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RESEARCH**

APPLICATION NUMBER:

22-315

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name Martin P. Nevitt, M.D., M.P.H.
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Established Name dexamethasone
intravitreal implant
(Proposed) Trade Name OZURDEX
Therapeutic Class Corticosteroid
Applicant Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

Priority Designation P

Formulation Intravitreal implant
Dosing Regimen Single intravitreal dose
Indication Treatment of Macular Edema
following Branch or Central
Retinal Vein Occlusion
Intended Population Patients with Macular Edema
following Branch or Central
Retinal Vein Occlusion

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1 Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

It is recommended from a clinical prospective that NDA 22-315, OZURDEX (dexamethasone intravitreal implant), be approved for the treatment of macular edema following branch retinal or central retinal vein occlusion with the labeling revisions listed in this review.

There is substantial evidence of safety and effectiveness consisting of adequate and well controlled studies which demonstrate that Dexamethasone intravitreal implant, dosed when macular edema is present following branch retinal or central retinal vein occlusion is effective for the treatment of macular edema.

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

Risk Benefit Assessment

Studies 206207-008 and 206207-009 demonstrate superiority over Sham injections for the primary efficacy endpoint of Time to Improvement of 15 or more letters of best corrected visual acuity (BCVA); these adequate and well controlled studies support the efficacy of Dexamethasone intravitreal implant for the treatment of macular edema following BRVO and CRVO.

Aside from the expected increase in intraocular pressure associated with an intravitreal injection of a steroid that was reported in the Dexamethasone intravitreal implant groups, pooled adverse event data for these trials demonstrate the adverse event profile was similar between the 3 treatment groups (dexamethasone intravitreal implant 0.7 mg versus dexamethasone intravitreal implant 0.35 mg versus Sham injections). Increased intraocular pressure occurred in 25.2 % versus 24.8 % versus 1.2 % for the dexamethasone intravitreal implant 0.7 mg group, dexamethasone intravitreal implant 0.35 mg group, and the Sham group, respectively.

Reviewer's comments:

The increase of intraocular pressure is to be expected secondary to the effects of the steroid class.

Recommendations for Postmarketing Risk Management Activities

No additional Phase 4 studies are recommended.

Recommendations for other Post Marketing Study Commitments

No additional Phase 4 studies are recommended.

2 Introduction and Regulatory Background

Product Information

Name: Dexamethasone intravitreal implant
Therapeutic Class: Corticosteroid
Indication: Treatment of Macular Edema following Branch or Central Retinal Vein Occlusion
Dosing Regimen: Single intravitreal dose

Tables of Currently Available Treatments for Proposed Indications

There are no approved drug products indicated for patients with macular edema secondary to BRVO or CRVO.

Availability of Proposed Active Ingredient in the United States

Corticosteroids, such as dexamethasone, are a class of products approved for steroid-responsive inflammatory conditions of the eye. Ophthalmic products available containing dexamethasone include:

- Maxidex (dexamethasone sodium phosphate 0.1%)
- Ocu-Dex (dexamethasone ophthalmic solution or ointment, 0.1%, 0.5%).

Important Safety Issues With Consideration to Related Drugs

The safety and efficacy effects seen with this product are class effects related to steroids.

Ocular steroids are contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and thus 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 perforation. Acute purulent infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

Summary of Presubmission Regulatory Activity Related to Submission

- January 10, 2005; Fast Track Designation for Dexamethasone intravitreal implant was granted by the United States Food and Drug Administration (FDA). Fast Track Designation for the indication of macular edema due to CRVO/BRVO was granted because there are no currently approved drug products indicated for patients with macular edema secondary to CRVO or BRVO
- October 30, 2007, at the pre-NDA Allergan, Inc. requested a Pediatric Waiver. The Agency agrees that studies are impossible or highly impractical because the number of pediatric patients with this diagnosis is so small.
- Additional meetings included an End-of-Phase 2 meeting on September 8, 2003, clinical meetings and discussions on December 8, 2003; February 26, 2007; May 16, 2007; June 4, 2007, and another pre-NDA meeting held on April 23, 2008.

During the course of these meetings; the Agency agreed that the primary efficacy comparison would be dexamethasone intravitreal implant 0.7 mg versus Sham and that a gate keeping approach would be acceptable. This agreement was based on Phase 2 data that demonstrated dexamethasone intravitreal implant 0.7 mg had better efficacy and similar safety to the 0.35 mg dose of the dexamethasone intravitreal implant. The two Phase 3 trials (206207-008 and 206207-009) would include both doses of the dexamethasone intravitreal implant (0.35 mg and 0.7 mg) and a needleless Sham control arm.

The Agency provided additional guidance's during these meetings, and there were no scientific disagreements.

Other Relevant Background Information

Dexamethasone intravitreal implant is an intraocular drug delivery system developed for treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The active ingredient, dexamethasone, is a corticosteroid with anti-inflammatory activity. Dexamethasone is combined with biodegradable polymers and is extruded into a small implant suitable for delivery into the posterior segment of the eye through a specifically designed applicator.

Dexamethasone intravitreal implant is injected into the posterior segment of the eye and releases a total dose of approximately 0.7 mg dexamethasone. While releasing dexamethasone, the implant gradually degrades completely over time so there is no need to remove the implant. By delivering a drug directly into the vitreous cavity, the blood-eye barriers are circumvented and intraocular therapeutic levels can be achieved.

Two phase 3 studies (206207-008 and 206207-009) are the basis of approval demonstrating safety and effectiveness in patients with macular edema following CRVO or BRVO. These Phase 3 studies were multicenter, masked, randomized, sham-controlled, safety and efficacy studies evaluating Dexamethasone intravitreal implant for 6 months, followed by a 6-month open-label extension period.

The primary efficacy variable across studies was best-corrected visual acuity (BCVA) in the study eye measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) method. In both phase 3 studies, the primary endpoint was based on time to improvement of 15 letters or more improvement in BCVA. For reference a 3-line worsening of visual acuity is equivalent to a doubling of the visual angle; a 15-letter change with the time to achieve a 15 letter or more improvement from baseline is considered a clinically significant endpoint for drug efficacy.

3 Ethics and Good Clinical Practices

Submission Quality and Integrity

In study 206207-008, the applicant closed 2 study sites in Mexico due to significant non-compliance: one site had enrolled 12 patients and another had enrolled 6 patients. Due to evidence of current Good Clinical Practice (cGCP) violations, the applicant discontinued shipment of study drug to those study sites and ended the investigators' study participation. Final close-out of these sites occurred in November 2007 and December 2007, respectively.

In study 206207-009, one patient was unmasked during the initial treatment period. Patient 4311-2126 experienced severe elevated intraocular pressure 164 days after her initial treatment (dexamethasone intravitreal implant 0.7 mg). The glaucoma specialist needed to know which treatment the patient had received in order to manage the event. The patient exited the study prematurely. Additionally, in Patient 0469-2611 the treatment procedure was performed but the injection of the study medication failed. Failure of the applicator revealed the treatment to be dexamethasone intravitreal implant 0.7 mg. The patient exited the study prematurely at the day 7 visit.

Reviewer's comments:

Study 206207-008 enrolled 599 subjects, and Study 206207-009 enrolled 668 subjects; the few cGCP violations noted above did not impact the data.

There were other no issues related to data quality or integrity identified that would affect the overall adequacy of the data.

Compliance with Good Clinical Practices

Other than the sites noted in section 3.1 of this review, there is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

Financial Disclosures

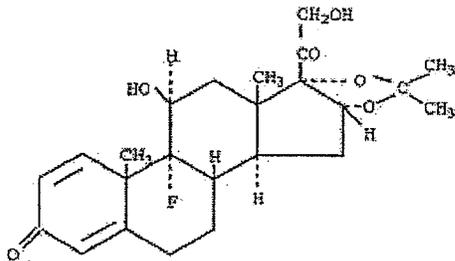
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by Allergan Inc. for the covered clinical studies submitted in this application: 206207-008 and 206207-009. There was no potential impact on the clinical studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry Manufacturing and Controls

Dexamethasone intravitreal implant contains 0.7 mg (700 µg) dexamethasone in the Novadur™ solid polymer drug delivery system. Dexamethasone intravitreal implant is preloaded into a single-use, specially designed applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The Novadur™ system contains poly (D,L-lactide-co-glycolide) PLGA biodegradable polymer matrix. Dexamethasone intravitreal implant is preservative-free.

The chemical name for dexamethasone is pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-,(11β,16α). 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.

Clinical Microbiology

This is not an anti-infective product, and no clinical microbiology studies were performed during this drug's development.

Preclinical Pharmacology/Toxicology

Corticosteroids are generally teratogenic in laboratory animals when administered systemically. Dexamethasone typically applied to the skin has been shown to be teratogenic in mice producing fetal resorptions and cleft palate. In the rabbit, dexamethasone produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1 mg/kg/day every other day for 28 days or at 10 mg/kg/day once or every other day on 3 or 5 days between gestation days 23 and 49 had fetuses with minor cranial abnormalities. A 1 mg/kg/dose in pregnant rhesus monkeys would be approximately 85 times higher than a Dexamethasone intravitreal implant injection in humans (assuming 60 kg body weight).

Clinical Pharmacology

Clinical pharmacology consisted of measurement of systemic exposure to dexamethasone during the 6 months following a single treatment with 0.7 mg or 0.35 mg applicator system in the identically designed phase 3 studies 206207-008 and 206207-009. These safety and efficacy studies were multicenter, masked, randomized, and sham-controlled, and were conducted in patients with macular edema following BRVO or CRVO. Both studies used the same pharmacokinetic methods. It was planned to obtain plasma samples from approximately 15 patients in each study. Samples were obtained from participating patients prior to administration and on days 1, 7, 30, 60, and 90 (and early exit when applicable).

In study 206207-008, samples were obtained from 16 patients (6 who received Sham treatment, 6 who received 0.7 mg and 4 who received 0.35 mg). In study 206207-009, samples were obtained from 17 patients (6 patients who received the Sham treatment, 7 who received 0.7 mg and 4 who received 0.35 mg). Only samples from patients receiving active treatment were included in the pharmacokinetic analysis.

In both studies, the majority of plasma dexamethasone concentrations were below the level of quantitation (BLQ). In the pooled studies, plasma dexamethasone concentrations from 10 of 73 samples in the dexamethasone intravitreal implant 0.7 mg group and from 2 of 42 samples in the dexamethasone intravitreal implant 0.35 mg group were above the LLOQ, and ranged from 0.0521 ng/mL to 0.0940 ng/mL. There were no apparent correlations between plasma dexamethasone concentration and age, body weight, or sex.

The single highest plasma dexamethasone concentration observed in the phase 3 studies was 0.0940 ng/mL which is only 13.4% of that reported by Weijtens (0.7 ng/mL) which was observed

following multiple ocular applications of 1 drop of dexamethasone disodium phosphate (0.1%) to one eye every 1.5 hours.

