

Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema Due to Retinal Vein Occlusion

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Objective: To evaluate the safety and efficacy of dexamethasone intravitreal implant (DEX implant; OZURDEX, Allergan, Inc., Irvine, CA) compared with sham in eyes with vision loss due to macular edema (ME) associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Design: Two identical, multicenter, masked, randomized, 6-month, sham-controlled clinical trials (each of which included patients with BRVO and patients with CRVO).

Participants: A total of 1267 patients with vision loss due to ME associated with BRVO or CRVO.

Intervention: A single treatment with DEX implant 0.7 mg (n = 427), DEX implant 0.35 mg (n = 414), or sham (n = 426).

Main Outcome Measures: The primary outcome measure for the pooled data from the 2 studies was time to achieve a ≥ 15 -letter improvement in best-corrected visual acuity (BCVA). Secondary end points included BCVA, central retinal thickness, and safety.

Results: After a single administration, the time to achieve a ≥ 15 -letter improvement in BCVA was significantly less in both DEX implant groups compared with sham ($P < 0.001$). The percentage of eyes with a ≥ 15 -letter improvement in BCVA was significantly higher in both DEX implant groups compared with sham at days 30 to 90 ($P < 0.001$). The percentage of eyes with a ≥ 15 -letter loss in BCVA was significantly lower in the DEX implant 0.7-mg group compared with sham at all follow-up visits ($P \leq 0.036$). Improvement in mean BCVA was greater in both DEX implant groups compared with sham at all follow-up visits ($P \leq 0.006$). Improvements in BCVA with DEX implant were seen in patients with BRVO and patients with CRVO, although the patterns of response differed. The percentage of DEX implant-treated eyes with intraocular pressure (IOP) of ≥ 25 mmHg peaked at 16% at day 60 (both doses) and was not different from sham by day 180. There was no significant between-group difference in the occurrence of cataract or cataract surgery.

Conclusions: Dexamethasone intravitreal implant can both reduce the risk of vision loss and improve the speed and incidence of visual improvement in eyes with ME secondary to BRVO or CRVO and may be a useful therapeutic option for eyes with these conditions.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2010;117:1134–1146 © 2010 by the American Academy of Ophthalmology.



*Group members listed online in Appendix 1 (available at <http://aaojournal.org>).

Retinal vein occlusion (RVO) is second only to diabetic retinopathy as a cause of vision loss due to vascular diseases of the retina; it may involve the central retinal vein or 1 or more hemicentral or branch retinal veins in various combinations and with varying degrees of ischemia and hemorrhage.^{1–3} Branch retinal vein occlusion (BRVO) involving a single vein is the most common type (prevalence of 0.6%–1.1%), whereas central retinal vein occlusion (CRVO) is less common (prevalence of 0.1%–0.4%).^{2,4} Ischemic CRVO (up to 25% of cases) is a particularly serious condition with a substantial risk of secondary ocular neovascu-

larization and vision loss. Many eyes with nonischemic CRVO are also at risk for significant vision loss because of macular edema (ME) and other less frequent complications.⁵ It is estimated that 12% to 33% of cases of CRVO that are nonischemic at the time of presentation may become ischemic within 4 years.^{6,7}

Macular edema is a common cause of vision loss in both BRVO and CRVO.⁸ The pathogenesis of ME in RVO is not completely understood but may result from a variety of factors, including hydrostatic effects from increased venous pressure, the presence of inflammatory cytokines (e.g., pros-

taglandins and interleukin-6), the dysregulation of endothelial tight junction proteins,⁹ or increased amounts of vascular permeability factors, such as vascular endothelial growth factor (VEGF).¹⁰

Several therapies are being investigated for the treatment of ME associated with RVO. These include laser photocoagulation,¹¹ the anti-VEGF therapy ranibizumab,^{10,12} and the corticosteroids triamcinolone acetonide^{11,13,14} and dexamethasone.¹⁵ Corticosteroids can help reduce many of the processes thought to play a role in the development of ME in RVO;^{9,16–19} they have potent anti-inflammatory effects, can reduce vascular permeability, inhibit fibrin deposition and leukocyte movement, suppress homing and migration of inflammatory cells, stabilize endothelial cell tight junctions, and inhibit the synthesis of VEGF, prostaglandins, and other cytokines.¹⁷ Intravitreal injections of the lipophilic corticosteroid triamcinolone acetonide have been shown to produce benefits in eyes with RVO, but several adverse events have been noted (with elevated intraocular pressure [IOP] being the most common).^{11,13,14,20–28} Other corticosteroids, however, have their own unique properties²⁹ and may have different clinical profiles in intravitreal use.

Dexamethasone is a potent, water-soluble corticosteroid that can be delivered to the vitreous cavity by the dexamethasone intravitreal implant (DEX implant; OZURDEX, Allergan, Inc., Irvine, CA). A DEX implant is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized dexamethasone. The drug-copolymer complex gradually releases the total dose of dexamethasone over a series of months after insertion into the eye through a small pars plana puncture using a customized applicator system. In a recent study in eyes with persistent ME from several different causes (including RVO), DEX implant 0.7 mg produced improvements in visual acuity, macular thickness, and fluorescein leakage that were sustained for up to 6 months.¹⁵

This 6-month study evaluated the safety and efficacy of DEX implant 0.35 mg and 0.7 mg compared with a sham procedure in eyes with vision loss due to ME associated with BRVO or CRVO. The time course of the response to treatment was also evaluated.

Materials and Methods

Study Design

Two randomized, prospective, multicenter, masked, sham-controlled, parallel-group clinical trials were conducted in compliance with regulatory obligations, the Declaration of Helsinki, and the institutional review board and informed consent regulations at each investigational site. These trials are registered at clinicaltrials.gov as NCT00168324 and NCT00168298. Two separate phase III clinical trials (each of which included patients with BRVO and patients with CRVO) were conducted for regulatory purposes; because the study designs for the 2 trials were identical, the results were pooled for analysis.

Study Population

Patients were recruited at 167 clinical sites in 24 countries throughout the world. Patients who were at least 18 years of age and had decreased visual acuity as a result of clinically detectable ME associated with either CRVO or BRVO were recruited into both studies. Duration of ME (defined as the time since initial diagnosis of ME) was required to be between 6 weeks and 9 months in patients with CRVO and between 6 weeks and 12 months in patients with BRVO. The investigator selected 1 eye per patient to be the study eye. If both eyes were eligible, then the eye with the shorter duration of ME was selected. Eligible patients had to have best-corrected visual acuity (BCVA) of between 34 letters (20/200) and 68 letters (20/50) in the study eye and better than 34 letters in the nonstudy eye. Retinal thickness in the central subfield (as measured by optical coherence tomography; OCT2 or OCT3) had to be $\geq 300 \mu\text{m}$ in the study eye.

Key exclusion criteria included the presence of a clinically significant epiretinal membrane, active retinal or optic disc neovascularization, active or history of choroidal neovascularization, presence of rubeosis iridis, any active infection, aphakia or anterior-chamber intraocular lens, clinically significant media opacity, glaucoma or current ocular hypertension requiring more than 1 medication to control IOP in the study eye, or a history of steroid-induced IOP increase in either eye. Patients were also excluded if they had diabetic retinopathy in either eye, had any uncontrolled systemic disease, were currently using or anticipating the use of systemic steroids or anticoagulants during the study, or had any ocular condition in the study eye that, in the opinion of the investigator, would prevent a 15-letter improvement in visual acuity.

