	2(-1,4.9)	3.5(0.7,6.4)
Phakic subjects with No Cataract related AE (3)	1.8(14.1)	1.2(14.3)	0.2(13.2)	1.7(-2,5.3)	1.1(-2.5,4.6)
(1)+ (3)	3.8(13.2)	3.5(12.7)	0.6(12.8)	3.2(0.6,5.7)	2.9(0.5,5.3)

Source: Reviewer's analysis. LOCF is used to impute missing data

Table 5: Summary of Adverse Events (AE) (Pooled: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=324	DEX 350 N=320	Sham N=328	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	310(95.7%)	311(97.2%)	260(79.3%)	16.4%(11.5%,21.3%)	17.9%(13.2%,22.7%)
Any Ocular AE	274(84.6%)	282(88.1%)	190(57.9%)	26.6%(20%,33.3%)	30.2%(23.8%,36.6%)
Any Serious AE	110(34%)	113(35.3%)	79(24.1%)	9.9%(2.9%,16.8%)	11.2%(4.2%,18.2%)
Any Ocular Serious AE	24(7.4%)	14(4.4%)	4(1.2%)	6.2%(3.1%,9.3%)	3.2%(0.6%,5.7%)
Any Severe AE	151(46.6%)	149(46.6%)	100(30.5%)	16.1%(8.7%,23.5%)	16.1%(8.7%,23.5%)
Any Ocular Severe AE	91(28.1%)	71(22.2%)	34(10.4%)	17.7%(11.8%,23.6%)	11.8%(6.2%,17.4%)
Any IOP Related AE	120(37%)	107(33.4%)	18(5.5%)	31.5%(25.7%,37.4%)	27.9%(22.2%,33.7%)
≥10 mm Hg IOP Change from Baseline at any visit	91(28.1%)	79(24.7%)	13(4%)	24.1%(18.8%,29.5%)	20.7%(15.5%,25.9%)
≥25 mm Hg IOP at any visit	106(32.7%)	86(26.9%)	15(4.6%)	28.1%(22.6%,33.7%)	22.3%(16.9%,27.7%)
≥35 mm Hg IOP at any	20(6.2%)	16(5%)	3(0.9%)	5.3%(2.4%,8.1%)	4.1%(1.5%,6.7%)

visit					
Glaucoma	4(1.2%)	3(0.9%)	1(0.3%)	0.9%(-0.4%,2.3%)	0.6%(-0.6%,1.8%)
IOP Lowering Procedures	4(1.2%)	1(0.3%)	1(0.3%)	0.9%(-0.4%,2.3%)	0%(-0.8%,0.9%)
Any Cataract Related AE Baseline Phakic Subjects	166(68.3%)	149(63.1%)	49(21.3%)	47%(39.1%,54.9%)	41.8%(33.7%,49.9%)
Cataract Surgery in Baseline Phakic Subjects	148(60.9%)	125(53%)	18(7.8%)	53.1%(46%,60.1%)	45.1%(37.9%,52.4%)
≥15 Letters Loss from Baseline	47(14.5%)	34(10.6%)	35(10.7%)	3.8%(-1.3%,8.9%)	0%(-4.8%,4.7%)
Death	9(2.8%)	14(4.4%)	5(1.5%)	1.3%(-1%,3.5%)	2.9%(0.2%,5.5%)
Escape Therapy	31(9.6%)	38(11.9%)	63(19.2%)	-9.6%(-15%, -4.3%)	-7.3%(-12.9%, -1.8%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 6: Summary of Adverse Events (AE) (Pooled: Psuedophakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=81	DEX 350 N=84	Sham N=98	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	77(95.1%)	83(98.8%)	84(85.7%)	9.3%(1%,17.7%)	13.1%(5.8%,20.4%)
Any Ocular AE	59(72.8%)	70(83.3%)	60(61.2%)	11.6%(-2.1%,25.3%)	22.1%(9.6%,34.6%)
Any Serious AE	29(35.8%)	36(42.9%)	36(36.7%)	-0.9%(-15.1%,13.2%)	6.1%(-8.1%,20.4%)
Any Ocular Serious AE	2(2.5%)	0(0%)	0(0%)	2.5%(-0.9%,5.8%)	
Any Severe AE	35(43.2%)	40(47.6%)	37(37.8%)	5.5%(-9%,19.9%)	9.9%(-4.5%,24.2%)
Any Ocular Severe AE	10(12.3%)	15(17.9%)	8(8.2%)	4.2%(-4.8%,13.2%)	9.7%(-0.1%,19.5%)
Any IOP Related AE	25(30.9%)	29(34.5%)	9(9.2%)	21.7%(10.1%,33.3%)	25.3%(13.7%,37%)
≥10 mm Hg IOP Change from Baseline at any visit	20(24.7%)	24(28.6%)	2(2%)	22.7%(12.9%,32.4%)	26.5%(16.5%,36.6%)
≥25 mm Hg IOP at any visit	21(25.9%)	24(28.6%)	6(6.1%)	19.8%(9.1%,30.5%)	22.4%(11.7%,33.2%)
≥35 mm Hg IOP at any visit	6(7.4%)	4(4.8%)	1(1%)	6.4%(0.3%,12.4%)	3.7%(-1.2%,8.7%)
Glaucoma	1(1.2%)	1(1.2%)	0(0%)	1.2%(-1.2%,3.6%)	1.2%(-1.1%,3.5%)
Any Cataract Related AE	4(4.9%)	0(0%)	2(2%)	2.9%(-2.6%,8.4%)	
Cataract Surgery	0(0%)	0(0%)	1 (1.0%)		
IOP Lowering Procedures	1(1.2%)	0(0%)	0(0%)	1.2%(-1.2%,3.6%)	
≥15 Letters Loss from Baseline	5(6.2%)	4(4.8%)	7(7.1%)	-1%(-8.3%,6.3%)	-2.4%(-9.2%,4.5%)
Death	1(1.2%)	3(3.6%)	2(2%)	-0.8%(-4.5%,2.9%)	1.5%(-3.3%,6.4%)
Escape Therapy	7(8.6%)	9(10.7%)	12(12.2%)	-3.6%(-12.5%,5.3%)	-1.5%(-10.8%,7.7%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 7: Summary of Number of Baseline Phakic Subjects who had Cataract Surgery by visit

Time of Surgery	Treatment: N (%)			Total N=291
	DEX 700 N=148	DEX 350 N=125	Sham N=18	
≤Month 6	5(3.4%)	6(4.8%)	3(16.7%)	14(4.8%)
> Month 6 ≤ Month 12	20(13.5%)	12(9.6%)	2(11.1%)	34(11.7%)
Month 15	12(8.1%)	10(8%)	3(16.7%)	25(8.6%)
Month 18	20(13.5%)	17(13.6%)	1(5.6%)	38(13.1%)
Month 21	25(16.9%)	18(14.4%)	2(11.1%)	45(15.5%)
Month 24	21(14.2%)	23(18.4%)	2(11.1%)	46(15.8%)
Month 27	20(13.5%)	13(10.4%)	1(5.6%)	34(11.7%)
Month 30	11(7.4%)	11(8.8%)	0 (0.0%)	22(7.6%)
Month 33	9(6.1%)	11(8.8%)	1(5.6%)	21(7.2%)
Month 36	4(2.7%)	4(3.2%)	3(16.7%)	11(3.8%)
Month 39	1(0.7%)	0 (0.0%)	0 (0.0%)	1(0.3%)

Table 8: Summary of Number of Baseline Phakic Subjects who had Cataract AE by visit

Time of Surgery	Treatment: N (%)			Total N=364
	DEX 700 N=166	DEX 350 N=149	Sham N=49	
≤Month 6				
> Month 6 ≤ Month 12				
Month 15				
Month 18				
Month 21				
Month 24				
Month 27				
Month 30				
Month 33				
Month 36				
Month 39				

Table 9: Summary of Number of Subjects who reported at least one IOP related AE by visit

Time of Surgery	Treatment: N (%)			Total N=245
	DEX 700 N=120	DEX 350 N=107	Sham N=18	
≤Month 6				
> Month 6 ≤ Month 12				
Month 15				
Month 18				
Month 21				
Month 24				
Month 27				
Month 30				
Month 33				
Month 36				
Month 39				

Table 10: Summary of Study duration by number of Injection by treatment (Month)

NUMINJ	DEX 700			DEX 350			Sham			Total		
	Mean (std)	Median	Min	Mean (std)	Median	Min	Mean (std)	Median	Min	Mean (std)	Median	Min
1	12(10.5)	7.5	1.5	15(15)	7.5	1	7.5(7.5)	6	1	10.5(10.5)	6	1
2	21(12)	15	6	21(10.5)	21	9	18(10.5)	12	6	21(10.5)	12	6
3	30(9)	36	12	27(9)	27	12	24(9)	21	15	27(9)	27	12
4	33(6)	36	21	30(6)	36	18	33(6)	36	18	30(6)	36	18
5	36(3)	36	24	33(3)	36	24	36(3)	36	27	36(3)	36	24
6	36(1.5)	36	30	36(1.5)	36	36	36(1.5)	36	36	36(1.5)	36	30
7	39(1)	39	39	39(1)	39	39	39(1)	39	36	39(1)	39	36
Overall												

Source: Reviewer's Analysis.