The pharmacokinetic results of studies 207207-008 and 206207-009 show that systemic exposure of dexamethasone was minimal but dose dependent in patients who received one 0.7 mg or one 0.35 mg dose.

4.1.1 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. Vascular endothelial growth factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular edema. It is a promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular edema.

4.1.2 Pharmacodynamics

Refer to Pharmacokinetics section 4.4.3.

4.1.3 Pharmacokinetics

In a 1 month rabbit vitrectomy study following a single intravitreal injection of Dexamethasone intravitreal implant in both the vitrectomized and nonvitrectomized rabbit eyes, the ocular pharmacokinetics of dexamethasone between vitrectomized and nonvitrectomized eyes was similar.

In a 6 month monkey study following a single intravitreal injection of Dexamethasone intravitreal implant, the rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humor > aqueous humor > plasma. Dexamethasone was released in the monkey vitreous up to 6 months.

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. This is consistent with results from rabbit and monkey ocular metabolism studies.

The Dexamethasone intravitreal implant matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water.

5 Sources of Clinical Data

Tables of Clinical Studies

Feature	206207-008	206207-009
Study Title	A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) 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 Macular Edema Following Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)	A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) 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 Macular Edema Following Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)
Randomization	Randomized ^a	Randomized ^a
Blinding	Double-masked ^a	Double-masked ^a
Active treatment	DEX PS DDS 700 µg and 350 µg applicator system	DEX PS DDS 700 µg and 350 µg applicator system
Control treatment	sham needleless applicator system ^a	sham needleless applicator system ^a
Patient population	patients with macular edema due to branch or central retinal vein occlusion	patients with macular edema due to branch or central retinal vein occlusion
Duration	6-month masked initial treatment followed by 6-month open-label extension	6-month masked initial treatment followed by 6-month open-label extension
Primary efficacy variable	BCVA using ETDRS method	BCVA using ETDRS method
Secondary and other efficacy variables	contrast sensitivity, OCT, fluorescein angiography, fundus photography, health-related quality of life questionnaires	contrast sensitivity, OCT, fluorescein angiography, fundus photography, health-related quality of life questionnaires

^a While remaining unaware of the initial randomized treatment, qualified patients were eligible to receive an open-label treatment with DEX PS DDS 700 µg applicator system at initial treatment day 180 (month 6).

Review Strategy

The applicant conducted two adequate and well controlled clinical trials. Studies 206207-008 and 206207-009 compared two active treatment groups, dexamethasone 0.7 mg intravitreal implant and dexamethasone 0.35 mg intravitreal implant, to the control group that received a sham needleless injection. These studies were designed as a 6-month masked treatment followed by a 6-month open label period. At day 180, all qualifying patients who remained unaware of the initial randomized treatment were eligible to receive treatment with open-label dexamethasone intravitreal implant 0.7 mg (up to 100 subjects could be enrolled). No sham or 0.35 mg procedures were conducted at this visit.

One hundred subjects from these studies received a second injection (dexamethasone intravitreal implant 0.7 mg) for the 6-month open-label treatment period. The safety data from these 100 subjects with 12 month follow-up are included in the safety review.

Discussion of Individual Studies

Safety and Efficacy Trials:

I. Study 206207-008 (Study 206207-009 is identical in design)

Title: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) 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 Macular Edema Following Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)

Selection of Patient Population

Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, at least 18 years of age
2. Macular edema in the study eye with all the following characteristics:
 - due to BRVO or CRVO
 - a duration of 3-9 months prior to qualification/baseline visit for CRVO patients and a duration of 3-12 months prior to qualification/baseline visit for BRVO patients
 - VA decrease attributable to the edema
 - in the investigator's opinion, unlikely to be adversely affected if not treated for 6 months
3. 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
4. Retinal thickness of > 300 µm by OCT in the central subfield of the study eye at qualification/baseline as determined by the investigator
5. Female patients of childbearing potential must have a negative urine pregnancy test at the randomization (day 0) visit
6. Written informed consent has been obtained

7. Written Authorization for Use and Release of Health and Research Study Information US sites only) has been obtained
8. Written Data Protection Consent (European sites only) has been obtained
9. Written document 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
2. Any ocular condition that in the opinion of the investigator would prevent a 15-letter improvement in visual acuity (eg, severe macular ischemia)
3. Presence of an epiretinal membrane 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
4. History of clinically significant IOP elevation in response to steroid treatment in either eye
5. History of glaucoma or optic nerve head change consistent with glaucoma damage, and/or glaucomatous visual field loss in the study eye
6. Ocular hypertension in the study eye requiring more than one medication (combination products should be considered as two medications) to maintain IOP < 22 mm Hg at qualification/baseline
7. Aphakia or presence of anterior chamber intraocular lens in the study eye
8. Active retinal neovascularization in the study eye at qualification/baseline
9. Diabetic retinopathy in either eye
10. Active or history of choroidal neovascularization in the study eye
11. Presence of rubeosis iridis in the study eye at qualification/ baseline
12. Any active ocular infection (ie, bacterial, viral, parasitic, or fungal) in either eye at qualification/baseline
13. History of herpetic ocular infection in the study eye or adnexa
14. Presence of active or inactive toxoplasmosis in either eye at qualification/baseline
15. Presence of visible scleral thinning or ectasia in the study eye at qualification/baseline
16. 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)
17. Intraocular surgery, including cataract surgery, and/or laser of any type in the study within 90 days prior to qualification/baseline
18. History of central serous chorioretinopathy in either eye
19. History of pars plana vitrectomy in the study eye
20. Anticipated need for ocular surgery in the study eye during the 12-month study period
21. Use of hemodilution for the treatment of retinal vein occlusion within 3 months prior to the qualification/baseline visit
22. History of use of intravitreal steroids or any intravitreal injectable drug in the study

- eye
23. Periocular depot of steroids to the study eye within 6 months prior to qualification/baseline
 24. Use of systemic steroids within 1 month prior to the qualification/baseline visit or anticipated use at any time during the study
 25. Use of carbonic anhydrase inhibitors within 1 month prior to the qualification/baseline visit or anticipated use at any time during the study
 26. For patients who participate in therapeutic drug monitoring evaluation only: current use (or use within 1 month prior to qualification/baseline) or anticipated use during the first 90 study days of dexamethasone in any form/route of administration
 27. 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
 28. Use of topical ophthalmic steroids or topical non-steroidal anti-inflammatory drugs (NSAIDs) within 1 month prior to qualification/baseline or anticipated use within the 12-month study period in the study eye
 29. Use of warfarin/heparin within 1 month prior to qualification/baseline or anticipated use within the 12-month study period
 30. BCVA score < 34 letters (approximately 20/200 Snellen equivalent) in the non-study eye using the ETDRS method at qualification/baseline
 31. Known allergy or hypersensitivity to the study medication or its components
 32. Known allergy or contraindication to the use of fluorescein or povidone iodine
 33. Contraindication to pupil dilation in either eye
 34. Previous enrollment in a DEXAMETHASONE INTRAVITREAL IMPLANT clinical trial
 35. 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
 36. Any condition (including inability to read visual acuity charts or language barrier) which precludes patient's ability to comply with the study requirements including completion of the study
 37. Female patients who are pregnant, nursing, or planning a pregnancy, or who are childbearing potential and not using a reliable means contraception
 38. Current enrollment in an investigational drug or device study or participation in such a study within the 30 days prior to qualification/baseline
 39. 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

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OZURDEX (dexamethasone intravitreal implant)

e Scleral depression (study eye only)
f Therapeutic drug monitoring samples should be taken if patient discontinues before or on Initial Treatment Visit Day 90
g Required for females of childbearing potential
h Includes assessment of treatment eligibility and assessment of insertion/intended insertion site after the study treatment procedure
i At day 180, all qualifying patients will receive treatment with open-label 700 µg DEX PS DDS Applicator System. No sham or 350 µg procedure will be conducted at this visit

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
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 OZURDEX (dexamethasone intravitreal implant)

Reviewer's comments:

The study design and exam schedule is acceptable.

Efficacy Variable

For the study eye, BCVA measured using ETDRS method will be used for the primary efficacy assessment. BCVA measured at the baseline/qualification visit will be considered as baseline. Change from baseline in the BCVA at the follow-up visits will be analyzed. Initial treatment day 180 will be considered at the primary time-point for efficacy assessment.

Subjects Enrolled: Study 206207-008

Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Prema Abraham, MD (4621) Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701	3	3	3
James Acton, MD (6653) 7A Oosterzee Street Belville, 7530 South Africa	7	7	7
Andrew N. Antoszyk, MD (4221) Charlotte Eye Ear Nose & Throat Associates PA 6035 Fairview Rd Charlotte, NC 28210	1	1	1
Jennifer Arnold, MD (4373) Marsden Eye Specialists 1/152 Marsden Street Parramatta, NSW 2150 Australia	4	4	4
Albert J. Augustin, MD (4353) Staedtisches Klinikum - Department of Ophthalmology Moltkestrasse 90 Karlsruhe, D- 76133 Germany	9	9	8
Adiel Barak, MD (4447) Department of Ophthalmology The Tel Aviv Sourasky Medical Center 6 Weizman Street Tel Aviv, 64239 Israel	26	26	25
Karl Ulrich Bartz-Schmidt, MD (4391) University Eye Hospital Tuebingen Schleichstrasse 12 Tuebingen, 72076 Germany	1	1	1
Caroline Bauman, MD (4224) New England Eye Center 750 Washington Street Box 450 Boston, MA 02111	1	1	1

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 OZURDEX (dexamethasone intravitreal implant)

Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in IUI	Number of Patients in PP
Abdish R. Bhavsar, MD (4228) 710 East 24 th Street #304 Minneapolis, MN 55404	2	2	2
Susanne Binder, MD (4342) Rudolf Foundation Clinic Ludwig Boltzmann Institute for Retinologia & Biomicroscopic Laser Surgery Juchgasse 25 Wien, A-1030 Austria	2	2	2
William Z. Bridges, MD (4230) Western Carolina Retinal Associates, a Division of Asheville Eye Associates, LLC 21 Medical Park Drive Asheville, NC 28803	1	1	1
Miguel A. Busquets, MD (6667) Associates in Ophthalmology 9970 Mountain View Drive West Mifflin, PA 15122	3	3	3
Gordon A. Bymes, MD (8294) The Retina Group of Washington 6355 Walker Lane Suite #502 Alexandria, VA 22310	3	3	3
Rene Alfredo Cano-Hidalgo, MD (4233) Instituto de Oftalmología Fundacion Conde de la Valenciana Chimalpopoca 14 Col. Obrera Mexico City, D.F. 6800 Mexico	6	6	5
Prof. Trevor Carmichael, MD (6655) Wits Donald Gordon Medical Centre Eton Road, Parktown Johannesburg 2157 South Africa	4	4	4
Lawrence P. Chong, MD (1671) (replaced Tom Shio-Min Chang (4335), MD who was PI from 3/01/2005 to 11/07/2005 at the same address) Doheny Eye Institute Department of Ophthalmology 1450 San Pablo Street, Room 4601 Los Angeles, CA 90033	5	5	3
William L. Clark, MD (4238) Palmetto Retina Center 124 Sunset Court West Columbia, SC 29169	2	2	2
Alan Cruess, MD (4341) Capital Health Suite 2035 Victoria West Building 1278 Tower Road Halifax, NS B3H 2Y9	10	10	9
Rufino Martins da Silva, MD (4398) AIBILI Azinhaga de Santa Comba - Celas Coimbra, 3000-354 Portugal	19	19	17