Randomization and Masking

Patients were randomized to either a sham procedure or treatment with 0.35 or 0.7 mg DEX implant using a 1:1:1 allocation ratio. Randomization was performed centrally (using an interactive voice response system) and stratified by the underlying cause of RVO (BRVO or CRVO). The treatment investigator performed the study treatment procedure, evaluated the quality of the OCT scans, and was responsible for the overall safety of study participants, but kept all study medication information confidential and did not collect efficacy information. Patients were masked with regard to study treatment, and the key efficacy variables were collected and evaluated by follow-up investigators who were also masked with regard to study treatment. A central reading center (University of Wisconsin Fundus Photograph Reading Center) was used to evaluate OCT measurements of central retinal thickness using standardized procedures and graders masked to study group assignment.

Study Treatment

On day 0, the study eye was anesthetized with topical and subconjunctival anesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection. The DEX implant was inserted into the vitreous cavity through the pars plana using a customized, single-use, 22-gauge applicator. The sham procedure followed the same protocol, including anesthetic and surgical preparation, but used a needleless applicator placed against the conjunctiva to simulate the placement of study medication. Patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure.

Nonstudy Treatments

Nonstudy treatments considered necessary for the best care of the patient could be given at the discretion of the investigator. Doses of any medication that could have an effect on study outcomes were to remain constant throughout the study. Unless required for patient care, the use of laser/surgical treatment, topical nonsteroidal anti-inflammatory agents, or intravitreal, periocular, or topical steroids in the study eye was prohibited during the study. The use of systemic steroids, immunosuppressants, immunomodulators, anticoagulants, antimetabolites, and alkylating agents was also prohibited. The use of prohibited therapies was recorded as an escape treatment. Patients who received prohibited treatments were not required to discontinue from the study, and their efficacy and safety outcomes were included in the intent-to-treat analyses. The data from patients who received prohibited medications that were considered major protocol violations were excluded from the per-protocol efficacy analyses.

Outcome Measures

The prospectively defined primary efficacy analysis for the pooled data from the 2 phase III studies was the time to reach a 15-letter improvement from baseline BCVA. Best-corrected visual acuity was measured using a standardized Early Treatment Diabetic Retinopathy Study protocol.³⁰ Testing was done at a standardized distance (4 m) under standardized lighting conditions.

These studies were the first designed to achieve Food and Drug Administration regulatory approval for a therapy indicated for the treatment of ME due to RVO, and 2 separate phase III trials were required. The Food and Drug Agency requested that the primary outcome for the first study be the proportion of eyes achieving at least a 15-letter improvement from baseline BCVA at day 180. The agency later requested that the prospective primary outcome measure for the second study be the time to reach a 15-letter improvement from baseline BCVA.

Secondary efficacy analyses for the pooled data included the assessment of the proportion of eyes achieving at least a 10-, 11-, 12-, 13-, 14-, or 15-letter improvement from baseline BCVA; the proportion of eyes exhibiting ≥ 15 letters of worsening from baseline BCVA; and the mean change from baseline BCVA. Subgroup analyses of changes in BCVA included a prospectively planned analysis based on RVO diagnosis (BRVO vs. CRVO) and a post hoc subgroup analysis based on duration of ME at baseline.

Secondary outcome measures also included central subfield retinal thickness measured using OCT. For the OCT analysis, images were obtained from each study eye after pupil dilation by a certified operator using an OCT2 (Carl Zeiss Meditec Inc., Dublin, CA; 1 site only) or OCT3 (Stratus OCT, Carl Zeiss Meditec Inc.; all other sites) system. Two images were obtained at the screening visit, and 6 images were obtained at the OCT follow-up visits (days 90 and 180); the central subfield retinal thickness used for statistical analyses was determined by taking the average of the 6 images obtained at each follow-up visit. Material obtained via OCT included retinal maps (especially the 6-mm variant and the 6 maps composing the radial pattern) and the 2 align (or align/normalize) prints from the 6 to 12 o'clock and 3 to 9 o'clock scans ("crosshairs") in the radial pattern. These materials were sent to the University of Wisconsin Fundus Photograph Reading Center for grading. Central retinal thickness was determined from the central 1-mm macular subfield (correlation between center point thickness and central subfield thickness was 0.98).

Safety parameters, including IOP assessments, slit-lamp biomicroscopy, ophthalmoscopy, and adverse events, were also assessed. The presence of nuclear, cortical, and posterior subcapsular

lens opacities was measured during the slit-lamp examination using standardized photographs.

Patients were evaluated at baseline and days 1, 7, 30, 60, 90, and 180 posttreatment. Best-corrected visual acuity, IOP, biomicroscopy, ophthalmoscopy, and adverse events were evaluated at each study visit. Fluorescein angiography and vital signs were assessed at baseline and day 180, and central retinal thickness was assessed at baseline, day 90, and day 180.

Data Analysis and Statistical Methods

The patient population used for the analyses of primary and secondary efficacy variables was the intent-to-treat population, which included all randomized patients. The analyses of safety variables included patients who received study treatment after randomization and were based on the actual treatment that each patient received. To confirm the robustness of the findings from the intent-to-treat analyses, a per-protocol analysis that excluded patients with major protocol violations was also performed on key efficacy variables.

The time to reach a 15-letter improvement from baseline was evaluated using the Kaplan–Meier method, and differences between the treatment groups were assessed using the log-rank test comparing the cumulative response rate curves across time during the 6-month study period. Categorical variables were analyzed using the Pearson chi-square test or Fisher exact test. Continuous variables were analyzed using analysis of variance. Pairwise between-group comparisons for categorical change from baseline BCVA (an ordinal response) were performed using the Wilcoxon rank-sum test. The comparisons for the secondary outcome measures were performed at the $\alpha = 0.05$ significance level. All tests were 2-sided.

Missing data were replaced by last observation carried forward for all BCVA analyses, except Kaplan–Meier analysis, using the intent-to-treat population. A gatekeeping procedure was used to control the overall type I error rate at 5% for multiple comparisons between groups in various efficacy variables.

For each of the 2 phase III studies, a sample size of 495 eyes (165 per group) was estimated to provide an 81% power for detecting an 11% difference between a DEX implant treatment group and the sham group in the proportion of eyes that achieved at least a 15-letter improvement in BCVA at day 180. This calculation was based on a 2-sided chi-square test at α level 0.05, assuming a 9% improvement rate for sham. Accounting for an estimated dropout rate of 10%, a total of 550 eyes was planned for each study.

Results

Patients were recruited into this study between November 2004 and March 2008. A total of 1267 patients (DEX implant 0.7 mg: $n = 427$; DEX implant 0.35 mg: $n = 414$; sham: $n = 426$) were enrolled, and the majority of patients (1196/1267; 94%) completed day 180 (Fig 1). There was no statistically significant between-group difference with regard to the number of patients who completed or withdrew from the study before day 180. Fifteen of 1267 patients (1.2%) withdrew from the study because of ocular adverse events; 2 cases were considered to be treatment related.