Table 11: Summary of selected adverse events by number of Injections

NUMINJ	IOP Related AE			Cataract Surgery			Serious Ocular AE		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
1	13/40(32.5)	10/34(29.4)	2/101(2)	2/28(7.1)	0/26(0)	3/74(4.1)	0/40(0)	0/34(0)	1/101(1)
2	19/51(37.3)	11/42(26.2)	3/51(5.9)	10/34(29.4)	5/32(15.6)	1/38(2.6)	7/51(13.7)	2/42(4.8)	0/51(0)
3	12/36(33.3)	9/37(24.3)	3/40(7.5)	9/22(40.9)	7/24(29.2)	1/23(4.3)	3/36(8.3)	0/37(0)	0/40(0)
4	12/37(32.4)	16/38(42.1)	3/23(13)	18/27(66.7)	16/27(59.3)	1/16(6.3)	5/37(13.5)	1/38(2.6)	1/23(4.3)

5	16/44(36.4)	12/37(32.4)	2/29(6.9)	31/40(77.5)	22/29(75.9)	3/24(12.5)	2/44(4.5)	3/37(8.1)	1/29(3.4)
6	35/85(41.2)	39/95(41.1)	3/49(6.1)	55/66(83.3)	54/71(76.1)	3/31(9.7)	4/85(4.7)	7/95(7.4)	0/49(0)
7	13/31(41.9)	10/37(27)	2/35(5.7)	23/26(88.5)	21/27(77.8)	6/24(25)	3/31(9.7)	1/37(2.7)	1/35(2.9)

Source: Reviewer's analysis. All subjects who received a rescue therapy are treated as treatment failures

Table 12: BCVA summary for the 22 subjects who had BCVA measurement at Month 39 but were not re-treated at Month 36

Treatment	# of subjects	Month 36			Month 39		
		Mean (Std)	Min	Max	Mean (Std)	Min	Max
DEX 350	11	-7.73 (22.7)	-44	30	1.00 (15.04)	-22	23
DEX 700	6	-3.67 (21.39)	-40	15	5.67 (7.86)	-6	15
Sham	5	2.00 (11.51)	-17	14	1.40 (8.68)	-9	15

Table 13: Mean BCVA Change from Baseline at Month 39/final visit (Month 36 BCVA used for the 22 subjects)

Study	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 10	4.13(13.9)	5.06(12.1)	0.79(11.9)	3.34(0.53,6.16)	4.27(1.7,6.87)
Study 11	0.02(17.8)	0.5(15.9)	0.85(13.6)	-0.83(-4.27,2.6)	-0.35(-3.6,2.9)
Pooled	2.06 (16.1)	2.83 (14.2)	0.82(12.7)	1.24 (-0.98, 3.47)	2.02 (-0.06,4.10)
Pseudophakic Subjects					
Study 10	9.52(10.5)	6.15(10.3)	2.68(10.4)	6.84(2.56,11.13)	3.47(-0.7,7.65)
Study 11	1.5(12.1)	5.71(10.9)	0.24(14)	1.26(-4.31,6.82)	5.47(0.1,10.78)
Pooled	5.80(11.8)	5.95(10.5)	1.47(12.3)	4.33(0.77,7.89)	4.48 (1.15,7.80)

Table 14: Proportion of subjects with ≥ 15 letters from baseline at Month 39/final visit

Study	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
Study 10	34 (20.9%)	31(18.7%)	19(10.9%)	9.9%(2.1%,17.8%)	7.8%(0.2%,15.4%)
Study 11	30(18.2%)	24(15.2%)	16(9.8%)	8.4%(0.9%,15.8%)	5.4%(-1.8%,12.6%)
Pooled					
Pseudophakic Subjects					
Study 10	14(31.8%)	7(14.9%)	8(16%)	15.8%(-1.3%,32.9%)	-1.1%(-15.5%,13.3%)
Study 11	3(7.9%)	5(13.2%)	3(6.1%)	1.8%(-9.1%,12.7%)	7%(-5.6%,19.7%)
Pooled	17 (20.7%)	12 (14.1%)	11 (11.1%)	9.6% (-1.1%, 20.4%)	4.9% (-6.6%, 12.7%)

*Month 36 BCVA was used for the 22 subjects who had a BCVA measure at Month 39 Without being re-treated at Month 36

Appendix

Table 15: The 22 subjects with BCVA at Month 39 without re-treatment at Month 36

USUBJID	TRTGRP	BASELENS	BCVA			Cataract surgery (1=Yes)	Cataract AE (1=Yes)	Month of surgery	IOP (1=Yes)
			Month 33	Month 36	Month 39				
206207010-3084-5018	DEX 350	Phakic	9	9	13	1	1	10.5	0
206207010-3193-5266	DEX 350	Phakic	-26	-29	-22	0	0		0
206207010-4258-4008	DEX 350	Phakic	6	-12	-18	0	1		1
206207010-4447-4315	DEX 350	Pseudophakic	6	6	8	0	0		1
206207010-4539-4385	DEX 350	Phakic	-4	1	-1	1	1	24	1
206207010-6415-4483	DEX 350	Phakic	30	30	23	1	1	15	1
206207011-2707-7106	DEX 350	Phakic	3	3	9	0	1		1
206207011-4220-7780	DEX 350	Phakic	-39	-39	5	1	1	36	1
206207011-4292-7080	DEX 350	Phakic	-17	-17	-20	0	0		1
206207011-4533-7311	DEX 350	Phakic	-44	-44	0	1	1	33	1
206207011-5255-8392	DEX 350	Phakic	7	7	14	1	1	21	1
206207010-4396-4585	DEX 700	Phakic	7	13	13	1	1	27	1
206207011-4220-7728	DEX 700	Pseudophakic	15	15	2	0	0		1
206207011-4220-7838	DEX 700	Phakic	-40	-40	8	1	1	36	1
206207011-4408-7497	DEX 700	Pseudophakic	-5	-17	-6	0	0		1
206207011-4498-7512	DEX 700	Phakic	9	9	15	1	0	18	0
206207011-4498-7986	DEX 700	Phakic	-2	-2	2	1	1	18	0
206207010-4396-4580	Sham	Phakic	-10	-17	-9	0	0		0
206207010-4396-4584	Sham	Phakic	9	14	15	0	0		0
206207010-4452-4338	Sham	Pseudophakic	6	6	0	0	0		0
206207011-4044-7475	Sham	Pseudophakic	5	5	2	0	0		0
206207011-4234-7190	Sham	Pseudophakic	2	2	-1	0	0		0

Source: Reviewer's Analysis.

Table 16: The 16 subjects with no BCVA at Month 39 after being re-treatment at Month 36

USUBJID	TRTGRP	BASELENS
206207010-4353-4746	Sham	Phakic
206207010-4353-5036	Sham	Pseudophakic
206207010-4377-4611	Sham	Phakic
206207010-4421-4825	Sham	Pseudophakic
206207010-4421-4857	DEX 350	Phakic
206207010-6415-4485	DEX 700	Pseudophakic
206207010-6685-4865	DEX 350	Phakic
206207010-6685-4866	Sham	Phakic
206207010-7871-4852	DEX 350	Pseudophakic
206207011-4242-7676	Sham	Phakic
206207011-4303-8069	Sham	Pseudophakic
206207011-4406-7058	Sham	Phakic
206207011-4580-7525	Sham	Phakic
206207011-4618-7282	Sham	Phakic
206207011-6684-7803	DEX 700	Phakic
206207011-6690-7944	DEX 700	Phakic

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/s/

MICHAEL J PUGLISI
04/29/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22315/S-009

**REVIEW EXTENSION –
EFFICACY SUPPLEMENT**

Allergan Inc.
Attention: Libette Luce, MA
Senior Manager, US Regulatory Affairs
200 Somerset Corporate Blvd.
Bldg. 200, #6001
Bridgewater, NJ 08807

Dear Ms. Luce:

Please refer to your Supplemental New Drug Application (sNDA) dated June 12, 2013, received June 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ozurdex (dexamethasone intravitreal implant) 0.7 mg.