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 NDA 22-315
 OZURDEX (dexamethasone intravitreal implant)

Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Frederick H. Davidorf, MD (0563) Retinal Consultants, Inc. 6805 Avery-Muirfield Road Suite 100 Dublin, OH 43017	4	4	3
Deon P. Doubell, MD (3077) Port Elizabeth Eye and Laser Clinic 205 Cape Road Port Elizabeth, 6045 South Africa	1	1	1
Richard F. Dreyer, MD (4243) Retina Northwest, P.C. 2525 NW Lovejoy, Suite 300 Portland, OR 97210	4	4	4
Zora Dubska, MD (6412) General University Hospital Clinic of Ophthalmology VFN Ocní klinika, U nemocnice 2 Prague 2, 12808 Czech Republic	5	5	4
Jan Ernest, MD (8907) General Military Hospital Ophthalmology Department U Vojenske nemocnice 1200 Prague 6, 16902 Czech Republic	2	2	2
Joseph T. Fan, MD (4461) Loma Linda University Department of Ophthalmology 11370 Anderson Street, Suite 1800 Loma Linda, CA 92354	1	1	1
Joseph R. Ferencz, MD (4449) Meir Medical Clinic 59 Tshamichovisky Sreet Kfar-Saba, 44281 Israel	27	27	25
Christina J. Flaxel, MD (4639) (replaced David J. Wilson, MD (4310) who was PI from 11/19/2004 to 10/11/2005 at the same address) Casey Eye Institute/OHSU 3375 SW Terwilliger Blvd Portland, OR 97239	2	2	2
Gregory M. Fox, MD (4250) Retina Associates, PA 9119 W. 74 th Street, Suite 268 Shawnee Mission, KS 66204	3	3	2
Carsten Framme, MD (9072) (replaced Helmut Sachs, MD (6686) who was PI from 9/16/2006 to 12/31/2007 at the same address) Universitäts Augenklinik Franz-Josef-Strauss Allee 11 Regensburg, 93053 Germany	2	2	2

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Alain Gaudric, MD (4347) Hopital Lariboisiere Service d'Ophthalmologie 2, rue Ambroise Pare Paris, 75010 France	13	13	11
Orna Geyer, MD (8305) (replaced Ehud Rechtman, MD (4506) who was PI from 8/09/2005 to 10/16/2006 at the same address) Department of Ophthalmology Carmel Medical Center 1 Michal Street Haifa, 34362 Israel	25	25	24
Prof. Mark Gillies, MD (4374) Save Sight Insitute University of Sydney Campus of Sydney Eye Hospital 8 Macquarie St Sydney NSW, 2000 Australia	21	21	21
David A. Glaser, MD (4252) Retina Associates of St. Louis 1224 Graham Rd, Suite 3011 Florissant, MO 63031	1	1	1
Petrus Gous, MD (3084) Pretoria Eye Institute 630 Schoeman Street Arcadia, Pretoria 0007 South Africa	10	10	10
Jeffrey Glenn Gross, MD (4254) Carolina Retina Center 7620 Trenholm Road Ext. Columbia, SC 29223	1	1	1
Prof. Dr. Anton Haas, MD (4343) Karl-Franzens Universitat Klinik fur Augenheilkunde Auenbruggerplatz 4 Graz, 8036 Austria	7	7	7
Mark E. Hammer, MD (4257) Retina Associates of Florida PA 602 South Mac Dill Avenue Tampa, FL 33609	2	2	2
Seenu M. Hariprasad, MD (5099) (replaced Willam Mieler, MD (5100) who was PI from 11/02/2005 to 06/30/2008 and Kourous A. Rezaei, MD (4292) who was PI from 5/27/2004 to 11/01/2005 at the same address) University of Chicago 5841 S. Maryland Ave, MC 2113 Department of Ophthalmology Chicago, IL 60637	5	5	4
Nancy M. Holekamp, MD (4261) Barnes Retina Institute Center for Advanced Medicine 4921 Parkview Place, Suite 12B St. Louis, MO 63110	2	2	2

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 Martin P. Nevitt, M.D., M.P.H.
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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Frank Holz, MD (4421) Universität Bonn Department of Ophthalmology Ernst Abbestrasse 2 Bonn, 53105 Germany	2	2	2
Timothy Isaacs, MD (4383) Lions Eye Institute 2 Verdun Street Nedlands, WA 6009 Australia	3	3	2
Judianne Kellaway, MD (4431) Robert Cizik Eye Clinic 6400 Fannin Street, Suite 1800 Houston, TX 77030	4	4	3
Itamar Klemperer, MD (2341) Soroka University Medical Center Helsinki Committee, POB 151 Beer Sheva, 84101 Israel	10	10	10
Jean-Francois Korobelnik, MD (4345) Hopital Pellegrin Service d'Ophthalmologie Unite Medicale du Segment Posterieur Place Amelie Raba-Léon Bordeaux, 33000 France	5	5	5
Stewart Lake, MD (6354) (replaced Russel Phillips, MD(3395) who was PI from 7/27/2005 to 6/18/2007 at the same address) Department of Ophthalmology, Flinders Medical Centre Flinders Drive Bedford Park South Australia, 5042 Australia	1	1	1
Arthur Levine Berebichez, MD (4270) Fundacion Hospital de Nuestra Senora de la Luz, I.A.P. Ezequiel Montes, 135 - Col Tabacalera Mexico, D.F. 06030 Mexico	12	12	12
Isaac A. Loose, MD (4227) Retina Research Center 3705 Medical Parkway, Suite 420/410 Austin, TX 78705	9	9	8
Da-Wen Lu, MD (6687) Tri-Service General Hospital No.325, Sec.2, Cheng- Kun Road Neihu District, Taipei 114 Taiwan	1	1	0
Steven Madreperla, MD (4631) Retina Associates of NJ 628 Cedar Lane Teaneck, NJ 07666	5	5	5

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Didier Malthieu, MD (4349) Centre Saint Victor Service d'Ophthalmologie 354 Boulevard de Beauville Amiens 80000 France	1	1	1
James H. Miller, MD (4280) Southeastern Retina Associates, PC 1124 Weisgarber Road, Suite 207 Knoxville, TN 37909	13	13	13
Gregory J. Mincey, MD (4281) Carolina Eye Associates 2170 Midland Road Southern Pines, NC 28387	6	6	6
Paul Mitchell, MD (4377) Westmead Eye Clinic Level 4a, Block B Westmead Hospital Hawkesbury Road, Westmead NSW 2145 Australia	9	9	9
Joseph Moisseiev, MD (4450) Sheba Medical Center The Goldschleger Eye Institute Tel Hashomer, 52621 Israel	10	10	10
Rodrigo Montemayor-Lobo, MD (4282) Centro Medico Hidalgo Oftalmologos Montemayor & Asociados Hidalgo 2425 Pte. Consultorio 705 Colonia Obispado 64060 Monterrey, Nuevo Leon Mexico	7	7	5
Darius M. Moshfeghi, MD (4337) California Vitreoretinal Research Center Stanford University 1225 Crane Street, Suite 202 Menlo Park, CA 94025	2	2	1
George S. Novalis, MD (4285) Retina Centers, P.C. 6585 North Oracle Road, Suite A Tucson, AZ 85704	8	8	8
Juan Orellana, MD (0448) Orellana Retina Associates, PLLC 3141 John Humphries Wynd Suite 290 Raleigh, NC 27612	1	1	1
Michel Paques, MD (4394) CHNO des Quinze-Vingts Service IV (Pr Sahel) 28 rue de Charenton 75012 Paris France	16	16	16

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Don J. Perez-Ortiz, MD (4289) International Eye Center Ophthalmologist/Retina Specialist 4506 Wishart Blvd Tampa, FL 33603	5	5	5
Ayala Pollack, MD (4451) Kaplan Medical Center Department of Ophthalmology POB 1 Rehovot, 76100 Israel	38	38	34
Jiri Rehak, MD (6415) University Hospital Olomouc Department of Ophthalmology I.P. Pavlova 6 Olomouc, 77520 Czech Republic	8	8	5
Kelvin Rivett, MD (3905) 18 St. James Road East London, 5201 South Africa	1	1	1
Jean-Paul Romanet, MD (2793) (replaced Michel Mouillon (2201), MD who was PI from 5/22/2006 to 8/31/2006 at the same address) CHU de Grenoble Hopital Michallon Service d'Ophthalmologie Boulevard de la Chantourne BP 217 Grenoble cedex 09, 38043 France	1	1	1
Daniel F. Rosberger, MD (4294) Macula Care 52 E. 72 nd Street New York, NY 10021	6	6	5
Ammar Safar, MD (5003) (replaced Bradley Hughes, MD who was PI from 11/15/2005 to 07/28/2006 at the same address) Jones Eye Institute University of Arkansas for Medical Sciences 4301 West Markham Street #523 Little Rock, AR 72205	1	1	1
Dirk Sandner, MD (8092) Universitäts - Augenlinik Dresden Fetcherstrasse 74 Dresden , 01307 Germany	1	1	1
Gil Sartani, MD (3983) HaEmek Medical Center Ophthalmology Department Afula, 18101 Israel	17	17	16
Prof. Dr. Ulrich Schonherr (6411) Konventhospital der Barmherzigen Brüder - Augenabteilung Seilerstätte 2 Linz, A-4021 Austria	2	2	2