Demographic and baseline characteristics of the study population are listed in Table 1. Approximately twice as many patients had BRVO (830/1267, 66%) as CRVO (437/1267, 34%), and a minority of patients (211/1267; 17%) had duration of ME < 90 days. At baseline, mean visual acuity was approximately 54 letters (20/80) in all groups, and mean central retinal thickness was approximately 550 μm . Ten percent of patients (131/1267) had a

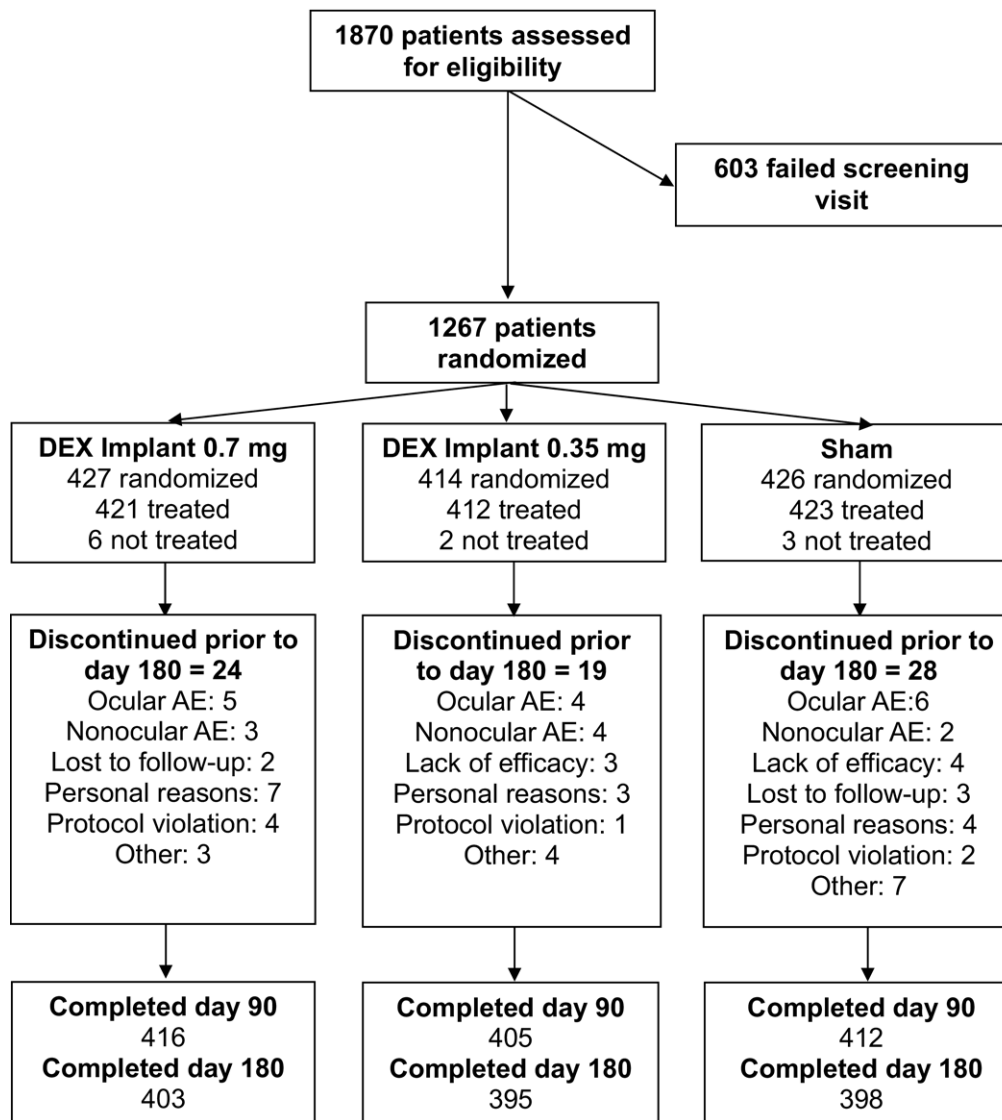


Figure 1. Patient flow through the study. AE = adverse event; DEX implant = dexamethasone intravitreal implant (OZURDEX, Allergan, Inc., Irvine, CA).

history of photocoagulation, and 801 of 1267 patients (63%) had hypertension. There was no statistically significant difference among the 3 treatment groups with regard to any demographic or baseline characteristic.

Efficacy Analysis

Visual Acuity. Eyes receiving DEX implant 0.7 or 0.35 mg achieved a 15-letter improvement in BCVA significantly faster than the eyes receiving sham treatment. This is seen in the cumulative response rate curves for the time to reach a 15-letter improvement from baseline BCVA (primary outcome measure; Fig 2; $P < 0.001$). The response rates in the DEX implant 0.7-mg group were often numerically higher than those in the DEX implant 0.35-mg group, but this difference was not statistically significant. At day 180, the cumulative response rate was 41% in the DEX implant 0.7-mg group, 40% in the DEX implant 0.35-mg group, and 23% in the sham group. Between-group differences in the time to a 15-letter gain were also statistically significant when each of the 2 phase III studies was analyzed separately (Fig 3, available

at <http://aojournal.org>) and in an analysis of the per-protocol population.

The proportion of eyes achieving at least a 15-letter improvement from baseline BCVA was significantly greater in both DEX implant treatment groups than in the sham group from day 30 to day 90 ($P < 0.001$; Fig 4A), with the greatest response (29%) at day 60. In the DEX implant 0.7-mg group, the proportion of eyes achieving at least a 15-letter improvement at day 180 was 22% (92/427), but this was not significantly different from the sham group (18%; 75/426). There were no statistically significant differences between the DEX implant 0.7-mg and 0.35-mg treatment groups at any follow-up visit. Similar results for this analysis were seen when the 2 phase III studies were analyzed separately. In addition, in an analysis of the day-180 results that excluded those patients whose last visit was later than day 180, the difference between the DEX implant 0.7-mg group (55/208; 26.4%) and the sham group (39/229; 17.0%) was statistically significant at day 180 ($P = 0.017$; Fig 4B).

When each of the phase III studies was evaluated separately, the first study did not meet its regulatory primary end point

Table 1. Demographic and Baseline Characteristics

Characteristic	DEX Implant 0.7 mg (n = 427)	DEX Implant 0.35 mg (n = 414)	Sham (n = 426)	Among-Group P Value*
Age (yrs)				0.453
Mean (range)	64.7 (33–90)	64.9 (31–96)	63.9 (31–91)	
Gender				0.268
Male	217 (50.8%)	220 (53.1%)	240 (56.3%)	
Female	210 (49.2%)	194 (46.9%)	186 (43.7%)	
Race				0.970 [†]
Caucasian	321 (75.2%)	312 (75.4%)	318 (74.6%)	
Black	15 (3.5%)	14 (3.4%)	20 (4.7%)	
Asian (excluding Japanese)	38 (8.9%)	36 (8.7%)	44 (10.3%)	
Japanese	0 (0.0%)	2 (0.5%)	1 (0.2%)	
Hispanic	37 (8.7%)	29 (7.0%)	25 (5.9%)	
Other	16 (3.7%)	21 (5.1%)	18 (4.2%)	
Iris color				0.195
Dark	241 (56.4%)	244 (58.9%)	265 (62.5%)	
Light	186 (43.6%)	170 (41.1%)	159 (37.5%)	
Diagnosis in study eye				0.264
BRVO	291 (68.1%)	260 (62.8%)	279 (65.5%)	
CRVO	136 (31.9%)	154 (37.2%)	147 (34.5%)	
Duration of macular edema				0.923
Mean duration (range)	157.6 (19–374)	153.0 (49–944)	156.1 (19–374)	0.673
<90 days	70 (16.4%)	76 (18.1%)	65 (15.3%)	
90–179 days	219 (51.3%)	218 (52.7%)	220 (51.6%)	
180–269 days	93 (21.8%)	89 (21.5%)	99 (23.2%)	
≥270 days	45 (10.5%)	32 (7.7%)	42 (9.9%)	
Mean baseline visual acuity, letters ± SD (Snellen equivalent)	54.3±9.93 (20/80)	53.9±10.41 (20/80)	54.8±9.86 (20/80)	NS
Mean baseline retinal thickness (μm±SD)	562±188	555±204	539±186	NS
Prior laser photocoagulation				0.814
BRVO	41 (10%)	44 (11%)	40 (9%)	
CRVO	37 (90%)	40 (91%)	36 (90%)	
CRVO	4 (10%)	4 (9%)	4 (10%)	
Other procedures for RVO				
Hemodilution	1 (0.2%)	1 (0.2%)	2 (0.5%)	
Intraocular injection	0	1 (0.2%)	1 (0.2%)	
Lens status [‡]				0.208
Phakic	373 (88%)	362 (87%)	387 (91%)	
Pseudophakic	53 (12%)	52 (13%)	39 (9%)	
Diabetes mellitus	64 (15%)	57 (14%)	63 (15%)	0.866
Hypertension	264 (62%)	264 (64%)	273 (64%)	0.761
Coronary artery disease	55 (13%)	49 (12%)	38 (9%)	0.165
IOP-lowering medication use at baseline	27 (6%)	24 (6%)	16 (4%)	0.210