We continue our review of the application and the associated labeling. We reference our requests for additional information dated March 26 (two) and March 27, 2014, and the Type-A meeting held on April 1, 2014. We acknowledge receipt of your meeting briefing package dated March 26, 2014, and amendments dated March 31 and April 7, 2014. We consider the April 7, 2014, submission a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 13, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 13, 2014.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

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

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/s/

RENATA ALBRECHT
04/10/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Transplant and Ophthalmology
Products

Review Comments Transmittal

DATE: 3/27/14

To: Allergan, Inc.	From: Michael Puglisi, Regulatory Project Manager
Attn: Libette Luce, MA	e-mail: Michael.puglisi@fda.hhs.gov
e-mail: luce_libette@allergan.com	Phone Number: 301-796-0791
Phone: 908-203-2645	

Subject: NDA 22315/S-009

Total no. of pages including cover: 3

Comments:

Dear Ms. Luce,

Attached please find additional Clinical/Stats comments concerning the Ozurdex (dexamethasone intravitreal implant) DME efficacy supplement. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike

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Review Comments:

In our analysis of **Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF)** sent on 3/26/2014, after excluding site 2707, subjects who received rescue therapy were set to the "no change (-5 to +5 letters)" category regardless of their last observed BCVA value before receiving rescue therapy. However, we have now reanalyzed the data based on the last BCVA value carried forward (LOCF) before rescue therapy for subjects with a BCVA change less than 5 and set subjects with a BCVA value ≥ 5 to the "no change (-5 to +5 letters)" category regardless of their last observed BCVA value before receiving rescue therapy. The revised table is presented below:

Revised Table: Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF)

BCVA Change	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163
≥ 15 Letters Improvement	32(19.6)	33(19.9)	18(10.9)	25(15.2)	21(13.3)	16(9.8)
≥ 10 and < 15 Letters Improvement	27(16.6)	21(12.7)	15(9.1)	18(10.9)	16(10.1)	19(11.7)
≥ 5 and < 10 Letters Improvement	27(16.6)	31(18.7)	20(12.1)	17(10.3)	31(19.6)	16(9.8)
No Change (-5 to +5 Letters)	45(27.6)	56(33.7)	75(45.5)	58(35.2)	42(26.6)	76(46.6)
≥ 5 and < 10 Letters Worsening	12(7.4)	12(7.2)	13(7.9)	10(6.1)	10(6.3)	13(8)
≥ 10 and < 15 Letters Worsening	5(3.1)	4(2.4)	7(4.2)	5(3.0)	13(8.2)	5(3.1)
≥ 15 Letters Worsening	15(9.2)	9(5.4)	17(10.3)	32(19.4)	25(15.8)	18(11.0)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy but fell into one of the "improvement" categories were set to the "no change" category.

In addition, please see the table below which lists the subjects who received rescue therapy but had a BCVA value of ≥ 15 letters imputed at Month 36. Please explain why subjects who are a “success” in the primary endpoint require rescue therapy.

Subjects who received a rescue therapy but had a BCVA value ≥ 15 imputed at Month 36

USUBJID	TRTGRP	Rescue therapy day	BCVA	DTYPE	BASELINE BCVA	CHG
206207011-5020-7214	DEX 350	277	80	VA-LOCF	58	22
206207011-4298-7027	DEX 350	645	77	VA-LOCF	42	35
206207011-6690-7944	DEX 700	358	64	VA-LOCF	48	16
206207011-4242-7677	DEX 700	659	74	VA-LOCF	51	23
206207011-4287-7078	DEX 700	409	64	VA-LOCF	47	17
206207010-4353-5037	DEX 700	491	53	VA-LOCF	36	17
206207011-4234-7191	DEX 700	894	74	VA-LOCF	58	16
206207010-6653-4655	DEX 700	542	78	VA-LOCF	62	16
206207010-4082-4025	Sham	231	83	VA-LOCF	66	17
206207010-4397-4829	Sham	196	72	VA-LOCF	56	16
206207010-4447-4961	Sham	534	55	VA-LOCF	35	20
206207011-9095-7761	Sham	286	57	VA-LOCF	41	16

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/s/

MICHAEL J PUGLISI
03/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			PEDIATRIC AND MATERNAL HEALTH STAFF REQUEST FOR CONSULTATION	
TO: CDER Pediatric and Maternal Health Staff <i>(please check)</i> Pediatrics <input type="checkbox"/> Maternal Health <input checked="" type="checkbox"/> Both <input type="checkbox"/>			FROM <i>(Name, Office/Division, and Phone Number of Requestor)</i> : Lori Kotch, Nonclinical Team leader OND/OAP/DTOP x64831	
DATE 3/27/14	IND NO.	NDA/BLA NO. 22315/S-009	TYPE OF DOCUMENT Efficacy supplement	DATE OF DOCUMENT 6/12/13
NAME OF DRUG Ozurdex (dexamethasone intravitreal implant) 0.7 mg		NAME OF FIRM Allergan, Inc.	CLASSIFICATION OF DRUG	PDUFA Goal Date 4/13/14
Requested Consult Completion Date: 3/31/14		<input checked="" type="checkbox"/> Urgent* (< 14 days)	<input type="checkbox"/> Priority (14-29 days)	<input type="checkbox"/> Routine \geq 30 days
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.				
REASON FOR REQUEST				
Pedicatrics: <input type="checkbox"/> Labeling Review <input type="checkbox"/> Written Request/PPSR <input type="checkbox"/> PREA PMR/General Regulatory Question <input type="checkbox"/> SPA <input type="checkbox"/> Action Letter Review <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Other Protocol Review <input type="checkbox"/> Meeting Attendance <input type="checkbox"/> PeRC Preparation Assistance <input type="checkbox"/> Other (please explain):			Maternal Health Team: <input checked="" type="checkbox"/> Labeling Review <input type="checkbox"/> Pregnancy Exposure Registry (protocol or report) <input type="checkbox"/> Clinical Lactation Study (protocol or report) <input type="checkbox"/> Pregnancy PK (protocol or report) <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Risk Management – Pregnancy Prevention and Planning <input type="checkbox"/> Evaluation of possible safety signal <input type="checkbox"/> Guidance development <input type="checkbox"/> Other (please explain):	
Link to electronic submission (if available): \\CDSESUB1\EVSPROD\NDA022315\022315.enx			Materials to be reviewed: 6/12/13 Efficacy Supplement (in EDR), Nonclinical Review dated 3/12/14 (in DARRTS), DTOP Proposed PI (link attached)	
1. Please briefly describe the submission including drug's indication(s): Indicated for treatment of diabetic macular edema. 2. Describe in detail the reason for your consult. Include specific questions: We would like some advice regarding how best to address dose/exposure multiples and communicate risk in section 8.1 of the label. Melissa Tassinari has already been in contact about this matter. Shaerepoint link to label (under negotiation with applicant): http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas/NDA%2022315%20S009%20Ozurdex/NDA%2022315S009%20Labeling.docx				
Review team: Project Manager: Mike Puglisi Clinical reviewer & Team Leader: Lucious Lim, William Boyd Pharmacology/Toxicology reviewer & Team Leader: Ilona Bebenek, Lori Kotch Clinical Pharmacology reviewer & Team Leader: Gerlie Gieser, Phil Colangelo Other:				
PRINTED NAME or SIGNATURE OF REQUESTOR: Lori Kotch			METHOD OF DELIVERY (Please check) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> HAND <input type="checkbox"/> OTHER	

Version: DARRTS 06/01/2011

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/s/

MICHAEL J PUGLISI
03/27/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Transplant and Ophthalmology
Products