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Steven D. Schwartz, MD (4210) (replaced Anurag Gupta, MD (4255) who was PI from 8/27/2004 to 3/02/2008 at the same address) Jules Stein Eye Institute/UCLA 100/200 Stein Plaza Los Angeles, CA 90095	8	8	8
Thomas Sheidow, MD (4462) University of Western Ontario Ivey Eye Institute 750 Commissioners Road East London, Ontario N6A 4G5 Canada	11	11	10
Shwu-Juan Sheu, MD (6690) Veterans General Hospital - Kaohsiung 386, Ta-Chung 1st Road Kaohsiung, 813 Taiwan	2	2	2
Michael A. Singer, MD (4298) Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240	9	9	9
Raymond N. Sjaarda, MD (4299) Retina Specialists 6569 North Charles Physicians Pavilion West, Suite 605 Towson, MD 21204	1	1	1
Peter L. Sonkin, MD (4365) Retina Vitreous Associates, P.C. Baptist North, Suite 603 2011 Murphy Avenue Nashville, TN 37203	4	4	4
Gisele Soubrane, MD (3059) Hopital Intercommunal Service d'Ophthalmologie 40, avenue de Verdun Creteil, 94010 France	21	21	19
Petr Soucek, MD (8093) The Eye Department University Hospital Královské Vinohrady Šrobárova 50 10034 Prague 10 Czech Republic	1	1	1
Jan Studnicka, MD (6417) University Hospital Hradec Kralove Department of Ophthalmology Sokolska 581 Hradec Kralove, 50005 Czech Republic	11	11	11
Harvey Siy Uy, MD (7871) Asian Eye Institute 9F Phinma Plaza Building Rockwell Center Makati, 1200 Philippines	16	16	13

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Igor Vicha, MD (6418) University Hospital Brno Ophthalmology Clinic Jihlavská 20 BRNO, 62500 Czech Republic	30	30	27
Linda Visser, MD (6654) Department of Ophthalmology Nelson R Mandela School of Medicine University of Kwazulu Natal Durban, 4001 South Africa	3	3	3
Cuong D. Vu, MD (4340) Retina Associates, PC 2002 Medical Parkway, Suite 450 Annapolis, MD 21401	1	1	1
Dov Weinberger, MD (4452) Rabin Medical Center Ophthalmology Department Petah Tiqva, 49100 Israel	19	19	17
Mark Wieland, MD (4308) Northern California Retina-Vitreous Associates, Inc. 2485 Hospital Drive, Suite 200 Mountain View, CA 94040	1	1	1
R. Geoff Williams, MD (4309) Calgary Retinal Consultants 103-49 Richard Way S.W. Calgary, T3E 7M8 Canada	9	9	9
Total	599	599	555

Subjects Enrolled: Study 206207-009

Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Suel Abujamra, MD (4220) Clínica de Olhos Dr. Suel Abujamra S/C Ltda Rua Tamandaré, 693 - 6 Andar Sao Paulo, SP 01525-001 Brazil	34	34	30
Fareed Ali, MD (4473) Canadian Centre for Advanced Eye Therapeutics 1880 Sismet Road Mississauga, Ontario L4W 1W9 Canada	9	9	7
Marcos Avila, MD (4223) Centro Brasileiro de Cirurgia de Olhos - CBCO Av. T-2, 401 - Setor Bueno Goiania, GO 74210-010 Brazil	4	4	4

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Prof. Francesco Bandello (4354) Clínica Oculística Università di Udine Piazzale Santa Maria della Misericordia, 15 Udine, 33100 Italia	21	21	20
Paul Beer, MD (4225) Retina Consultants, PLLC Lions Eye Institute 35 Hackett Blvd Albany, NY 12208	2	2	2
Rubens Belfort Junior, MD (0469) Universidade Federal de Sao Paulo, Escola Paulista de Medicina, Hospital São Paulo Rua Botucatu, 820/822/824 Vila Clementino Sao Paulo, SP 04023-062 Brazil	31	31	28
Jeffrey Benner MD (4226) Retina Consultants of Delmarva, PA 6511 Deer Point Drive Salisbury, MD 21804	7	7	7
Muna Bhende, MD (4614) Sankara Nethralaya 18 College Road, Nungambakkam Chennai, Tamil Nadu 600 006 India	5	5	4
Reagan Bradford, MD (4229) Dean A. McGee Eye Institute 608 Stanton L Young Blvd Oklahoma City, OK 73104	6	6	6
David Brown, MD (4231) Vitreoretinal Consultants 6560 Fannin St., Suite 750 Houston, TX 77030	12	12	12
Ken B. Carnevale, MD (4234) Ophthalmic Consultants of Long Island 360 Merrick Road, 3 rd Floor Lynbrook, NY 11563	8	8	7
Antonio Marcelo Barbante Casella, MD (4453) Ambulatório do Hospital de Clínicas da Universidade Estadual de Londrina Rodovia Celso Garcia Cid, S/Nº. PR 445. Km 380 Campus Universitário Londrina, PR 86051-990 Brazil	2	2	2
Victor Chong, MD (4360) King's College Hospital - Eye Dept. 1st Floor, Normanby Building Denmark Hill, SE5 9RS United Kingdom	6	6	6

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Hum Chung, MD (7872) Department of Ophthalmology Seoul National University Hospital 28 Yongun-Dong, Chongno-Gu Seoul, 110-744 Korea	10	10	10
Brian P. Conway, MD (4239) Department of Ophthalmology University of Virginia 1 Jefferson Park Ave Charlottesville, VA 22908	3	3	3
Joel Corwin, MD (4082) Miramar Eye Specialists Medical Group 3085 Loma Vista Road Ventura, CA 93003	5	5	5
Bernard Dorf, MD (4242) Retina Vitreous Consultants 3501 Forbes Ave, Suite 500 Pittsburgh, PA 15213	12	12	12
Mark Donaldson, MD (4379) Ophthalmic Department ADHB Building 4, 2 nd Floor Greenlane Clinical Centre Greenlane Road West Auckland, New Zealand Epsom 1003	10	10	10
Catherine Egan, MD (4392) Moorfields Eye Hospital 162 City Road London, EC1V 2PD United Kingdom	9	9	8
Philip M. Falcone, MD (4583) Connecticut Retina Consultants, LLC 4920 Main Street, Suite 309 Bridgeport, CT 06606	5	5	4
Alvaro Fernandez Vega Sanz, MD (4397) Instituto Oftalmologico Fernandez Vega Avenida Fernandez Vega, 114 Oviedo, 33012 Spain	4	4	2
Joao Luiz Lobo Ferreira, MD (4454) CCRV – Centro Catarinense de Retina e Vitreo Rua Deputado Leoberto Leal, 14 – Centro Florianopolis, SC 88015-080 Brazil	10	10	10
Marta Suarez de Figueroa, MD (4416) Hospital Oftalmológico de Madrid (Vissum) c/ Santa Hortensia, 58 Madrid, 28002 Spain	6	6	6
Bradley Foster, MD (5020) New England Retina Consultants, PC 3640 Main Street, Suite 201 Springfield, MA 01107	3	3	3

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
William R. Freeman, MD (4361) UCSD Jacobs Retina Center 9415 Campus Point Drive La Jolla, CA 92037	8	8	8
Bruce Garretson, MD (4336) Associated Retinal Consultants, P.C. 3535 W. 13 Mile Rd, Suite 344 Royal Oak, MI 48073	9	9	8
Alan Gordon, MD (9241) (replaced J. Bryan Shepard (5313), MD who was PI from 5/01/2006 to 5/23/2007 at the same address) Associated Retina Consultants, Ltd. 7600 N. 15 th Street, Suite 155 Phoenix, AZ 85020	7	7	7
Lawrence Halperin, MD (4256) Retina Group of Florida 5601 North Dixie Highway, Suite 307 Ft. Lauderdale, FL 33334	9	9	9
Dennis Peter Han, MD (4258) Eye Institute – Medical College of Wisconsin 925 N. 87 th Street Milwaukee, WI 53226	1	1	1
Patricia Harvey, MD (4259) University Health Network Toronto Western Hospital Department of Ophthalmology 399 Bathurst Street Toronto, Ontario M5T 2S8 Canada	6	6	5
Jeffrey Heier, MD (4260) Ophthalmic Consultants of Boston 50 Staniford Street, Suite 600 Boston, MA 02114	12	12	11
Randy Katz, MD (4456) Florida Eye Microsurgical Institute, Inc. 1717 Woolbright Road Boyton Beach, FL 33426	1	1	1
Shalesh Kaushal, MD (4266) University of Florida Department of Ophthalmology 1600 SW Archer Road Gainesville, FL 32610-0234	3	3	3
Derek Y. Kunitomo, MD (9341) (replaced Scott R. Sneed (4300), MD who was PI from 06/15/2004 to 6/05/2007 at the same address) Retinal Consultants of Arizona, Ltd 1101 East Missouri Ave Phoenix, AZ 85014	24	24	23
Prof. Dennis Lam (4432) Dept of Ophthalmology & Visual Sciences Hong Kong Eye Hospital 147K Argyle Street Kowloon Hong Kong SAR	6	6	5

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Rosangela Lattanzio, MD (4401) (replaced Rosario Brancato (2916), MD who was PI from 11/15/2004 to 6/16/2006 at the same address) Dipartimento di Oftalmologia e Scienze della Visione Ospedale San Raffaele Via Olgettina, 60 Milano, 20132 Italia	10	10	10
Jaco Lavinsky, MD (4269) Hospital de Clinicas de Porto Alegre Rua Ramiro Barcelos, 2350 Departamento de Oftalmologia Zona 17 Porto Alegre, RS 90035-007 Brazil	4	4	4
Seoung Young Lee, MD (4630) Retina Research Institute of Texas 5441 Health Center Drive Abilene, TX 79606	7	7	4
Prof. Won-Ki Lee (7873) Department of Ophthalmology Kangnam St Mary's Hospital #505 Banpo-Dong, Seocho-Gu Seoul, 137-040 Korea	17	17	16
Peck-Lin Lip, MD (4502) Aston Academy of Life Sciences Aston University Aston Triangle Birmingham, B4 7ET United Kingdom	4	4	3
Jose A. Martinez, MD (4276) Austin Retina Associates 801 West 38th St., Suite 200 Austin, TX 78705	15	15	15
Annie Mathai, MD (4573) LV Prasad Eye Institute LV Prasad Marg, Banjara Hills Hyderabad, 500034 India	8	8	8
Raj Maturi, MD (4277) Midwest Eye Institute 201 Pennsylvania Pkwy Indianapolis, IN 46280	11	11	11
Martin McKibbin, MD (4359) St James University Hospital Eye Clinic Beckett Street Leeds, LS9 7TF United Kingdom	5	5	5
Mark Michels, MD (4406) Retina Care Specialists 3399 PGA Blvd, Suite 220 Palm Beach Gardens, FL 33410	8	8	7