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DEX implant = dexamethasone intravitreal implant (OZURDEX, Allergan Inc., Irvine, CA); IOP = intraocular pressure; NS = not significant; RVO = retinal vein occlusion; SD = standard deviation.

*P values were based on analysis of variance for age and the Pearson chi-square test for other variables.

[†]Caucasian versus non-Caucasian.

[‡]Based on biomicroscopic data at baseline.

(proportion of eyes achieving at least 15 letters of improvement from baseline BCVA) at day 180 ($P = 0.087$ for DEX implant 0.7 mg vs. sham), although the difference between the DEX implant 0.7-mg group and sham groups was statistically significant on days 30 to 90 ($P \leq 0.039$). The second study did meet its primary end point (time to 15-letter gain; $P < 0.001$ for DEX implant 0.7 mg vs. sham).

The proportion of eyes achieving at least 10, 11, 12, 13, or 14 letters of improvement from baseline BCVA (Table 2) was significantly greater in both DEX implant groups than in the sham group at days 30, 60, and 90 ($P < 0.001$). At day 180, the percentage of eyes achieving at least 10, 12, 13, or 14 letters of improvement was still significantly greater in the DEX implant 0.7-mg group than in the sham group ($P \leq 0.040$), but the difference between the DEX

implant 0.35-mg group and the sham group was no longer statistically significant. Throughout the study, eyes treated with DEX implant were less likely than sham-treated eyes to experience a decrease in vision of ≥ 15 letters (Fig 5).

The mean increase from baseline visual acuity was significantly greater in both DEX implant treatment groups than in the sham group from day 30 to day 180 ($P \leq 0.006$; Fig 6), with the greatest between-group difference (~ 7 letters) at day 60. There were no statistically significant differences between the DEX implant 0.7-mg and 0.35-mg treatment groups at any follow-up visit.

Retinal Thickness. The mean decrease in central subfield retinal thickness was significantly greater with DEX implant 0.7 mg ($208 \pm 201 \mu\text{m}$) and 0.35 mg ($177 \pm 197 \mu\text{m}$) than with sham treatment ($85 \pm 173 \mu\text{m}$; $P < 0.001$) at day 90 but not at day 180

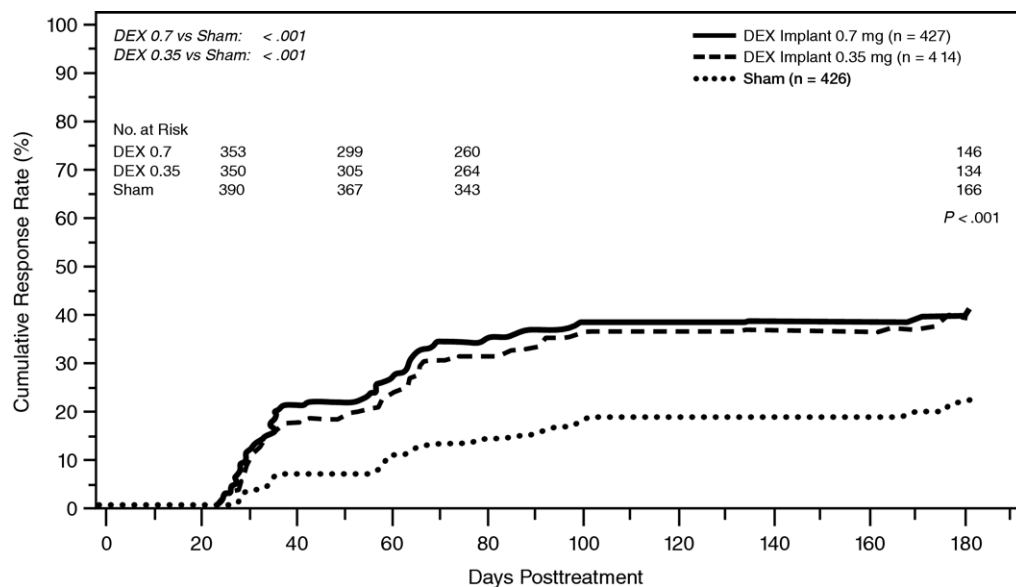


Figure 2. Time to achieve 15 letters of improvement from baseline BCVA. BCVA = best corrected visual acuity; DEX = dexamethasone intravitreal implant.

(Table 3). The number of eyes with retinal thickness $\leq 250 \mu\text{m}$ at day 90 was 141 of 389 (36.3%) in the DEX implant 0.7-mg group, 131 of 384 (34.1%) in the DEX implant 0.35-mg group, and 62 of 397 (15.6%) in the sham group ($P < 0.001$, among group).

Subgroup Analysis by Baseline Retinal Vein Occlusion Diagnosis. The key efficacy analyses (time to 15-letter improvement, proportion of eyes achieving at least a 15-letter improvement, and mean change from baseline BCVA) were evaluated for the BRVO and CRVO populations separately (prospectively defined subgroup analysis). In general, the response to treatment in both subgroups was qualitatively similar to the responses seen in the overall population, but the response in the sham group was greater in the BRVO subgroup than in the CRVO subgroup in all efficacy analyses (Fig 7). The difference between the sham groups was particularly marked in the analysis of mean change from baseline BCVA (Fig 7C). Mean BCVA slowly improved over the course of the study among BRVO eyes treated with sham, but gradually declined to below baseline levels among CRVO eyes treated with sham.

Subgroup Analysis by Duration of Macular Edema at Baseline. A post hoc subgroup analysis based on the duration of ME at baseline found that the response to treatment was often greater among eyes with a shorter duration of ME at baseline (≤ 90 days) compared with a longer duration of ME. For example, at day 60 (peak response) in the DEX implant 0.7-mg group, the proportion of eyes improving by ≥ 15 letters was 38% in eyes with ME duration ≤ 90 days and 27% in eyes with ME duration > 90 days; in the DEX implant 0.35-mg group, the proportion of eyes improving ≥ 15 letters was 35% in eyes with ME duration ≤ 90 days and 27% in eyes with ME duration > 90 days. Similarly, the peak mean change from baseline BCVA (day 60) in the DEX implant 0.7-mg group was 11.7 letters in eyes with ME duration ≤ 90 days and 9.4 letters in eyes with ME duration > 90 days; in the DEX implant 0.35-mg group, the peak mean change was 9.9 letters in eyes with ME duration ≤ 90 days and 9.6 letters in eyes with ME duration > 90 days. Improvements in the sham group were also greater among patients with shorter duration of ME. Greater improvements in BCVA with shorter ME duration were also seen in the BRVO subgroup. In eyes with CRVO, however, improvements

in the sham group were greater with shorter duration of ME, but the response to treatment was not.