Review Comments Transmittal

DATE: 3/26/14

To: Allergan, Inc.	From: Michael Puglisi, Regulatory Project Manager
Attn: Libette Luce, MA	e-mail: Michael.puglisi@fda.hhs.gov
e-mail: luce_libette@allergan.com	Phone Number: 301-796-0791
Phone: 908-203-2645	

Subject: NDA 22315/S-009

Total no. of pages including cover: 4

Comments:

Dear Ms. Luce,

Attached please find additional Clinical/Stats comments concerning the Ozurdex (dexamethasone intravitreal implant) DME efficacy supplement. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike

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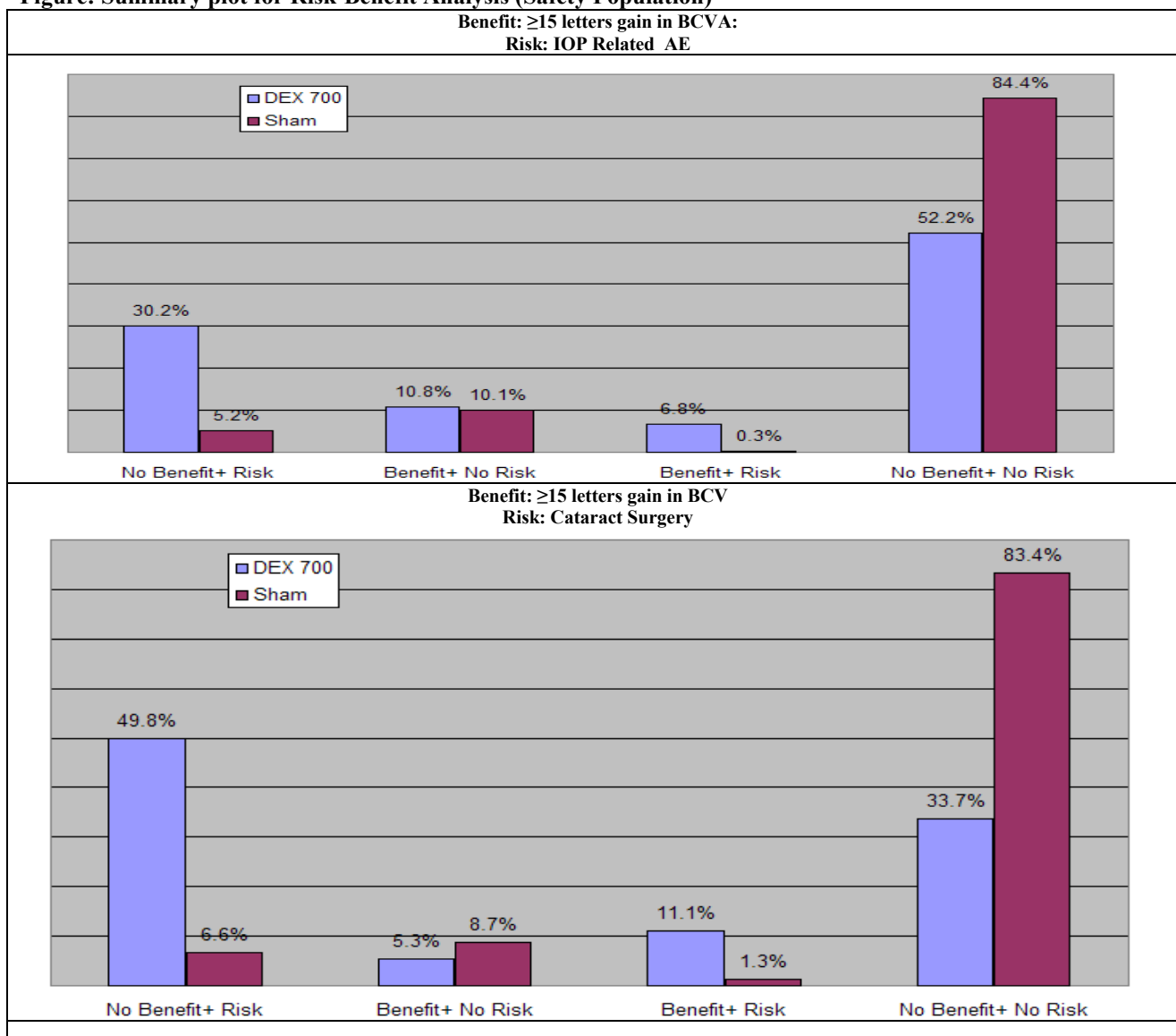
Review Comments:

Please look at the risk benefit from the two trials and confirm/reproduce the attached figures/tables showing our analysis.

These figures are for the DEX 700 and sham doses. Please also perform the same analyses for the DEX 350 and sham control arms.

Please check and confirm/reproduce the analysis of Categorical Summary of BCVA change from baseline at 3 years (ITT LOCF) and discuss the higher rates of 15 or more letters of Worsening in BCVA seen in Study -011.

Figure: Summary plot for Risk-Benefit Analysis (Safety Population)



Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Table: Summary of Risk-Benefit Analysis (Safety Population)

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		DEX 700 N=324	Sham N=327	DEX 700 N=324	Sham N=327	DEX 700 N=324	Sham N=327	DEX 700 N=324	Sham N=327
BCVA improvement of ≥ 15 letters	Any AE	2(0.6%)	0(0%)	255(78.7%)	225(68.8%)	55(17%)	34(10.4%)	12(3.7%)	68(20.8%)
	Any Ocular AE	11(3.4%)	11(3.4%)	228(70.4%)	166(50.8%)	46(14.2%)	23(7%)	39(12%)	127(38.8%)
	Any Serious AE	34(10.5%)	20(6.1%)	87(26.9%)	64(19.6%)	23(7.1%)	14(4.3%)	180(55.6%)	229(70%)
	Any Ocular Serious AE	53(16.4%)	33(10.1%)	20(6.2%)	2(0.6%)	4(1.2%)	1(0.3%)	247(76.2%)	291(89%)
	Any Severe AE	27(8.3%)	19(5.8%)	121(37.3%)	84(25.7%)	30(9.3%)	15(4.6%)	146(45.1%)	209(63.9%)
	Any Severe Ocular AE	40(12.3%)	33(10.1%)	74(22.8%)	32(9.8%)	17(5.2%)	1(0.3%)	193(59.6%)	261(79.8%)
	Any IOP Related AE	35(10.8%)	33(10.1%)	98(30.2%)	17(5.2%)	22(6.8%)	1(0.3%)	169(52.2%)	276(84.4%)
	≥ 10 mm Hg IOP Change from Baseline at any visit	44(13.6%)	34(10.4%)	78(24.1%)	13(4%)	13(4%)	0(0%)	189(58.3%)	280(85.6%)
	≥ 25 mm Hg IOP at any visit	42(13%)	34(10.4%)	91(28.1%)	15(4.6%)	15(4.6%)	0(0%)	176(54.3%)	278(85%)
	≥ 35 mm Hg IOP at any visit	55(17%)	34(10.4%)	18(5.6%)	3(0.9%)	2(0.6%)	0(0%)	249(76.9%)	290(88.7%)
	Cataract Surgery in Phakic Subjects	13(5.3%)	20(8.7%)	121(49.8%)	15(6.6%)	27(11.1%)	3(1.3%)	82(33.7%)	191(83.4%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Subjects who required escape therapy were set as treatment failures.

Table: Categorical Summary of BCVA Change from Baseline at 3 Years (ITT LOCF)

BCVA Change	Study 206207-010			Study 206207-011		
	Treatment: N (%)			Treatment: N (%)		
	DEX 700 N=163	DEX 350 N=166	Sham N=165	DEX 700 N=165	DEX 350 N=158	Sham N=163
≥15 Letters Improvement	32 (19.6)	33(19.9)	18(10.9)	25(15.2)	21(13.3)	16(9.8)
≥10 and <15 Letters Improvement	27(16.6)	21(12.7)	15(9.1)	18(10.9)	16(10.1)	19(11.7)
≥5 and <10 Letters Improvement	27(16.6)	31(18.7)	20(12.1)	17(10.3)	31(19.6)	16(9.8)
No Change (-5 to +5 Letters)	49 (30.1)	58(34.9)	85(51.5)	66(40)	49(31)	85(52.1)
>=5 and <10 Letters Worsening	12(7.4)	12(7.2)	8(4.8)	8(4.8)	8(5.1)	9(5.5)
>=10 and <15 Letters Worsening	5(3.1)	3(1.8)	6(3.6)	5(3)	11(7)	4(2.5)
>=15 Letters Worsening	11(6.7)	8(4.8)	13(7.9)	26(15.8)	22(13.9)	14(8.6)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Subjects who received escape therapy were set to the "no change" category.