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Prof. Edoardo Midena (4355) Dipartimento di Oftalmologia Universita di Padova Via Giustiniani, 2 Padova, 35128 Italia	1	1	0
Carlos Augusto Moreira Jr., MD (4455) Hospital de Olhos do Paraná Rua Coronel Dulcideo 199 2º Andar Curitiba, PR 80420-170 Brazil	3	3	3
Lawrence S. Morse, MD (4283) University of California Davis Medical Center Department of Ophthalmology 4860 Y Street, Suite 2400 Sacramento, CA 95817	9	9	8
Richard Newsom, MD (4393) Eye Unit - South Hampton General Hospital Tremona Road Hampshire South Hampton, SO16 6YD United Kingdom	10	10	10
Nicola Orzalesi, MD (0914) Clinica Oculistica Università degli Studi di Milano Ospedale San Paolo Via A. di Rudini, 8 Milano, 20142 Italia	5	5	3
Kirk Packo, MD (4567) Rush University Medical Center 1725 W. Harrison Street, Suite 909 Chicago, IL 60612	2	2	2
Maurizio Battaglia Parodi, MD (4498) Clinica Oculistica Ospedale Maggiore Piazza Ospendale, 1 Trieste, 34129 Italia	7	7	6
Augusto Paranhos Junior, MD (4582) Hospital Israelita Albert Einstein Av. Albert Einstein, 627/701 2 Subsolo Sao Paulo, SP 05651-901 Brazil	13	13	12
Jose Carlos Pastor Jimeno, MD (2519) Instituto Universitario de Oftalmobiologia Aplicada Facultad de Medicina, 3a Planta Avenida Ramon y Cajal 7 Valladolid, 47005 Spain	7	7	6

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Peter Reed Pavan, (4287) (replaced Burton G. Goldstein (4409), MD who was PI from 12/07/2004 to 1/23/2006 at the same address) University of South Florida Ophthalmology Department 2020 Laurel Drive Tampa, FL 33612	5	5	5
Ian Pearce, MD (4395) Royal Liverpool University Hospital 8Z Link Corridor, St.Pauls' Eye Unit Prescot Street Liverpool, L7 8XP United Kingdom	5	5	5
Krystyna Pecold, MD (6426) Samodzielny Publiczny Szpital Kliniczny NR 1 Przemienienia Panskiego Poznan Katedra I Klinika Okulistyki Akademia Medyczna w Posnan Ul. Długa ½ Poznan, 61-848 Poland	4	4	4
Prof. Chee Soon Phaik, (4378) Singapore Eye Research Institute 11 Third Hospital Avenue, Singapore, 168751	3	3	3
Michael Potter, (4291) UBC/VGH Eye Care Centre 2550 Willow St., Section B Vancouver, BC V5Z 3N9 Canada	3	3	3
Kim Ramasamy, MD (4572) Aravind Eye Hospital 1, Anna Nagar Madurai, 625020 Tamil Nadu, India	16	16	14
Emilio Rapizzi, MD (4402) Dipartimento di Scienze Chirurgiche Oto-Neuro- Oftalmologiche Clinica Oculistica II Universita di Firenze Ospedal di Careggi Viale Morgagni, 85 Firenze, 50134 Italia	10	10	10
Francisco Jose Rodríguez Alvira, MD (4580) Fundacion Oftalmologica Nacional – FUNDONAL Calle 50, n 13 - 50, 6th Floor Bogota - Colombia	9	9	8
Steven J. Rose, (4338) Retina Associates of Western New York 160 Sawgrass Drive, Suite 200 Rochester, NY 14620	10	10	9
Jose Ruiz Moreno, MD (4396) Instituto Oftalmologico de Alicante (Visum Alicante) C/ Cabañal 1, Planta 4 Alicante, 03016 Spain	8	8	8

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Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in ITT	Number of Patients in PP
Kenneth Sall, MD (2707) Sall Research Center 11423 187th Street, Suite 200 Artesia, CA 90701	9	9	8
Lawrence J. Singerman, MD (1680) Retina Associates of Cleveland 3401 Enterprise Parkway #300 Beachwood, OH 44122	3	3	3
Prof. Giovanni Staurenghi, (4408) Università degli Studi di Milano Dipartimento di Scienze Otorinolaringologiche e Oftalmologiche, Clinica Oculistica – Ospedale Maggiore IRCCS Milano Via Francesco Sforza, 35 Milano, 20122 Italia	8	8	8
Walter Takahashi, MD (4303) Hospital das Clinicas da Faculdade Medicina da Universidade de Sao Paulo Av. Dr. Eneas de Carvalho Aguiar, 255- 6 Andar Sao Paulo, SP 05403-010 Brazil	12	12	11
Stephen James Talks, MD (4399) Royal Victoria Infirmary Eye Department Queen Victoria Road Newcastle, NE1 4LP United Kingdom	6	6	6
Giorgio Tassinari, MD (4400) Divisione di Oculistica Ospedale Maggiore di Bologna Largo Nigrisoli, 2 Bologna, 40133 Italia	3	3	3
David S. Boyer, MD (4207) (replaced Edgar Thomas (4304), MD who was PI from 5/03/2004 to 4/03/2008 at the same address) Retina Vitreous Associates Medical Group 8641 Wilshire Blvd, Suite 210 Beverly Hills, CA 90211	5	5	5
Lawrence Ulanski II, MD (4523) University of Illinois at Chicago 1905 West Taylor, MC 648 Chicago, IL 60612	1	1	1
Monica Varano, MD (9095) Fondazione G.B. Bietti per lo Studio e la ricerca in oftalmologia IRCCS Via Livenza, 3 Roma, 00198 Italy	3	3	3
Robert Wang, MD (4446) Texas Retina Associates 7150 Greenville Avenue, Suite 400 Dallas, TX 75231	5	5	5
Frederick Weidman III, MD (4307) Horizon Eye Care PA 135 South Sharon Amity Road Suite 100 Charlotte, NC 28211	1	1	1

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 OZURDEX (dexamethasone intravitreal implant)

Principal Investigator Name & Address	Number of Patients Enrolled	Number of Patients in IFT	Number of Patients in RF
Daniel Will, MD (4570) Keystone Eye Associates 9126 Blue Grass Road Philadelphia, PA 19114	1	1	1
Glenn L. Wing, MD (4311) National Ophthalmic Research Institute 6901 International Center Blvd. Fort Myers, FL 33912	9	9	9
Jiong Yan, MD (4458) (replaced Enrique Garcia-Valenzuela (4562), MD who was PI from 6/23/2004 to 4/07/2005 at the same address) Emory University Eye Center 1365B Clifton Road, NE Rm 3402 Atlanta, GA 30322	16	16	15
Yit Chung Yang, MD (4358) Wolverhampton Eye Infirmary Compton Road Wolverhampton, WV10 0QP United Kingdom	3	3	3
Prof. Young-Hee Yoon (4618) Department of Ophthalmology Asan Medical Center 388-1, Pungnap2-dong, Songpa-gu Seoul Korea	45	45	43
Lucy Young, MD (4313) Harvard Medical School Retina Service Massachusetts Eye and Ear Infirmary 243 Charles St. Boston, MA 02114	4	4	3
Ingrid Zimmer-Galler, MD (4314) Wilmer Eye Institute 600 North Wolfe Street MAUMENEE 749 Baltimore, MD 21287	5	5	4
Total	668	668	623

6 Review of Efficacy

Efficacy Summary

Indication

6.1.1 Methods

Studies 206207-008 and 206207-009 were multicenter, masked, randomized, sham-controlled, safety and efficacy studies evaluating Dexamethasone intravitreal implant for 6 months, followed by a 6-month open-label extension period.

To demonstrate efficacy, the agency recommended that the primary endpoint be based on Time to Improvement of 15 letters or more in BCVA. A 15-letter change with the time to achieve a 15 letter or more improvement from baseline is considered a clinically significant endpoint for drug efficacy.

6.1.2 Demographics

Characteristic	Study 206207-008 N= 599	Study 206207-009 N= 668
Age (years)		
mean	65.5	63.6
range	(32 – 91)	(31 – 96)
Sex		
male	327 (54.6%)	350 (52.4%)
female	272 (45.4%)	318 (47.6%)
Race		
Caucasian	502 (83.8%)	449 (67.2%)
Black	18 (3.0%)	31 (4.6%)
Asian	26 (4.3%)	92 (13.8%)
Japanese	0	3 (0.4%)
Hispanic	44 (7.3%)	47 (7.0%)
Other	9 (1.5%)	46 (6.9%)
Iris Color		
Dark	344 (57.6%)	406 (60.8%)
Light	253 (42.4%)	262 (39.3%)
Diagnosis in study eye		
CRVO	205 (34.2%)	232 (14.4%)
BRVO	394 (65.8%)	436 (65.3%)

Reviewer's comments:

There were no significant differences between the various treatment groups.

6.1.3 Patient Disposition

Disposition of Patients (Studies 206207-008 and 206207-009)

Duration Disposition	Dexamethasone intravitreal implant 0.7 mg N = 421	Dexamethasone intravitreal implant 0.35 mg N = 412	Sham N = 423
Safety population ^a	421 (100%)	412 (100%)	423 (100%)
Completed day 180	401 (95.2%)	396 (96.1%)	399 (94.3%)
Discontinued:	20 (4.8%)	16 (3.9%)	24 (5.7%)
Adverse events	7 (1.7%)	8 (1.9%)	8 (1.9%)
Lack of efficacy	0 (0.0%)	3 (0.7%)	4 (0.9%)
Administrative	8 (1.9%)	3 (0.7%)	7 (1.7%)

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Protocol violation	2 (0.5%)	0 (0.0%)	1 (0.2%)
Other	3 (0.7%)	2 (0.5%)	4 (0.9%)
Study ^b			
Mean	176.1	177.2	174.8
Range	7 – 215	22 – 270	0 – 259

a Safety population is defined as all randomized and treated subjects.

b Study days = day of last visit – injection date at day 0.

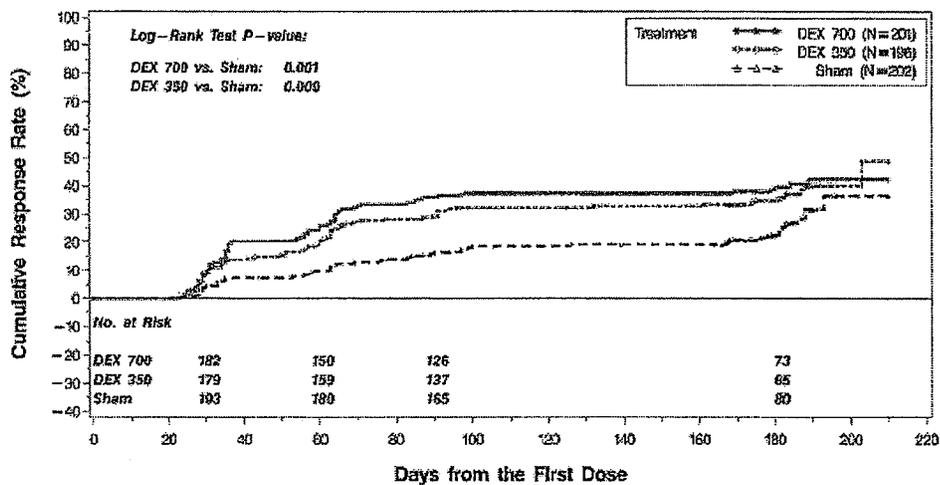
Patient disposition and duration of initial treatment period are summarized in the Disposition of Patients. The mean number of days in the study was similar for patients in each of the 3 treatment groups (176.1 days for dexamethasone intravitreal implant 0.7 mg, 177.2 days for dexamethasone intravitreal implant 0.35 mg, and 174.8 days for Sham), and a similar percentage of patients in each group discontinued from the study because of adverse events (1.7% [7/421] for dexamethasone intravitreal implant 0.7mg, 1.9% [8/412] dexamethasone intravitreal implant 0.35 mg, and 1.9% [8/423] for Sham).