Safety Analysis

The overall incidence of ocular adverse events was significantly higher in the DEX implant 0.7-mg group (62.9%) and DEX implant 0.35-mg group (61.9%) than in the sham group (42.8%; $P < 0.001$). Ocular adverse events in the study eye reported by more than 2% of patients in any treatment group or for which there was a statistically significant difference between a DEX implant group and sham are listed in Table 4. The only adverse events that occurred significantly more frequently in either DEX implant treatment group than in the sham group were eye pain ($P = 0.023$), ocular hypertension ($P \leq 0.002$), and anterior chamber cells ($P \leq 0.031$). The incidence of retinal neovascularization was significantly lower in the DEX implant 0.7-mg group than the sham group ($P = 0.032$). There was no statistically significant difference in the ocular adverse event incidence between the DEX implant 0.7-mg and 0.35-mg groups.

Total cataract adverse events during the study (including cortical, nuclear, and subcapsular) were reported in the study eye for 7.3% of patients (31/423) in the DEX implant 0.7-mg group, 4.1% of patients (17/411) in the DEX implant 0.35-mg group, and 4.5% of patients (19/422) in the sham group ($P = 0.079$). For 21 of these 67 patients, the cataract adverse events were bilateral. The number of cataracts that were subcapsular was 7 of 31 in the DEX implant 0.7-mg group, 4 of 17 in the DEX implant 0.35-mg group, and 3 of 19 in the sham group ($P = 0.443$). Three patients (1 in each group) had cataract extraction during the study.

Two patients had retinal detachments in the study eye: 1 in the sham group and 1 in the DEX implant 0.7-mg group; none occurred in the nonstudy eye. There was no statistically significant difference between the treatment groups in the incidence of vitreous or retinal hemorrhage. No cases of endophthalmitis were reported.

Ocular hypertension was reported as an adverse event in significantly more eyes in both DEX implant groups than in the sham group ($P \leq 0.002$; Table 4). Changes in IOP in the DEX implant groups peaked at day 60 and were no different from sham by day

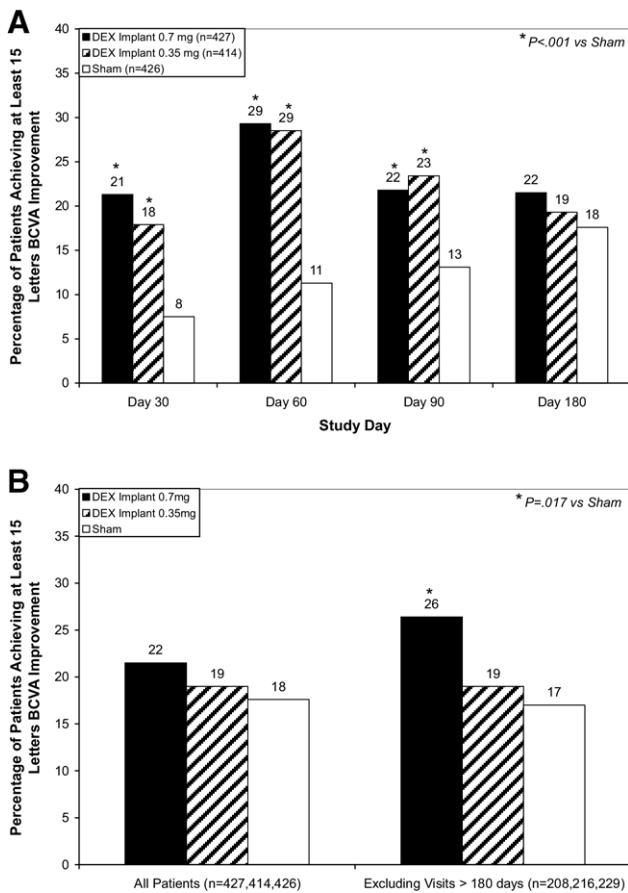


Figure 4. Percentage of eyes achieving at least 15 letters of improvement from baseline BCVA. P values are for DEX implant 0.7 or 0.35 mg versus sham. **A,** Percentage of eyes achieving at least 15 letters of improvement at each study visit. **B,** Percentage of eyes achieving at least 15 letters of improvement at day 180. Showing the data for all patients and the data after excluding patients who returned for the day 180 visit after day 180 (per protocol analysis). BCVA = best-corrected visual acuity; DEX implant = dexamethasone intravitreal implant.

180 (Fig 8). Most eyes with increases in IOP were successfully managed with topical IOP-lowering medication, but 5 eyes (3 in the DEX implant 0.7-mg group, 2 in the DEX implant 0.35-mg group) required a procedure to reduce IOP (e.g., trabeculoplasty, tube insertion, deep sclerectomy, or cyclocryotherapy). Of these, 1

eye in each of the DEX implant groups had its procedure for neovascular glaucoma rather than treatment-related increased IOP. The percentage of eyes receiving IOP-lowering medication increased in the DEX implant treatment groups from approximately 6% at the beginning of the study to approximately 24% by day 180; there was no change in the sham group.

The overall rate of nonocular adverse events was similar in the 3 treatment groups (DEX implant 0.7 mg: 830%; DEX implant 0.35 mg: 29%; sham: 31%). There were no statistically significant among-group differences at baseline or in the change from baseline in any vital signs or physical findings.

Serious Adverse Events. The overall incidence of serious adverse events was 5.0% (21/421) in the DEX implant 0.7-mg group, 6.6% (27/412) in the DEX implant 0.35-mg group, and 5.9% (25/423) in the sham group (no statistically significant between-group difference). One additional patient in the sham group developed a recurrence of melanoma in the right axilla, which met the criteria for a serious event but was reported as nonserious by the investigator.

Discussion

A single treatment with DEX implant 0.7 or 0.35 mg produced significantly greater improvements in visual acuity than did a sham procedure in eyes with vision loss due to ME associated with BRVO or CRVO. This was evident in the results for several efficacy measures, including the time to achieve a 15-letter improvement from baseline BCVA (primary outcome measure for the 2 pooled studies), the proportion of eyes achieving at least a 15-letter improvement, the proportion of eyes with BCVA worsening of at least 15 letters, and mean change from baseline BCVA. The greater improvements in visual acuity with DEX implant were accompanied by greater decreases in OCT-measured central retinal thickness than were seen with sham treatment. Although the improvements in various efficacy measures trended higher in eyes receiving DEX implant 0.7 mg compared with DEX implant 0.35 mg, the differences were not statistically significant.

A statistically significant difference between the sham group and both DEX implant groups was seen as early as the first efficacy visit at day 30 and often persisted until day 180 in the DEX implant 0.7-mg group. In the primary efficacy measure of time to at least 15-letter gain, the cumulative response rate curves for the DEX implant treat-

Table 2. Percentage of Eyes Achieving Improvements from Baseline Best-Corrected Visual Acuity of 10 to 14 Letters

DEX Implant Dose	Percentage of Eyes/P Value vs. Sham							
	Day 30		Day 60		Day 90		Day 180	
	0.7 mg	0.35 mg	0.7 mg	0.35 mg	0.7 mg	0.35 mg	0.7 mg	0.35 mg
≥10 letters increase	44%/<0.001	38%/<0.001	51%/<0.001	50%/<0.001	44%/<0.001	43%/<0.001	37%/0.037	36%/NS
≥11 letters increase	40%/<0.001	34%/<0.001	47%/<0.001	44%/<0.001	40%/<0.001	38%/<0.001	32%/NS	31%/NS
≥12 letters increase	34%/<0.001	29%/<0.001	42%/<0.001	41%/<0.001	34%/<0.001	36%/<0.001	30%/0.040	27%/NS
≥13 letters increase	29%/<0.001	26%/<0.001	38%/<0.001	37%/<0.001	30%/<0.001	31%/<0.001	27%/0.039	24%/NS
≥14 letters increase	24%/<0.001	21%/<0.001	33%/<0.001	32%/<0.001	27%/<0.001	27%/<0.001	25%/0.033	21%/NS

DEX implant = dexamethasone intravitreal implant; NS = not statistically significant (P≥0.05).