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/s/

MICHAEL J PUGLISI
03/26/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Transplant and Ophthalmology
Products

Review Comments Transmittal

DATE: 3/26/14

To: Allergan, Inc.	From: Michael Puglisi, Regulatory Project Manager
Attn: Libette Luce, MA	e-mail: Michael.puglisi@fda.hhs.gov
e-mail: luce_libette@allergan.com	Phone Number: 301-796-0791
Phone: 908-203-2645	

Subject: NDA 22315/S-009

Total no. of pages including cover: 6

Comments:

Dear Ms. Luce

Attached please find Clinical/Stats comments concerning the Ozurdex (dexamethasone intravitreal implant) DME efficacy supplement. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike

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Review Comments:

We have reanalyzed the data for study 11 by excluding study site 2707, and we have the following new analyses.

The analysis is Month 36 in the ITT population (with LOCF). Any patients who received rescue therapy in the trials are classified as failure.

Please confirm that you can reproduce these new analyses.

Please generate figures for the efficacy outcome using the data derived from the new analyses for the two studies.

Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years

(Excluding subjects from Study 206207-011, site 2707)

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	32/163(19.6%)	33/166(19.9%)	18/165(10.9%)	8.7% (1.0%, 16.5%)	9.0% (1.3%, 16.7%)
011	25/165(15.2%)	21/158(13.3%)	16/163(9.8%)	5.3%(-1.8%, 12.5%)	3.5%(-3.5%, 10.5%)

LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

Mean Change from Baseline in BCVA at 3 Years
(Excluding subjects from Study 206207-011, site 2707)

Studies	Treatment: N (%)			%Diff (95% CI)	
	DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	3.71(14.1)	5.10(12.3)	1.02(11.6)	2.67(-0.1,5.5)	4.10(1.5,6.7)
011	-0.33(17.6)	-0.01(15.7)	0.70(13.4)	-1.03(-4.4,2.4)	-0.7(-3.9,2.5)

LOCF was used for imputing missing data.

Proportion of Pseudophakic and Phakic Subjects with a ≥ 15 letter Improvement in BCVA from Baseline at 3 Years in Studies -010 and -011
(Excluding subjects from Study 206207-011, site 2707)

Studies	Population	Treatment: N (%)			%Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	Phakic	18(15.1%)	25(21%)	10(8.7%)	6.4%(-1.8%, 14.7%)	12.3% (3.4%, 21.3%)
	Pseudophakic	14(31.8%)	8(17%)	8(16%)	15.8%(-1.3%, 32.9%)	1% (-13.8%, 15.8%)
011	Phakic	22(17.3%)	17(14.2%)	13(11.4%)	5.9%(-2.9%, 14.7%)	2.8% (-5.8%, 11.3%)
	Pseudophakic	3(7.9%)	4(10.5%)	3(6.1%)	1.8%(-9.1%, 12.7%)	4.4% (-7.4%, 16.2%)
Pooled	Phakic	40(16.3%)	42(17.6%)	23(10%)	6.2% (0.2%, 12.3%)	7.5% (1.3%,13.7%)
	Pseudophakic	17(20.7%)	12(14.1%)	11(11.1%)	9.6% (-1.1%, 20.4%)	3% (-6.6%, 12.7%)

LOCF was used for imputing missing data. Subjects who received escape therapy were set as treatment failures.

**Mean Change from Baseline in BCVA in Pseudophakic and Phakic Patients
in Studies -010 and -011 at 3 Years
(Excluding subjects from Study 206207-011, site 2707)**

Studies	Population	Treatment: Mean (Std)			Mean Diff (95% CI)	
		DEX 700	DEX 350	Sham	DEX 700 vs. Sham	DEX 350 vs. Sham
010	Phakic	1.6(14.7)	4.6(13)	0.3(12)	1.3(-2.1,4.8)	4.2(1,7.5)
	Pseudophakic	9.3(10.8)	6.5(10.2)	2.6(10.4)	6.7(2.3,11)	3.8(-0.3,8)
011	Phakic	-0.9(18.9)	-1.6(16.8)	1(13.2)	-1.8(-6,2.3)	-2.6(-6.5,1.3)
	Pseudophakic	1.5(11.9)	5(10.7)	0.1(13.9)	1.4(-4.1,6.9)	4.9(-0.3,10.2)
Pooled	Phakic	0.3(17)	1.5(15.3)	0.6(12.6)	-0.3(-3,2.4)	0.8(-1.7,3.4)
	Pseudophakic	5.7(11.9)	5.8(10.4)	1.4(12.2)	4.3(0.8,7.9)	4.5(1.2,7.7)

LOCF was used for imputing missing data.