Reviewer’s comments:

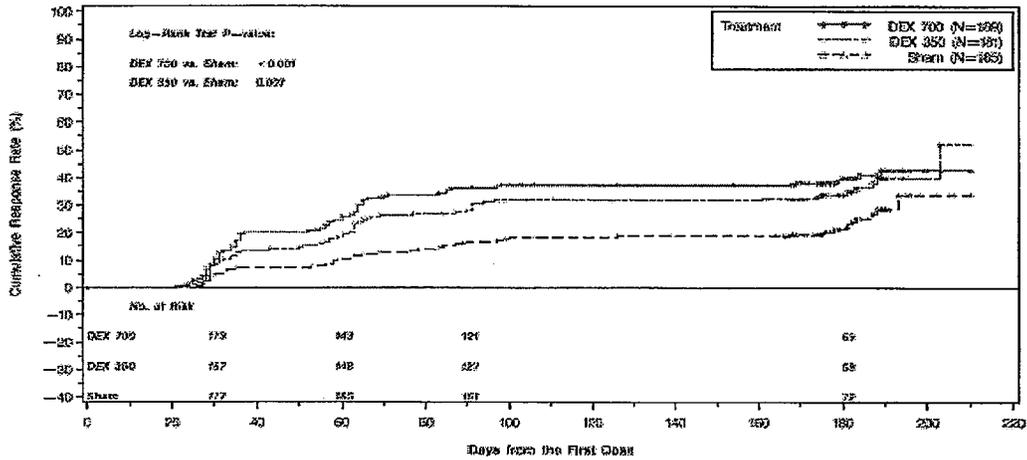
There are no significant differences in patients who completed the trials or discontinued from the study.

6.1.4 Analysis of Primary Endpoint(s)

Time to Achieve 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity (Study 008, ITT Population)

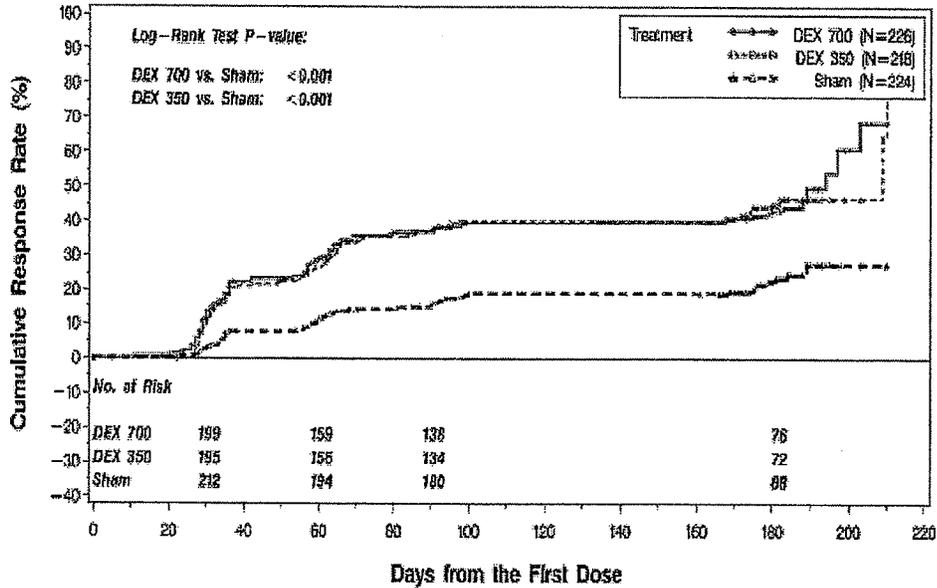


**Time to Achieve 15 or More Letters Improvement from Baseline
 Best-Corrected Visual Acuity (Study 008, PP Population)**

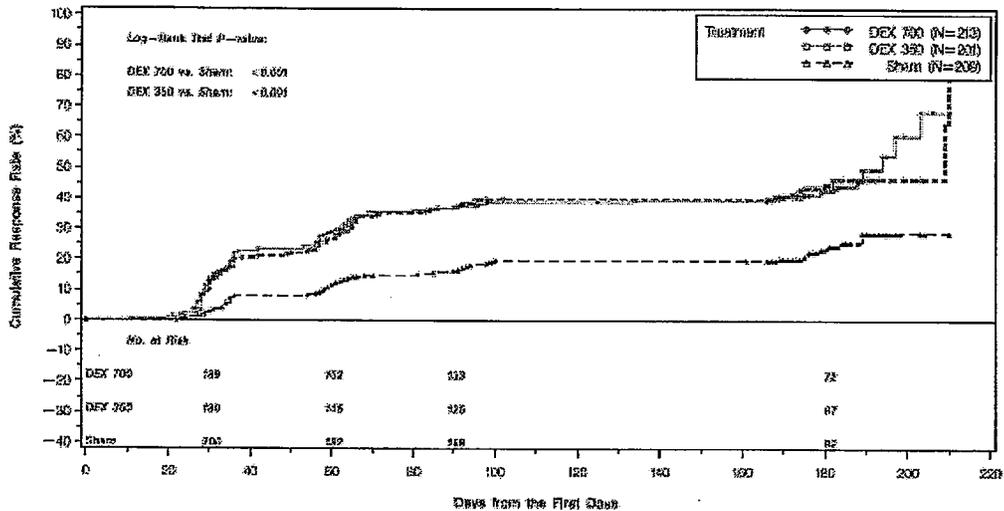


In Study 206207-008 the time to achieve a treatment response of ≥ 15 letters improvement from baseline BCVA was evaluated over the entire initial treatment period using survival analysis methods. Overall the cumulative response rate curves were significantly different for the dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg groups compared to the Sham group ($p < 0.001$). Response rates were consistently higher with dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg compared to Sham throughout the 180-day initial treatment period. There was a separation of curves as early as day 30, without crossover at any subsequent visit. The effect of dexamethasone intravitreal implant treatment was also similar in the BRVO and CRVO patients.

Time to Achieve 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity (Study 009, ITT Population)



Time to Achieve 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity (Study 009, PP Population)



In study 206207- 009, analysis of time to treatment response of 15 or more letters improvement from baseline BCVA in the study eye was determined. Overall, the cumulative response rate

curves were significantly different for the dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg groups compared to the Sham group ($p < 0.001$). Response rates were consistently higher with dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.350 mg than with Sham, with separation of curves as early as day 30 and no crossover during the initial treatment period. The effect of Dexamethasone intravitreal implant treatment was also similar in the BRVO and CRVO patients.

Reviewer’s comments:

Both -008 and -009 demonstrated efficacy based on the Time to Improvement of 15 or more letters of BCVA compared to the control group (Sham injection).

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints included: proportion of patients with BCVA improvement of 15 or more letters and mean change from baseline BCVA.

Proportion of patients with BCVA Improvement of 15 or More Letters from Baseline Best Corrected Visual Acuity in the Study Eye

Visit	Study 206207-009			Study 206207-008			Pooled 008 and 009		
	Dex. implant 0.7 mg N=226	Dex. implant 0.35 mg N=218	Sham N=224	Dex. implant 0.7 mg N=210	Dex. implant 0.35 mg N=196	Sham N=202	Dex. implant 0.7 mg N=427	Dex. implant 0.35 mg N=414	Sham N=426
Day 30	22.6% ^a	20.6% ^a	7.6	19.9% ^a	14.8% ^e	7.4%	21.3% ^a	17.9 ^a	7.5%
Day 60	29.6% ^a	31.2 ^a	12.1%	28.9% ^a	25.5% ^a	10.4%	29.3% ^a	28.5% ^a	11.3%
Day 90	21.2 ^b	25.7% ^c	13.8%	22.4% ^d	20.9% ^f	12.4%	21.8% ^a	23.4% ^a	13.1%
Day 180	23.5%	22.0%	17.0%	19.4%	16.3%	18.3%	21.5%	19.3%	17.6%

a Proportion significantly higher with Dexamethasone intravitreal implant compared to Sham ($p < 0.001$)

b Proportion significantly higher with Dexamethasone intravitreal implant compared to Sham ($p = 0.039$)

c Proportion significantly higher with Dexamethasone intravitreal implant compared to Sham ($p = 0.002$)

d Proportion significantly higher with Dexamethasone intravitreal implant compared to Sham ($p = 0.008$)

e Proportion significantly higher with Dexamethasone intravitreal implant compared to Sham ($p = 0.019$)

f Proportion significantly higher with Dexamethasone intravitreal implant compared to Sham ($p = 0.022$)

In each of the phase 3 studies, patients receiving Dexamethasone intravitreal implant achieved significantly higher rates of 15 or more letters improvement in BCVA from baseline compared to Sham in the first 3 months.

In study 009 at day 180, the difference (95% confidence interval) between dexamethasone intravitreal implant 0.7 mg and Sham in the percent of patients was 6.5% (-0.9% to 13.9%), $p = 0.087$. In study 008, the difference between groups at Day 180 was less than 1%.

Mean Change from Baseline in Number of Letters read Correctly in the Study Eye

Visit	Study 206207-009			Study 206207-008			Pooled 008 and 009		
	Dex. implant 0.7 mg N=226	Dex. implant 0.35 mg N=218	Sham N=224	Dex. implant 0.7 mg N=210	Dex. implant 0.35 mg N=196	Sham N=202	Dex. implant 0.7 mg N=427	Dex. implant 0.35 mg N=414	Sham N=426
Day 30	8.5 ^a	8.3 ^a	2.7	7.6 ^a	7.1 ^a	2.5	8.1 ^a	7.8 ^a	2.6
Day 60	10.1 ^a	10.2 ^a	3.2	9.5 ^a	9.0 ^a	3.1	9.8 ^a	9.7 ^a	3.1
Day 90	7.3 ^a	8.4 ^a	3.5	7.2 ^a	6.2 ^d	2.8	7.2 ^a	7.3 ^a	3.2
Day 180	5.5 ^b	6.1 ^c	2.5	4.6	4.1	2.7	5.1 ^c	5.2 ^f	2.6

a Mean change from baseline significantly greater with Dexamethasone intravitreal implant compared to Sham (p < 0.001)

b Mean change from baseline significantly greater with Dexamethasone intravitreal implant compared to Sham (p = 0.016)

c Mean change from baseline significantly greater with Dexamethasone intravitreal implant compared to Sham (p = 0.004)

d Mean change from baseline significantly greater with Dexamethasone intravitreal implant compared to Sham (p = 0.003)

e Mean change from baseline significantly greater with Dexamethasone intravitreal implant compared to Sham (p = 0.006)

f Mean change from baseline significantly greater with Dexamethasone intravitreal implant compared to Sham (p = 0.005)

In each of the phase 3 studies 008 and 009, and the pooled analysis, patients receiving Dexamethasone intravitreal implant showed greater increases in BCVA from baseline than Sham. The treatment group differences peaked at day 60, with a difference of approximately 7 letters.