P values are listed for the comparison of DEX implant versus sham for each dosing group at each follow-up visit.

Shading indicates differences that reached statistical significance.

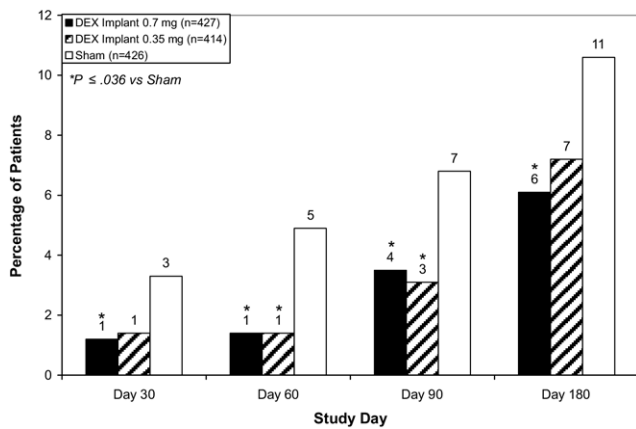


Figure 5. Percentage of eyes experiencing at least a 15-letter worsening from baseline BCVA. BCVA = best corrected visual acuity; DEX implant = dexamethasone intravitreal implant.

ment groups separated from the curve for the sham group as early as day 30 (Fig 2; $P < 0.001$). A statistically significant difference between the sham group and both DEX implant groups was also seen as early as day 30 in the proportion of eyes with at least a 15-letter improvement. The proportion of eyes with at least a 15-letter improvement peaked at day 60 and was maintained through day 90 (Fig 4A), but there was no statistically significant difference between either DEX implant group and the sham group at day 180 (Fig 4A). Of potential significance is the fact that approximately half of all patients (614/1267) had their day-180 study visit considerably later than day 180. Because the DEX implant was designed to deliver therapeutic levels of dexamethasone for only 6 months, these patients may have had subtherapeutic drug levels at the time of their last study visit. When these patients were excluded from the analysis, the difference between the DEX implant 0.7-mg group and the sham group was statistically significant at day 180 ($P = 0.017$) (Fig 4B).

Eyes treated with DEX implant were less likely to experience a 15-letter decrease in BCVA than were eyes receiving sham treatment (Fig 5); this difference remained statistically significant through day 180. This finding provides further information on the natural history of RVO by confirming that significant numbers of patients with untreated RVO (particularly those with CRVO; Fig 7C) will continue to lose visual acuity over time. It also demonstrates that treatment with DEX implant can both reduce the risk of further vision loss and increase the chance of improvements in visual acuity.

Both DEX implant 0.7 mg and 0.35 mg produced significantly greater mean improvements from baseline BCVA than did sham treatment ($P \leq 0.006$) throughout the study period.

The improvements in visual acuity outcomes persisted longer than the reduction in retinal thickness as measured by OCT. Although there were statistically significant between-group differences favoring DEX implant 0.7 mg over sham in several visual acuity measures at day 180, there was no between-group difference in change in retinal thickness at

this time point. This suggests that factors in addition to changes in central retinal thickness may be affecting visual acuity in RVO eyes with ME treated with DEX implant.

A possible criticism of this study is that it included patients with BRVO and patients with CRVO. This study was aimed at evaluating the response to treatment with DEX implant in eyes with ME due to BRVO or CRVO. Although BRVO and CRVO are arguably different disease entities (e.g., differing in natural history and the sites of occlusion), they share numerous characteristics, including risk factors, and there is no compelling evidence that the ME resulting from the occlusive events in either BRVO or CRVO differs substantively in terms of pathophysiology. Nonetheless, although patients with BRVO and patients with CRVO were included in this study, a prospectively defined subgroup analysis based on baseline diagnoses (BRVO/CRVO) was included in the protocol to address concerns that one group might have a differential response that caused the benefits of the drug therapy on the other group to be either under- or overestimated. The results of this analysis confirm previous observations that CRVO is a more visually disabling disorder than BRVO. Eyes with CRVO did not respond as well to therapy as eyes with BRVO, and they were less likely to improve without therapy. The percentage of eyes in the DEX implant groups achieving at least a 15-letter improvement from baseline BCVA was sustained at a slightly higher rate for longer among eyes with BRVO than eyes with CRVO. In addition, in the sham groups mean BCVA gradually improved with time in the BRVO eyes, whereas mean BCVA steadily declined with time in the CRVO eyes (Fig 7C).

A potentially important finding of a post hoc analysis in this study was that shorter ME duration at baseline was associated with greater improvements in BCVA after DEX implant. A similar effect of ME duration was seen in the Standard Care vs. Corticosteroid for RVO Study (SCORE Study).^{11,13}

The adverse events that occurred at a significantly higher rate in the DEX implant treatment group than in the sham group were eye pain, ocular hypertension, and anterior

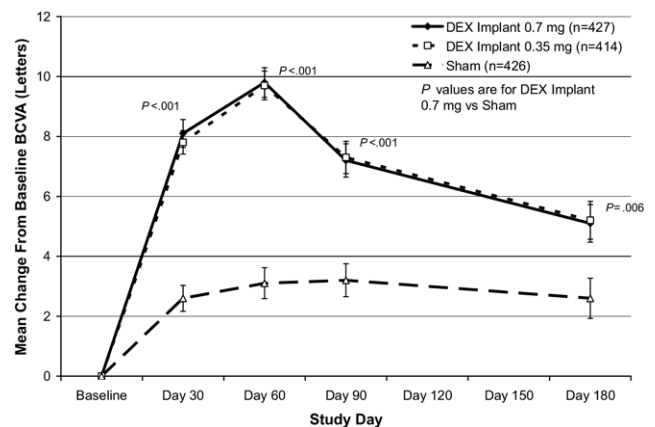


Figure 6. Mean change from baseline BCVA. P values are for DEX implant 0.7 mg versus sham. BCVA = best-corrected visual acuity; DEX implant = dexamethasone intravitreal implant.

Table 3. Mean Change in Central Retinal Thickness

	DEX Implant 0.7 mg (n = 427)	DEX Implant 0.35 mg (n = 414)	Sham (n = 426)	P Value vs. Sham 0.35 mg/0.7 mg
Day 90				
All eyes ($\mu\text{m}\pm\text{SD}$)	-208 \pm 201	-177 \pm 197	-85 \pm 173	<0.001/<0.001
Day 180				
All eyes ($\mu\text{m}\pm\text{SD}$)	-119 \pm 203	-123 \pm 212	-119 \pm 188	NS/NS

DEX implant = dexamethasone intravitreal implant; NS = not statistically significant ($P\geq 0.05$); SD = standard deviation.

chamber cells (Table 4); these are all adverse events that have been associated with intravitreal injection or corticosteroid therapy.^{14,20,25,26,31,32} There was no statistically significant difference between the treatment groups in the incidence of vitreous or retinal hemorrhage, and no cases of endophthalmitis were reported.