Table xx: Summary of Adverse Events (AE) (Pooled: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=324	DEX 350 N=320	Sham N=328	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	310(95.7%)	311(97.2%)	260(79.3%)	16.4%(11.5%,21.3%)	17.9%(13.2%,22.7%)
Any Ocular AE	274(84.6%)	282(88.1%)	190(57.9%)	26.6%(20%,33.3%)	30.2%(23.8%,36.6%)
Any Serious AE	110(34%)	113(35.3%)	79(24.1%)	9.9%(2.9%,16.8%)	11.2%(4.2%,18.2%)
Any Ocular Serious AE	24(7.4%)	14(4.4%)	4(1.2%)	6.2%(3.1%,9.3%)	3.2%(0.6%,5.7%)
Any Severe AE	151(46.6%)	149(46.6%)	100(30.5%)	16.1%(8.7%,23.5%)	16.1%(8.7%,23.5%)
Any Ocular Severe AE	91(28.1%)	71(22.2%)	34(10.4%)	17.7%(11.8%,23.6%)	11.8%(6.2%,17.4%)
Any IOP Related AE	120(37%)	107(33.4%)	18(5.5%)	31.5%(25.7%,37.4%)	27.9%(22.2%,33.7%)
≥10 mm Hg IOP	91(28.1%)	79(24.7%)	13(4%)	24.1%(18.8%,29.5%)	20.7%(15.5%,25.9%)
Change from Baseline at any visit					
≥25 mm Hg IOP at any visit	106(32.7%)	86(26.9%)	15(4.6%)	28.1%(22.6%,33.7%)	22.3%(16.9%,27.7%)
≥35 mm Hg IOP at any visit	20(6.2%)	16(5%)	3(0.9%)	5.3%(2.4%,8.1%)	4.1%(1.5%,6.7%)
Glaucoma	4(1.2%)	3(0.9%)	1(0.3%)	0.9%(-0.4%,2.3%)	0.6%(-0.6%,1.8%)
IOP Lowering Procedures	4(1.2%)	1(0.3%)	1(0.3%)	0.9%(-0.4%,2.3%)	0%(-0.8%,0.9%)
Cataract Surgery in Baseline Phakic Subjects	148(60.9%)	125(53%)	18(7.8%)	53.1%(46%,60.1%)	45.1%(37.9%,52.4%)
≥15 Letters Loss from Baseline	47(14.5%)	34(10.6%)	35(10.7%)	3.8%(-1.3%,8.9%)	0%(-4.8%,4.7%)
Death	9(2.8%)	14(4.4%)	5(1.5%)	1.3%(-1%,3.5%)	2.9%(0.2%,5.5%)
Escape Therapy	31(9.6%)	38(11.9%)	63(19.2%)	-9.6%(-15%,-4.3%)	-7.3%(-12.9%,-1.8%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table xx1: Summary of Adverse Events (AE) (Study 10: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=160	DEX 350 N=155	Sham N=164	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	153(95.6%)	162(98.2%)	124(75.6%)	20%(12.7%,27.3%)	22.6%(15.7%,29.5%)
Any Ocular AE	139(86.9%)	147(89.1%)	85(51.8%)	35%(25.8%,44.3%)	37.3%(28.3%,46.3%)
Any Serious AE	52(32.5%)	52(31.5%)	34(20.7%)	11.8%(2.2%,21.3%)	10.8%(1.4%,20.2%)
Any Ocular Serious AE	9(5.6%)	7(4.2%)	2(1.2%)	4.4%(0.5%,8.4%)	3%(-0.5%,6.5%)
Any Severe AE	71(44.4%)	77(46.7%)	42(25.6%)	18.8%(8.6%,29%)	21.1%(10.9%,31.2%)
Any Ocular Severe AE	45(28.1%)	38(23%)	17(10.4%)	17.8%(9.4%,26.1%)	12.7%(4.7%,20.6%)
Any IOP Related AE	65(40.6%)	60(36.4%)	5(3%)	37.6%(29.5%,45.6%)	33.3%(25.5%,41.1%)
≥10 mm Hg IOP	51(31.9%)	46(27.9%)	4(2.4%)	29.4%(21.8%,37%)	25.4%(18.2%,32.7%)
Change from Baseline at any visit					
≥25 mm Hg IOP at any visit	62(38.8%)	55(33.3%)	5(3%)	35.7%(27.7%,43.7%)	30.3%(22.6%,37.9%)
≥35 mm Hg IOP at any visit	14(8.8%)	12(7.3%)	1(0.6%)	8.1%(3.6%,12.7%)	6.7%(2.5%,10.8%)
Glaucoma	3(1.9%)	2(1.2%)	1(0.6%)	1.3%(-1.2%,3.7%)	0.6%(-1.4%,2.7%)
IOP Lowering Procedures	3(1.9%)	1(0.6%)	1(0.6%)	1.3%(-1.2%,3.7%)	0%(-1.7%,1.7%)
Cataract Surgery in Baseline Phakic Subjects	72(61.5%)	72(61%)	8(7%)	54.6%(44.6%,64.5%)	54.1%(44.1%,64%)
≥15 Letters Loss from Baseline	15(9.4%)	9(5.5%)	17(10.4%)	-1%(-7.5%,5.5%)	-4.9%(-10.7%,0.9%)
Death	4(2.5%)	5(3%)	3(1.8%)	0.7%(-2.5%,3.8%)	1.2%(-2.1%,4.5%)
Escape Therapy	10(6.3%)	17(10.3%)	23(14%)	-7.8%(-14.3%,-1.3%)	-3.7%(-10.8%,3.3%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table xx2: Summary of Adverse Events (AE) (Study 11: All Treated Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=160	DEX 350 N=165	Sham N=164	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	157(95.7%)	149(96.1%)	136(82.9%)	12.8%(6.3%,19.3%)	13.2%(6.7%,19.7%)
Any Ocular AE	135(82.3%)	135(87.1%)	105(64%)	18.3%(8.9%,27.7%)	23.1%(14%,32.1%)
Any Serious AE	58(35.4%)	61(39.4%)	45(27.4%)	7.9%(-2.1%,17.9%)	11.9%(1.6%,22.2%)
Any Ocular Serious AE	15(9.1%)	7(4.5%)	2(1.2%)	7.9%(3.2%,12.6%)	3.3%(-0.4%,7%)
Any Severe AE	80(48.8%)	72(46.5%)	58(35.4%)	13.4%(2.8%,24%)	11.1%(0.4%,21.8%)
Any Ocular Severe AE	46(28%)	33(21.3%)	17(10.4%)	17.7%(9.4%,26%)	10.9%(3%,18.9%)
Any IOP Related AE	55(33.5%)	47(30.3%)	13(7.9%)	25.6%(17.3%,33.9%)	22.4%(14.1%,30.7%)
≥10 mm Hg IOP	40(24.4%)	33(21.3%)	9(5.5%)	18.9%(11.5%,26.3%)	15.8%(8.5%,23.1%)
Change from Baseline at any visit					
≥25 mm Hg IOP at any visit	44(26.8%)	31(20%)	10(6.1%)	20.7%(13%,28.4%)	13.9%(6.6%,21.2%)
≥35 mm Hg IOP at any visit	6(3.7%)	4(2.6%)	2(1.2%)	2.4%(-0.9%,5.8%)	1.4%(-1.6%,4.4%)
Glaucoma	1(0.6%)	1(0.6%)	0(0%)	0.6%(-0.6%,1.8%)	0.6%(-0.6%,1.9%)
IOP Lowering Procedures	1(0.6%)		0(0%)	0.6%(-0.6%,1.8%)	0%(-1.7%,1.7%)
Cataract Surgery in Baseline Phakic Subjects	76(60.3%)	53(44.9%)	10(8.7%)	51.6%(41.6%,61.6%)	36.2%(25.9%,46.6%)
≥15 Letters Loss from Baseline	32(19.5%)	25(16.1%)	18(11%)	8.5%(0.8%,16.3%)	5.2%(-2.4%,12.7%)
Death	5(3%)	9(5.8%)	2(1.2%)	1.8%(-1.3%,5%)	4.6%(0.5%,8.6%)
Escape Therapy	21(12.8%)	21(13.5%)	40(24.4%)	-11.6%(-19.9%,-3.3%)	-10.8%(-19.3%,-2.3%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table xx2: Summary of Adverse Events (AE) (Pooled: Pseudophakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	DEX 700 N=81	DEX 350 N=84	Sham N=98	DEX 700 vs. Sham	DEX 350 vs. Sham
Any AE	77(95.1%)	83(98.8%)	84(85.7%)	9.3%(1%,17.7%)	13.1%(5.8%,20.4%)
Any Ocular AE	59(72.8%)	70(83.3%)	60(61.2%)	11.6%(-2.1%,25.3%)	22.1%(9.6%,34.6%)
Any Serious AE	29(35.8%)	36(42.9%)	36(36.7%)	-0.9%(-15.1%,13.2%)	6.1%(-8.1%,20.4%)
Any Ocular Serious AE	2(2.5%)	0(0%)	0(0%)	2.5%(-0.9%,5.8%)	
Any Severe AE	35(43.2%)	40(47.6%)	37(37.8%)	5.5%(-9%,19.9%)	9.9%(-4.5%,24.2%)
Any Ocular Severe AE	10(12.3%)	15(17.9%)	8(8.2%)	4.2%(-4.8%,13.2%)	9.7%(-0.1%,19.5%)
Any IOP Related AE	25(30.9%)	29(34.5%)	9(9.2%)	21.7%(10.1%,33.3%)	25.3%(13.7%,37%)
≥10 mm Hg IOP Change from Baseline at any visit	20(24.7%)	24(28.6%)	2(2%)	22.7%(12.9%,32.4%)	26.5%(16.5%,36.6%)
≥25 mm Hg IOP at any visit	21(25.9%)	24(28.6%)	6(6.1%)	19.8%(9.1%,30.5%)	22.4%(11.7%,33.2%)
≥35 mm Hg IOP at any visit	6(7.4%)	4(4.8%)	1(1%)	6.4%(0.3%,12.4%)	3.7%(-1.2%,8.7%)
Glaucoma	1(1.2%)	1(1.2%)	0(0%)	1.2%(-1.2%,3.6%)	1.2%(-1.1%,3.5%)
IOP Lowering Procedures	1(1.2%)	0(0%)	0(0%)	1.2%(-1.2%,3.6%)	
≥15 Letters Loss from Baseline	5(6.2%)	4(4.8%)	7(7.1%)	-1%(-8.3%,6.3%)	-2.4%(-9.2%,4.5%)
Death	1(1.2%)	3(3.6%)	2(2%)	-0.8%(-4.5%,2.9%)	1.5%(-3.3%,6.4%)
Escape Therapy	7(8.6%)	9(10.7%)	12(12.2%)	-3.6%(-12.5%,5.3%)	-1.5%(-10.8%,7.7%)

Source: Reviewer's analysis. IOP lowering procedures (Trabeculectomy, Iridectomy and Iridotomy). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

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/s/

MICHAEL J PUGLISI
03/26/2014



David E. I. Pyott
Chairman of the Board and CEO
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

Dear Mr. Pyott:

Between December 12, 2013, and December 23, 2013, Ms. Diane C. Van Leeuwen representing the Food and Drug Administration (FDA), conducted an investigation [and met with you to review your conduct as the sponsor of the clinical investigations of the investigational drug dexamethasone intravitreal implant (Ozurdex[®]):

Protocol 206207-010, entitled “ A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to assess the Safety and Efficacy of 700 µg 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema”,

and

Protocol 206207-011, entitled “ A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to assess the Safety and Efficacy of 700 µg 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema”.