Reviewer's comments:

Secondary endpoints, "Proportion of patients with BCVA Improvement of 15 or More Letters from Baseline Best Corrected Visual Acuity in the Study Eye" and "Mean Change from Number of Letters Read," provide additional supportive evidence of the effectiveness of the drug product.

6.1.6 Other Endpoints

No other endpoints were required to establish efficacy of the drug product.

6.1.7 Subpopulations

Patients are predominately elderly and Caucasian. No clinically relevant differences are observed between the treatment groups comparing the demographic characteristics (i.e., age, race, sex, and iris color) of the population when integrated across studies, as well as within each individual clinical study.

Analyses by age category (adults and elderly), gender, race, and iris color did not identify any efficacy (or safety) concerns for any demographic subpopulation.

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

The safety and efficacy effects seen with this product are class effects related to steroids as well as the risk of intravitreal injections.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and thus 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.

Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection.

6.1.10 Additional Efficacy Issues/Analyses

No additional analyses were required.

7 Review of Safety

Safety Summary

Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The applicant conducted two adequate and well controlled clinical trials: studies 206207-008 and 206207-009. These studies were designed as a 6-month masked treatment followed by a 6-month open label period. At day 180, all qualifying patients who remained unaware of the initial randomized treatment, were eligible to receive treatment with open-label dexamethasone intravitreal implant 0.7 mg. No sham or dexamethasone intravitreal implant 0.350 mg procedures were conducted at this visit.

One hundred subjects from these studies received a second injection (dexamethasone intravitreal implant 0.7 mg) for the 6-month open-label treatment period. The safety data from these 100 subjects with 12 month follow-up are also included within this safety review. See Section 7.4.5.

7.1.2 Adequacy of Data

See Section 3.1.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Refer to the listing of Adverse Events in Section 7.3.4.

Adequacy of Safety Assessments

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

Refer to Section 7.5.1. The Patient Exposure and Safety Assessments were adequate.

7.1.5 Explorations for Dose Response

The intravitreal doses studied in the trials were dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg. Refer to Section 7.5.1 for patient exposure.

7.1.6 Special Animal and/or In Vitro Testing

In a 1 month rabbit vitrectomy study following a single intravitreal injection of Dexamethasone intravitreal implant in both the vitrectomized and nonvitrectomized rabbit eyes, the ocular pharmacokinetics of dexamethasone between vitrectomized and nonvitrectomized eyes was similar.

In a 6 month monkey study following a single intravitreal injection of Dexamethasone intravitreal implant, the rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humor > aqueous humor > plasma. Dexamethasone was released in the monkey vitreous up to 6 months.

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. This is consistent with results from rabbit and monkey ocular metabolism studies.

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.

7.1.7 Routine Clinical Testing

There were no statistically significant among-group differences at baseline or in the change from baseline to initial treatment day 180 in diastolic and systolic blood pressure or pulse rate.

Refer to Clinical Pharmacology Section 4.4. Given the well established profile of dexamethasone, and the published literature and clinical experience with dexamethasone, no additional clinical laboratory data were collected.

7.1.8 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology Section 4.4. Given the well established profile of dexamethasone, and the published literature and clinical experience with dexamethasone, no additional clinical laboratory data were collected.

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

The safety and efficacy effects seen with this product are class effects related to steroids.

Ocular steroids are contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and thus 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 perforation. Acute purulent infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

Major Safety Results

7.1.10 Deaths

There were three deaths that occurred during study 206207-008 and one death that occurred during study 206207-009.

In study 206207-008, one subject died due to accidental drowning and two due to myocardial infarctions. In study 206207-009, the subject died due to a myocardial infarction.

Reviewer's comments:

None of the deaths were considered to be related to study treatment.

7.1.11 Nonfatal Serious Adverse Events

Serious Adverse Events in Any Treatment Group
 (Studies 206207-008 and 206207-009, Initial 6-Month Period)

System Organ Class Preferred Term ^a	Dexamethasone intravitreal implant 0.7 mg N = 421	Dexamethasone intravitreal implant 0.35 mg N = 412	Sham N = 423
Ocular Events			
Intraocular pressure Increased	2 (0.5%)	3 (0.7%)	0 (0.0%)
Ocular hypertension	1 (0.2%)	0 (0.0%)	0 (0.0%)
Retinal vein occlusion	0 (0.0%)	1 (0.2%)	0 (0.0%)
Blindness	0 (0.0%)	1 (0.2%) ^b	0 (0.0%)
Glaucoma	0 (0.0%)	1 (0.2%) ^b	1 (0.2%)
Non-Ocular Events^c			
Cardiac Disorders			
Myocardial infarction	2 (0.5%)	5 (1.2%)	0 (0.0%)
Angina pectoris	2 (0.5%)	1 (0.2%)	0 (0.0%)
Cardiac failure congestive	1 (0.2%)	0 (0.0%)	2 (0.5%)
General Disorders			
Chest pain	0 (0.0%)	0 (0.0%)	2 (0.5%)
Infections			
Urinary tract infection	0 (0.0%)	0 (0.0%)	2 (0.5%)
Nervous System Disorders			
Cerebrovascular accident	1 (0.2%)	2 (0.5%)	1 (0.2%)
Syncope	0 (0.0%)	1 (0.2%)	2 (0.5%)

a Preferred terms based on MeDRA, version 11.0.

b Events occurred in same patient eye

c Events listed occurring in 2 or more subjects

The rates of ocular serious events and non-ocular serious events were similar among the 3 treatment groups.

Reviewer's comments:

There was not a significant difference in the Serious Adverse Events reported by dose or for each clinical study (-008 and -009).

7.1.12 Dropouts and/or Discontinuations

Subjects With Adverse Events in Any Treatment Group Leading to Discontinuation (Studies 206207-008 and 206207-009, Initial 6-Month Period)

Treatment Patient	Adverse Events ^a Leading to Discontinuation
Dexamethasone intravitreal implant 0.7 mg	
2013	Cardiac arrest
2126	Intraocular pressure increased
3438	Retinal vein occlusion
2387	Aortic aneurysm
0422	Asthenia
0007	Macular edema
	Retinal hemorrhage
0394	Visual acuity reduced
Dexamethasone intravitreal implant 0.35 mg	
2357	Vitreous hemorrhage
3654	Intraocular pressure increased
0146	Drowning
0652	Blindness
0777	Cardiogenic shock
	Myocardial infarction
	Renal failure acute
	Respiratory failure
1201	Pneumonia viral
1802	Myocardial infarction
1186	Intraocular pressure increased
	Vitreous hemorrhage
Sham	
2662	Retinal neovascularization
2621	Cellulitis
2205	Macular cyst
3699	Maculopathy
3011	Iris neovascularization
	Retinal neovascularization
0213	Iris neovascularization
0022	Visual acuity reduced
0303	Back pain

^a Preferred terms based on MeDRA, version 11.0.

Few patients withdrew from the initial treatment period of the phase 3 studies due to adverse events. Adverse events leading to discontinuation in the initial treatment period for the pooled phase 3 studies were reported for 1.7% (7/421) in the dexamethasone intravitreal implant 0.7 mg group, 1.9% (8/412) in the dexamethasone intravitreal implant 0.35 mg group, and 1.9% (8/423) in the Sham group.

7.1.13 Significant Adverse Events

Adverse Events Occurring in > 2 % of Patients in Any Treatment Group (Studies 206207-008 and 206207-009, Initial 6-month Period)

System Organ Class Preferred Term ^a	Dexamethasone intravitreal implant 0.7 mg N = 421	Dexamethasone intravitreal implant 0.35 mg N = 412	Sham N = 423
Ocular Events			
Intraocular pressure increased ^b	106 (25.2%)	102 (24.8%)	5 (1.2%)
Conjunctival hemorrhage	85 (20.2%)	72 (17.5%)	63 (14.9%)
Eye pain	31 (7.4%)	17 (4.1%)	16 (3.8%)
Conjunctival hyperemia	28 (6.7%)	27 (6.6%)	20 (4.7%)
Maculopathy	19 (4.5%)	22 (5.3)	23 (5.4%)
Ocular hypertension ^c	17 (4.0%)	16 (3.9%)	3 (0.7%)
Cataract	15 (3.6%)	7 (1.7%)	6 (1.4%)
Vitreous floaters	13 (3.1%)	5 (1.2%)	6 (1.4%)
Vitreous detachment	12 (2.9%)	12 (2.9%)	8 (1.9%)
Retinal hemorrhage	12 (2.9%)	8 (1.9%)	10 (2.4%)
Foreign body sensation	11 (2.6%)	7 (1.7%)	11 (2.6%)
Vitreous hemorrhage	10 (2.4%)	13 (3.2%)	12 (2.8%)
Retinal exudates	10 (2.4%)	4 (1.0%)	14 (3.3%)
Conjunctival edema	9 (2.1%)	16 (3.9%)	7 (1.7%)
Visual acuity reduced	7 (1.7%)	7 (1.7%)	9 (2.1%)
Retinal neovascularization	3 (0.7%)	4 (1.0%)	11 (2.6%)
Non-ocular events			
Influenza	9 (2.1%)	4 (1.0%)	2 (0.5%)
Headache	14 (3.3%)	10 (2.4%)	7 (1.7%)
Hypertension	17 (4.0%)	13 (3.2%)	15 (3.5%)

a Preferred terms based on MeDRA, version 11.0.

b P-value < 0.001 for DEX 700 vs Sham; < 0.001 for DEX 350 vs Sham; and 0.888 for DEX 700 vs DEX 350

c P-value 0.004 for DEX 700 vs Sham; 0.006 for DEX 350 vs Sham; and 0.909 for DEX 700 vs DEX 350

There were no notable differences in the adverse event profile between the 2 studies. The overall incidence of adverse events in the initial treatment period for the pooled phase 3 studies was significantly higher in the dexamethasone intravitreal implant 0.7 mg group (72.4%) and dexamethasone intravitreal implant 0.35 mg group (71.8%) compared to Sham (57.0%). There was no significant difference between the dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg doses. Ocular adverse events were likewise more commonly reported with dexamethasone intravitreal implant 0.7 mg (64.1%) and dexamethasone intravitreal implant 0.35 mg (64.6%) than with Sham (45.4%). The adverse event profile was similar between the 3 treatment groups, aside from the expected increase in intraocular pressure associated with intravitreal injection of a steroid.

The adverse event profile for the BRVO patients was generally similar to that observed for CRVO, and to the overall population.