Results from a previous phase 2 trial of DEX implant in patients with persistent ME found a lower rate of both cataract and IOP increases than has been reported with other corticosteroids (including triamcinolone acetonide).^{14,15,20} There was no statistically significant difference in the rate of cataract among the treatment groups in the present study, but 180 days may not be a long enough study period to detect an effect of treatment on cataract formation. The majority of eyes treated with DEX implant did not experience a substantial increase in IOP. At peak (day 60), less than 16% of all eyes had an increase in IOP to ≥ 25 mmHg. Increases in IOP were typically transient, and there was no difference between the DEX implant groups and the sham group by day 180 (Fig 8). Nearly all cases of elevated IOP were managed with observation or topical medications alone. Notably, the incidence of retinal neovascularization was significantly lower in the DEX implant 0.7-mg group

than in the sham group ($P = 0.032$). This finding, combined with the lower rate of visual loss in the active treatment groups, raises the possibility that DEX implant may have an impact on ischemia and disease progression, as well as increasing the chance of improvements in visual acuity.

Randomized, controlled clinical trials have also demonstrated the efficacy of laser photocoagulation,¹¹ the corticosteroid triamcinolone acetonide,^{11,13} and the anti-VEGF therapy ranibizumab¹² in the treatment of ME secondary to RVO. In the SCORE study, grid photocoagulation and repeated injections of triamcinolone acetonide 1 or 4 mg seemed to be equally effective in producing improvements in BCVA in patients with ME due to BRVO: a 15-letter gain in BCVA from baseline to month 12 in 29% of patients treated with grid photocoagulation and 26% and 27% of patients treated with triamcinolone acetonide 1 or 4 mg, respectively.¹³ Rates of elevated IOP and cataract were similar for the grid laser and 1-mg triamcinolone groups, but higher in the 4-mg triamcinolone group; 41% of patients treated with triamcinolone acetonide 4 mg initiated IOP-lowering medication during the 12-month study.¹³ In a separate report of the SCORE study regarding eyes with ME due to CRVO, triamcinolone acetonide 1 mg and 4 mg were

Table 4. Ocular Adverse Events in the Study Eye Reported for >2% of Patients in any Treatment Group or for Which There Was a Statistically Significant Difference between a DEX Implant Group and Sham

	DEX Implant 0.7 mg (n = 421)	DEX Implant 0.35 mg (n = 412)	Sham (n = 423)	P Value vs. Sham 0.35 mg/0.7 mg
Conjunctival hemorrhage	85 (20.2%)	72 (17.5%)	63 (14.9%)	NS/NS
Eye pain	31 (7.4%)	17 (4.1%)	16 (3.8%)	0.023/NS
Conjunctival hyperemia	28 (6.7%)	27 (6.6%)	20 (4.7%)	NS/NS
Maculopathy	19 (4.5%)	22 (5.3%)	23 (5.4%)	NS/NS
Ocular hypertension	17 (4.0%)	16 (3.9%)	3 (0.7%)	0.001/0.002
Cataract*	31 (7.3%)	17 (4.1%)	19 (4.5%)	NS/NS
Vitreous floaters	13 (3.1%)	5 (1.2%)	6 (1.4%)	NS/NS
Vitreous detachment	12 (2.9%)	12 (2.9%)	8 (1.9%)	NS/NS
Retinal hemorrhage	12 (2.9%)	8 (1.9%)	10 (2.4%)	NS/NS
Foreign-body sensation	11 (2.6%)	7 (1.7%)	11 (2.6%)	NS/NS
Vitreous hemorrhage	10 (2.4%)	13 (3.2%)	12 (2.8%)	NS/NS
Retinal exudates	10 (2.4%)	4 (1.0%)	14 (3.3%)	NS/NS
Conjunctival edema	9 (2.1%)	16 (3.9%)	7 (1.7%)	NS/NS
Visual acuity reduced	7 (1.7%)	7 (1.7%)	9 (2.1%)	NS/NS
Retinal neovascularization	3 (0.7%)	4 (1.0%)	11 (2.6%)	NS/0.032
Anterior chamber cells	5 (1.2%)	7 (1.7%)	0 (0.0%)	0.031/0.007

DEX implant = dexamethasone intravitreal implant; NS = not statistically significant ($P\geq 0.05$).

*Includes adverse events listed as cataract, cataract cortical, cataract nuclear, or cataract subcapsular.

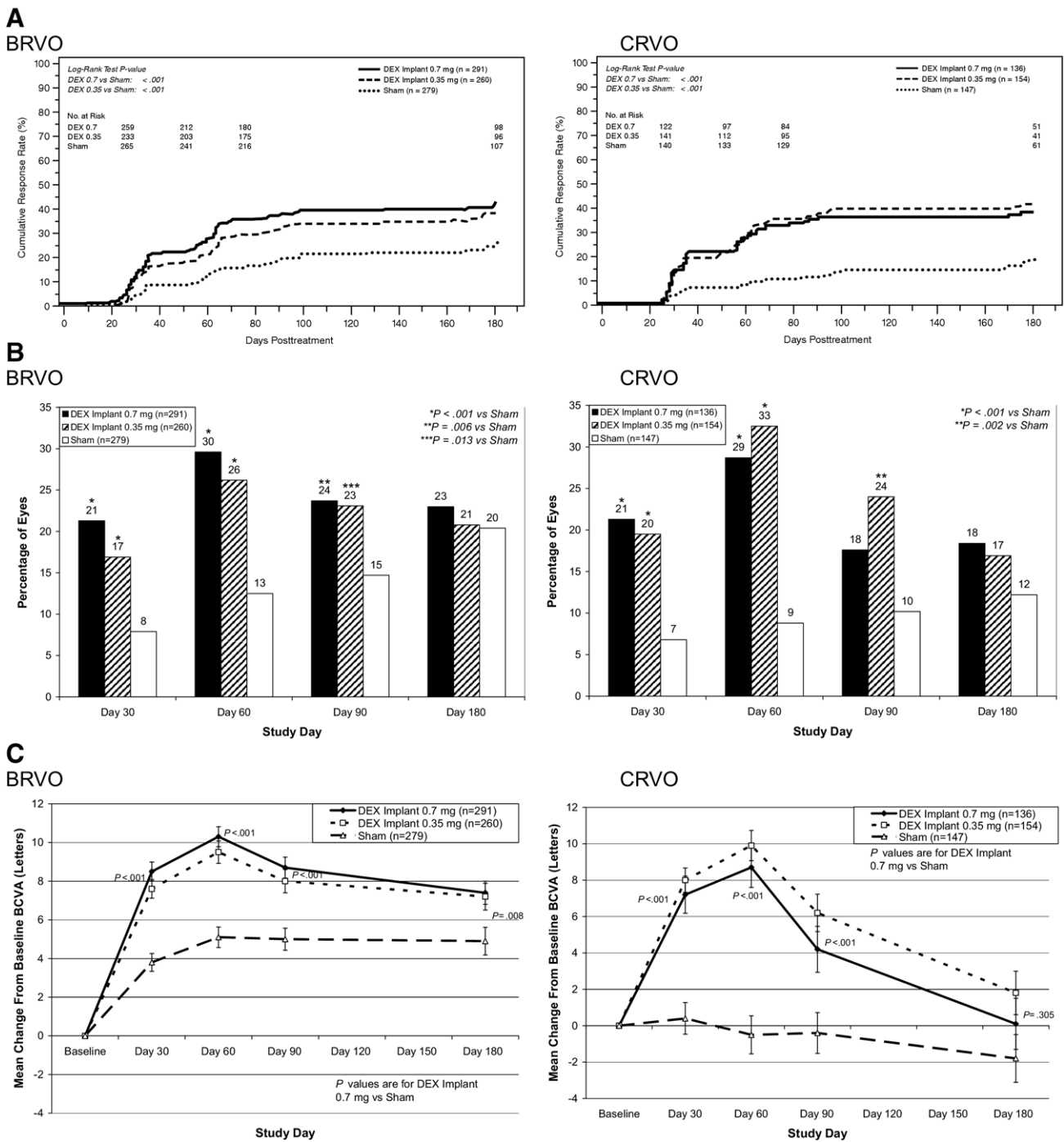


Figure 7. Efficacy comparison for BRVO and CRVO subgroups. **A**, Time to achieve 15 letters of improvement from baseline. **B**, Percentage of eyes achieving 15 letters of improvement from baseline BCVA. **C**, Mean change from baseline BCVA. BCVA = best-corrected visual acuity. BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DEX implant: dexamethasone intravitreal implant.