This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Van Leeuwen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.

Branch Chief

Good Clinical Practice Enforcement Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

Office of Compliance

Center for Drug Evaluation and Research

Food and Drug Administration

Building 51, Room 5370

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

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/s/

SUSAN D THOMPSON
02/06/2014

KASSA AYALEW
02/08/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Kenneth N. Sall, M.D.
11423 187th St. Suite 200
Sall Research Medical Center, Inc.
Artesia, CA 90701-5657

Dear Dr. Sall:

Between September 3, 2013 and September 11, 2013, Ms. Diane C. Van Leeuwen, representing the U.S. Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical investigation Protocol 206207-011, entitled "A 3-Year, Phase 3, Multicenter, Masked Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema") of the investigational drug dexamethasone intravitreal implant (Ourdex[®]), performed for Allergan, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Van Leeuwen presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge that during the inspection and in your September 22, 2013 written response to the inspection findings, you indicated that you have implemented corrective actions to prevent the recurrence of the inspection findings actions.

We appreciate the cooperation shown to Investigator Van Leeuwen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5370
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

SUSAN D THOMPSON
02/06/2014

KASSA AYALEW
02/08/2014



Glenn L. Wing, M.D.
National Ophthalmic Research Institute
6901 International Center Blvd.
Fort Myers, FL 33912

Dear Dr. Wing:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site from August 26, 2013, to September 12, 2013. Mr. David P. King, representing the FDA, reviewed your conduct of a clinical investigation Protocol 206207-010, titled "A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema" of the investigational drug dexamethasone intravitreal implant (Ozurdex[®]), performed for Allergan, Inc.

This inspection was conducted as a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator King during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5370
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

SUSAN D THOMPSON
01/28/2014

KASSA AYALEW
01/29/2014



Steven Rose, M.D.
2100 South Clinton Avenue
Rochester Ophthalmological Group, PC
Rochester, NY 14618

Dear Dr. Rose,

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site from October 15, 2013, to October 21, 2013. Ms. Karen Kosar, representing the FDA, reviewed your conduct of a clinical investigation (Protocol 206207-01, titled "A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled trial to Assess the Safety and Efficacy of 700 µg and 350 ug Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema") of the investigational drug dexamethasone intravitreal implant (Ozurdex[®]), performed for Allergan, Inc.

This inspection was conducted as a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Kosar during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Kassa Ayalew, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5370
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Silver Spring, MD 20993-0002

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/s/

SUSAN D THOMPSON
01/28/2014

KASSA AYALEW
01/28/2014

Puglisi, Michael

From: Puglisi, Michael
Sent: Monday, December 02, 2013 1:55 PM
To: McAllister_James (Mcallister_James@Allergan.com)
Subject: Statistician's Information Request for NDA 22315/S-009

Hi James,

Below please find an information request from our statistician concerning the Ozurdex DME efficacy supplement (NDA 22315/S-009). Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Please provide the analysis results at each visit by treating patients who received escape therapy (as defined in the protocol) at or prior to the given visit as treatment failure and present the results using the same format as Table 2.7.3.-6 (see below) provided in your summary-clin-efficacy-dme.pdf.

Table 2.7.3-6 Number (%) of Patients with 15 or More Letters Improvement from Baseline BCVA in the Study Eye (Studies 206207-010 and 206207-011, ITT Population)

Visit	Study 206207-010			Study 206207-011			Pooled Studies 206207-010 and 206207-011	
	DEX 700 (N = 163)	DEX 350 (N = 166)	Sham (N = 165)	DEX 700 (N = 188)	DEX 350 (N = 181)	Sham (N = 185)	DEX 700 (N = 351)	DEX 350 (N = 347)
Month 1.5	20 (12.3)*	18 (10.8)*	6 (3.6)	21 (11.2)*	23 (12.7)*	3 (1.6)	41 (11.7)*	41 (11.8)
Month 3	23 (14.1)*	23 (13.9)*	10 (6.1)	22 (11.7)*	26 (14.4)*	5 (2.7)	45 (12.8)*	49 (14.1)
Month 4.5	25 (15.3)*	21 (12.7)	11 (6.7)	22 (11.7)*	23 (12.7)*	7 (3.8)	47 (13.4)*	44 (12.6)
Month 6	23 (14.1)	17 (10.2)	13 (7.9)	16 (8.5)*	11 (6.1)	6 (3.2)	39 (11.1)*	28 (8.1)
Month 7.5	26 (16.0)*	26 (15.7)*	13 (7.9)	27 (14.4)*	24 (13.3)	14 (7.6)	53 (15.1)*	50 (14.4)
Month 9	31 (19.0)*	30 (18.1)*	14 (8.5)	29 (15.4)*	26 (14.4)*	13 (7.0)	60 (17.1)*	56 (16.1)
Month 10.5	26 (16.0)*	29 (17.5)*	13 (7.9)	26 (13.8)	26 (14.4)	16 (8.6)	52 (14.8)*	55 (15.7)
Month 12	22 (13.5)	25 (15.1)	15 (9.1)	24 (12.8)	18 (9.9)	18 (9.7)	46 (13.1)	43 (12.4)
Month 15	25 (15.3)*	27 (16.3)*	12 (7.3)	24 (12.8)	26 (14.4)	18 (9.7)	49 (14.0)*	53 (15.3)
Month 18	28 (17.2)	16 (9.6)	18 (10.9)	23 (12.2)	19 (10.5)	17 (9.2)	51 (14.5)	35 (10.1)
Month 21	27 (16.6)*	25 (15.1)	15 (9.1)	29 (15.4)	17 (9.4)	19 (10.3)	56 (16.0)*	42 (12.2)
Month 24	23 (14.1)	25 (15.1)	18 (10.9)	34 (18.1)*	17 (9.4)	19 (10.3)	57 (16.2)*	42 (12.2)
Month 27	33 (20.2)	32 (19.3)	21 (12.7)	31 (16.5)	22 (12.2)	19 (10.3)	64 (18.2)*	54 (15.6)
Month 30	27 (16.6)	33 (19.9)*	19 (11.5)	35 (18.6)*	22 (12.2)	19 (10.3)	62 (17.7)*	55 (15.8)
Month 33	36 (22.1)*	29 (17.5)	19 (11.5)	35 (18.6)*	26 (14.4)	18 (9.7)	71 (20.2)*	55 (15.6)
Month 36	34 (20.9)*	33 (19.9)	21 (12.7)	37 (19.7)*	30 (16.6)	20 (10.8)	71 (20.2)*	63 (18.2)
Month 39/Final	36 (22.1)*	31 (18.7)	22 (13.3)	42 (22.3)*	33 (18.2)*	20 (10.8)	78 (22.2)*	64 (18.4)

* indicates statistically significant ($p \leq 0.05$) difference between DEX 700 or DEX 350 versus Sham

BCVA = best-corrected visual acuity, ITT = intent-to-treat

Note: Missing values are imputed by last observation carried forward at the follow-up visits. For the by-study analyses, p-values were based on the Fisher's exact test. For the pooled analysis, p-values were based on the Cochran-Mantel-Haenszel (CMH) general association test stratified by study. Source: Module 5.3.5.1, CSR 206207-010, [Table 14.2-4.1](#); Module 5.3.5.1, CSR 206207-011, [Table 14.2-4.1](#); Module 5.3.5.3, ISE [Table 14.2-4.1](#)

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/s/

MICHAEL J PUGLISI
12/02/2013

Puglisi, Michael

From: Puglisi, Michael
Sent: Wednesday, November 20, 2013 2:45 PM
To: McAllister_James (Mcallister_James@Allergan.com)
Subject: Clinical Information Request for NDA 22315/S-009

Hi James,

Below please find an information request from our clinical reviewer for NDA 22315/S-009. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewers Comments:

Please provide the following analyses:

- *Time to cataract extraction in phakic subjects at baseline by treatment group [Integrated Safety Population (206207-010 and 206207-011combined)]*
- *Mean BCVA letter score for phakic subjects at baseline by treatment group over time [Integrated analysis (206207-010 and 206207-011combined) for ITT with LOCF population]*
- *Mean BCVA letter score for pseudophakic subjects at baseline by treatment group over time [Integrated analysis (206207-010 and 206207-011combined) for ITT with LOCF population]*

If these analyses have been included already in the supplemental NDA submission, please provide their exact location.