Reviewer's comments:

The greatest percentage events reported in the drug treatment groups were an increase in intraocular pressure and conjunctival hemorrhage that were reported in more than 20 % of patients. These events are expected given the route of administration of the drug product is an intravitreal injection.

The adverse events reported were not significantly different between the two clinical trials (-008 and -009).

Based on its risk profile, the drug is a safe and effective treatment for macular edema following BRVO or CRVO.

7.1.14 Submission Specific Primary Safety Concerns

The Adverse Event profile was similar for age [mid-age (45 to 65 years) and older (> 65 years) patients], sex and race.

Supportive Safety Results

7.1.15 Common Adverse Events

Refer to Section 7.3.4 for a listing of Adverse Events.

7.1.16 Laboratory Findings

Given the well established profile of dexamethasone, and the published literature and clinical experience with dexamethasone, no additional clinical laboratory data were collected.

7.1.17 Vital Signs

There were no statistically significant among-group differences at baseline or in the change from baseline to initial treatment day 180 in diastolic and systolic blood pressure or pulse rate.

7.1.18 Electrocardiograms (ECGs)

Given the well established profile of dexamethasone, and the published literature and clinical experience with dexamethasone, no additional clinical laboratory data were collected.

7.1.19 Special Safety Studies

Safety data are included for 100 patients who received dexamethasone intravitreal implant 0.7 mg in the initial masked treatment period and a second dexamethasone intravitreal implant 0.7

mg in the open-label extension, and completed 1-year follow-up after the initial treatment. These 100 patients were randomly selected from a pool of patients who entered the open-label extension period and received a second dexamethasone intravitreal implant 0.7 mg injection and completed the required open-label day 180 visit.

At day 180, qualifying patients who remained unaware of the initial randomized treatment (up to 100 subjects) were eligible to receive treatment with an open-label dexamethasone intravitreal implant 0.7 mg. No sham or 0.35 mg implant procedures were conducted at this visit.

One hundred subjects from these studies received an open-label dexamethasone intravitreal implant 0.7 mg for the 6-month open-label treatment period. The Adverse Event profiles follows:

**Adverse Events Occurring in > 2 % of Patients
 (Initial Treatment Period and Open-Label Extension)**

System Organ Class Preferred Term ^a	Initial Treatment Dexamethasone intravitreal implant 0.7 mg N = 100	Open-Label Extension Only Dexamethasone intravitreal implant 0.7 mg/ Dexamethasone intravitreal implant 0.7 mg N = 100	Initial Treatment plus Open-label Extension Dexamethasone intravitreal implant 0.7 mg / Dexamethasone intravitreal implant 0.7 mg N = 100
Ocular Events			
Intraocular pressure increased ^b	23 (23 %)	28 (28 %)	33 (33 %)
Conjunctival hemorrhage	27 (27 %)	27 (27 %)	32 (32 %)
Conjunctival hyperemia	10 (10 %)	8 (8 %)	15 (15 %)
Cataract	7 (7 %)	14 (14 %)	14 (14 %)
Cataract subcapsular	3 (3 %)	12 (12 %)	13 (13 %)
Eye pain	8 (8 %)	10 (10 %)	13 (13 %)
Vitreous detachment	8 (8 %)	11 (11 %)	11 (11 %)
Macular edema	3 (3 %)	9 (9 %)	10 (10 %)
Maculopathy	4 (4 %)	8 (8 %)	9 (9 %)
Retinal hemorrhage	6 (6 %)	9 (9 %)	9 (9 %)
Ocular hypertension ^c	5 (5 %)	4 (4 %)	7 (7 %)
Vitreous hemorrhage	4 (4 %)	4 (4 %)	6 (6 %)
Cataract nuclear	2 (2 %)	4 (4 %)	5 (5 %)
Dry eye	0 (0 %)	5 (5 %)	5 (5 %)
Optic disc vascular disorder	3 (3 %)	5 (5 %)	5 (5 %)
Retinal exudates	3 (3 %)	2 (2 %)	5 (5 %)
Visual acuity reduced	3 (3 %)	4 (4 %)	5 (5 %)
Vitreous floaters	3 (3 %)	2 (2 %)	5 (5 %)
Conjunctival edema	3 (3 %)	2 (2 %)	4 (4 %)
Anterior chamber cell	3 (3 %)	1 (1 %)	3 (3 %)
Blepharitis	3 (3 %)	2 (2 %)	3 (3 %)
Cataract cortical	1 (1 %)	3 (3 %)	3 (3 %)
Eye irritation	2 (2 %)	1 (1 %)	3 (3 %)
Eye pruritus	2 (2 %)	1 (1 %)	3 (3 %)

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Photopsia	2 (2 %)	1 (1 %)	3 (3 %)
Punctuate keratitis	2 (2 %)	1 (1 %)	3 (3 %)
Retinal degeneration	1 (1 %)	2 (2 %)	3 (3 %)
Retinal pigmentation	0 (0 %)	3 (3 %)	3 (3 %)
Retinal vein occlusion	1 (1 %)	3 (3 %)	3 (3 %)
Vision blurred	2 (2 %)	1 (1 %)	3 (3 %)
Vitritis	3 (3 %)	0 (0 %)	3 (3 %)
Non-ocular events			
Nasopharyngitis	3 (3 %)	5 (5 %)	6 (6 %)
Fall	3 (3 %)	0 (0 %)	3 (3 %)
Headache	2 (2 %)	1 (1 %)	3 (3 %)
Dyspnea	0 (0 %)	3 (3 %)	3 (3 %)
Hypertension	4 (4 %)	6 (6 %)	6 (6 %)

a Preferred terms based on MeDRA, version 11.0.

The adverse event profile was similar between the 3 treatment groups, aside from the expected increase in intraocular pressure and the development of cataract formation associated with an intravitreal injection of a steroid.

Reviewer's comments:

As expected, with additional exposure to dexamethasone, there remains the risk of increased intraocular pressure and the development of cataract.

The adverse events reported were not significantly different between the two clinical trials (-008 and -009).

7.1.20 Immunogenicity

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.

Other Safety Explorations

7.1.21 Dose Dependency for Adverse Events

Patient Exposure to Dexamethasone intravitreal implant

Study	Follow-up Duration	Dexamethasone intravitreal implant 0.7 mg	Dexamethasone intravitreal implant 0.35 mg	Control (Sham)
206207-008	6 months following initial treatment	196	197	202
206207-009	6 months following initial treatment	225	215	221
206207-009	12 months following initial treatment	100 ^a	0	0

^a Patients already counted under study 206207-009 (6 months); not included in total.

In the phase 3 studies patients received their assigned masked treatment on day 0 and were followed for 180 days in the initial treatment period. At month 6, qualified patients were eligible to receive open-label Dexamethasone intravitreal implant 0.7 mg. All patients (whether they received the open-label treatment or not) are being followed for safety up to an additional 6 months after the initial treatment Day 180 visit. Data are reported here through the initial 6-month period.

Reviewer's comments:

Patient exposure to Dexamethasone intravitreal implant was adequate to determine the safety and effectiveness of the drug product. See Section 7.4.5.

7.1.22 Time Dependency for Adverse Events

Refer to Section 7.4.5.

7.1.23 Drug-Demographic Interactions

No Drug-Demographic differences were noted.

7.1.24 Drug-Disease Interactions

No Drug-Disease interactions are expected.

7.1.25 Drug-Drug Interactions

No interaction studies were performed, however due to the low systemic levels of dexamethasone, drug interactions are not expected.

Additional Safety Explorations

7.1.26 Human Carcinogenicity

No adequate studies in animals have been conducted 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.

7.1.27 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.

7.1.28 Pediatrics and Effect on Growth

Safety and effectiveness of Dexamethasone intravitreal implant in pediatric patients has not been established.

7.1.29 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose and drug abuse with Dexamethasone intravitreal implant has not been reported in the clinical trials. Overdose is unlikely given the drug is administered by a physician.

The need for gradual withdrawal of oral or topical corticosteroid therapy is well established. However, because Dexamethasone intravitreal implant is placed directly into the vitreous cavity, the total amount of drug delivered is small compared with other routes of corticosteroid administration, and systemic effects are unlikely.

Additional Submissions

On April 22, 2009, the 120 Safety Update was submitted. Based upon this submission with its supplemental 1-year of follow-up data the information provided the following conclusions:

- The beneficial effects of dexamethasone intravitreal implant 0.7 mg included prevention of vision loss. At the end of 6 months' initial treatment (6 month follow-up period), the proportion of patients experiencing ≥ 3 lines worsening in BCVA was significantly lower with dexamethasone intravitreal implant 0.7 mg (5.9%) compared to Sham (10.9%), $p = 0.021$, while the proportion with dexamethasone intravitreal implant 0.35 mg (7.1%) was intermediate. At the end of the open-label extension (1-year study), the proportion worsening was significantly lower with dexamethasone intravitreal implant 0.7 mg / 0.7 mg (6.2%) compared to Sham /

dexamethasone intravitreal implant 0.7 mg (11.3%), $p = 0.021$, and also compared to dexamethasone intravitreal implant 0.35 mg / 0.7 mg (11.4%), $p = 0.023$.

- During the initial treatment period, the adverse event profile was similar between the 3 treatment groups, aside from the expected intraocular pressure increase and cataracts associated with intravitreal injection of a steroid. During the open-label extension, the adverse event profile was similar between the 3 re-treated groups, each of whom had received dexamethasone intravitreal implant 0.7 mg as their second injection. The incidences of cataracts and subcapsular cataracts were however higher in patients who had received 2 doses of Dexamethasone intravitreal implant compared to those who had initially received Sham.
- For patients receiving 2 doses of Dexamethasone intravitreal implant, the most common adverse events and incidences were similar during the initial treatment period and the open-label extension. Elevated intraocular pressure was reported at comparable rates following the first and second injections of Dexamethasone intravitreal implant. As expected, the incidences of cataracts and subcapsular cataracts however were higher following reinjection.
- IOP ≥ 25 mm Hg or 35 mm Hg, and IOP increases ≥ 10 mm Hg, peaked at day 60 but declined to near baseline levels by 6 months following the first or second injection of Dexamethasone intravitreal implant. The majority of elevations were managed with standard IOP-lowering medications, and only 7 re-treated patients and 6 single treatment patients required surgery.

Reviewer's comments:

Injections of Dexamethasone intravitreal implant were well tolerated with an acceptable 1-year safety profile.

8 Postmarketing Experience

OZURDEX (dexamethasone intravitreal implant) is neither approved nor marketed in any country; thus no marketing data are available.

9 Appendices

Literature Review/References

Dexamethasone intravitreal implant is not currently marketed and no additional articles were found.

Labeling Recommendations

Attached is the recommended labeling for the drug product.

Advisory Committee Meeting

No Advisory Committee Meeting was needed or required.

8 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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