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/s/

MICHAEL J PUGLISI
11/20/2013

Puglisi, Michael

From: Puglisi, Michael
Sent: Wednesday, November 20, 2013 8:43 AM
To: McAllister_James (McAllister_James@Allergan.com)
Subject: Statistician's Information Request for NDA 22315/S-009

Hi James,

Below please find an information request from our statistician for the Ozurdex DME efficacy supplement. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

According to your study protocol (section 5.5.2), subjects who require escape therapy would be treated as treatment failures, However, our analysis identified 12 subjects who received escape medication prior to the final visit but were not treated as treatment failures in your primary efficacy analysis. Please provide an explanation why these set of subjects were not set as treatment failures in your primary efficacy analysis. Please provide the analysis results for the primary efficacy endpoint with these subjects set as treatment failures.

SUBJID	TRTGRP	IMP15L
7027	DEX 350	Yes
7214	DEX 350	Yes
5037	DEX 700	Yes
4655	DEX 700	Yes
7191	DEX 700	Yes
7677	DEX 700	Yes
7078	DEX 700	Yes
7944	DEX 700	Yes
4025	Sham	Yes
4829	Sham	Yes
4961	Sham	Yes
7761	Sham	Yes

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/s/

MICHAEL J PUGLISI
11/20/2013

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, November 12, 2013 2:18 PM
To: McAllister_James (Mcallister_James@Allergan.com)
Subject: Clinical Information Request re: NDA 22315/S-009

Hi James,

Below please find an information request from our clinical team for the Ozurdex DME efficacy supplement. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Regarding Study 206207-011 and Investigator Kenneth Sall, M.D. (Site #10022/ Investigator # 2707):

We request an analysis of the primary efficacy variable for this trial with the subjects enrolled by Dr. Sall excluded. If there is a difference between the results of this analysis and analyses where Dr. Sall's subjects are included, we request that you provide an explanation.

If this analysis has been included already in the supplemental NDA submission, please provide its exact location.

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/s/

MICHAEL J PUGLISI
11/12/2013

Puglisi, Michael

From: Puglisi, Michael
Sent: Thursday, October 31, 2013 8:56 AM
To: McAllister_James (Mcallister_James@Allergan.com)
Subject: Clinical Information Request for NDA 22315/S-009

Hi James,

Below please find a request from our clinical reviewer concerning the Ozurdez efficacy supplement for DME. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comment:

Please provide an explanation for the marked difference in the number of patients (N) at the Month 36 Visit versus the Month 39/Final Visit in Table 14.2-4.3 (Study 206207-010) and Table 14.2-4.3 (Study 206207-011).

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/s/

MICHAEL J PUGLISI
10/31/2013



NDA 22315/S-009

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Allergan, Inc.
Attention: James McAllister, MBA
Manager, Global Regulatory Affairs
2525 Dupont Drive
P.O.Box 19534
Irvine, CA 92623-9534

Dear Mr. McAllister:

Please refer to your Supplemental New Drug Application (sNDA) dated June 12, 2013, received June 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ozurdex (dexamethasone intravitreal implant) 0.7 mg.

This supplemental application proposes the additional indication of treatment of diabetic macular edema.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is April 13, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests the week of March 17, 2014, approximately.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material

identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

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

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/s/

WILEY A CHAMBERS
08/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**		
TO: Christine Corser/ CDER-OPDP-RPM			FROM: (Name/Title, Office/Division/Phone number of requestor) Mike Puglisi/ Regulatory Project Manager OAP/DTOP 301-796-0791		
REQUEST DATE July 15, 2013	IND NO.	NDA NO. 22315/S-009	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) NDA Efficacy Supplement		
NAME OF DRUG Ozurdex (dexamethasone intravitreal implant) 0.7 mg	PRIORITY CONSIDERATION Standard Review		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) March 4, 2014	
NAME OF FIRM: Allergan, Inc.			PDUFA Date: April 13, 2014		
TYPE OF LABEL TO REVIEW					
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING LABELING REVISION	
EDR link to submission: The link to the EDR is below. \\CDSESUB1\EVSPROD\NDA022315\022315.enx					
COMMENTS/SPECIAL INSTRUCTIONS: Please provide a labeling review for this efficacy supplement once substantially complete labeling is available.					
SIGNATURE OF REQUESTER					
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND		

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/s/

MICHAEL J PUGLISI
07/30/2013

Puglisi, Michael

From: Puglisi, Michael
Sent: Friday, July 19, 2013 3:48 PM
To: McAllister_James (McAllister_James@Allergan.com)
Subject: Information Request for NDA 22315/S-009

Hi James,

Below please find information requests from our Biostatistics and Nonclinical reviewers for NDA 22315/S-009. Please confirm you have received this message and let me know if you have any questions about anything.

Biostatistics Reviewer Comments:

Based on our preliminary review of your submission, we have the following requests. Please respond as soon as possible in order for us to complete our reviews in a timely manner.

- 1. Please conduct safety and efficacy analysis for gender, racial, and geriatric subgroups for study 206207-010 and study 206207-011 in the same manner as you did for ISE and ISS reports.*
- 2. Please include the list of reasons for discontinuation specified under “Others”, personal reasons and protocol violations in the patient disposition table.*
- 3. Three variables “WINDOW” (window name), “ADT” (analysis date) and “ADY” (analysis day) appear to be derived differently for different datasets and it is not clear to us how these variables were defined. For example, the following table presents your definition for “WINDOW” and “ADT” in some of the datasets in the ISE folder. Please provide a detailed definition of these variables in all the datasets that included these variables. Please also include a variable in the dataset “cp.xpt” to indicate the exact date of each procedure.*

“WINDOW”	Source/Computational Method
va.xpt	No definition was provided.
cp.xpt	Derived from WINDNUM: use window definition 1b, see Timing Variables worksheet for details.
io.xpt	Derived using window definition 1d, see Timing Variables worksheet for details.
“ADT”	
va.xpt	No definition was provided.
cp.xpt	Derived from conprocs.cpdttvc: convert to a SAS date.
io.xpt	Derived from iop.iovdt: rename.

4. Please provide the summary of the proportion of subjects with ≥ 15 -letter BCVA improvement and the mean change in BCVA from baseline at each time point grouped by the number of injections received.

Nonclinical Reviewer Comments:

It is preferable to provide exposure multiples based on systemic AUC data in nonclinical section 8. If adequate pharmacokinetic/ toxicokinetic data are available, please calculate exposure multiples based on systemic AUC data, and submit the dataset(s) and assumptions used to make these calculations.

If systemic AUC data are not available, but other estimates of systemic exposure are available, it is recommended that all available data be used to estimate systemic exposure and that the package insert describe the method used to estimate the exposure multiple.

Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

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/s/

MICHAEL J PUGLISI
07/19/2013

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, July 09, 2013 9:58 AM
To: McAllister_James (Mcallister_James@Allergan.com)
Subject: Information Request for NDA 22315/S-009

Hi James,

Below please find an information request from our clinical reviewer for NDA 22315/S-009. Please confirm you have received this request and let me know if you have any questions about it.

Reviewer's Comments:

For Protocol 206207-010 and 206207-01:

Please provide efficacy analyses by individual site. If this information is already provided in the NDA submission, please describe its exact location.

Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

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/s/

MICHAEL J PUGLISI
07/09/2013



NDA 22315/S-009

**ACKNOWLEDGEMENT -
PRIOR APPROVAL SUPPLEMENT**

Allergan, Inc.
Attention: James McAllister, MBA
Manager, Global Regulatory Affairs
2525 Dupont Drive
P.O.Box 19534
Irvine, CA 92623-9534

Dear Mr. McAllister:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22315
SUPPLEMENT NUMBER: S-009
PRODUCT NAME: Ozurdex (dexamethasone intravitreal implant) 0.7 mg.
DATE OF SUBMISSION: June 12, 2013
DATE OF RECEIPT: June 13, 2013

This supplemental application proposes the additional indication of treatment of diabetic macular edema.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 12, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please call me at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Michael Puglisi
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MICHAEL J PUGLISI
07/03/2013