shown to produce a 15-letter gain in BCVA from baseline to month 12 in 27% and 26%, respectively. The rates of cataract and elevated IOP were similar for the observation and 1-mg groups, but higher in the 4-mg group; 35% of patients with CRVO treated with triamcinolone acetonide 4 mg initiated IOP-lowering medication during the 12-month study.¹¹ In 2 recently completed, but as yet unpublished, 6-month clinical

trials of ranibizumab (BRAVO and CRUISE studies; presented at Retina Congress 2009),¹² ranibizumab 0.5 mg injected monthly produced a 15-letter gain in BCVA from baseline to 6 months in 61% of patients with BRVO and 48% of patients with CRVO. In the absence of well-controlled clinical trials that directly compare these therapeutic approaches with dexamethasone, it is difficult to make mean-

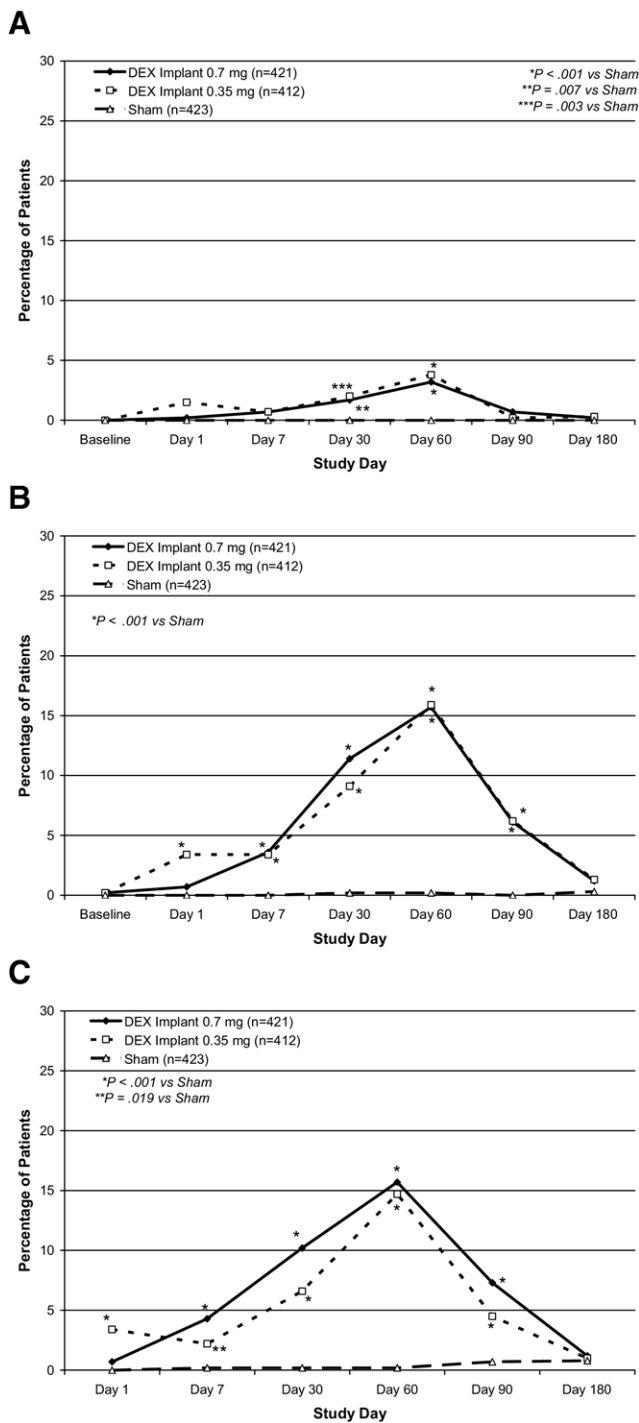


Figure 8. Percentage of eyes with notable changes in IOP. **A**, Percentage of eyes with IOP of at least 35 mmHg. **B**, Percentage of eyes with IOP of at least 25 mmHg. **C**, Percentage of eyes with an increase in IOP of at least 10 mmHg. DEX implant = dexamethasone intravitreal implant; IOP = intraocular pressure.

ingful statements about the relative merits of these different treatments. This difficulty is compounded by the differences between the patient populations and the study designs of the DEX implant, triamcinolone, and ranibizumab clinical tri-

als. For example, in the BRAVO, CRUISE, and SCORE studies, eyes had ME of short duration relative to the DEX implant studies. In the SCORE study, 37% to 44% of patients had a duration of ME of less than 3 months,^{11,13} compared with 14% to 17% of patients in the present study. Post hoc analyses of both the present study and the SCORE study data suggest that patients with shorter duration of ME may have a greater response to treatment.^{11,13} The studies also had different inclusion criteria and visit schedules, among other protocol differences that may have affected some study outcomes.

As has been seen with other medical therapies for RVO, the response to treatment with DEX implant is of limited duration, lasting between 90 and 180 days depending on the patient population and outcome measure. Further study is needed to determine the response to repeated treatments and the optimum retreatment interval. A long-term study of repeated treatment has recently been completed and is being prepared for publication.

A potential limitation of the present study was the use of sham treatment rather than laser treatment as the control group. Sham treatment was chosen on the basis of the phase 2 trial data and because this study included patients with BRVO and CRVO in a single trial, and there is evidence suggesting that laser photocoagulation can improve vision in eyes with ME associated with BRVO, but not CRVO.³³⁻³⁶ Moreover, 33% to 50% of eyes with BRVO may regain vision of $\geq 20/40$ within 6 months, and 70% may gain ≥ 2 lines of vision in 12 months without any treatment at all.³⁷ Approximately 10% of cases of nonischemic CRVO may also resolve completely without treatment (although most eyes continue to lose vision, and the natural history of the disease is generally unfavorable).⁵ Consequently, it can be difficult to differentiate the benefits of any intervention from the natural course of the disease without an untreated control group.

Another potential limitation of the study was that patients with CRVO were not screened for perfused or ischemic disease. The relatively good vision ($>20/200$) of the patient population at baseline suggests that most patients had perfused disease, but the development of neovascularization in 2.6% of sham patients suggests that at least some patients had ischemic disease. The presence of some patients with ischemic disease might have caused the benefits of treatment on the larger population of patients with perfused disease to be slightly underestimated. Moreover, despite the apparent inclusion of some patients with ischemic CRVO, no conclusions should be drawn from the present study regarding the effectiveness of DEX implant in ischemic patients.

In conclusion, the results of the present study demonstrate that DEX implant can both reduce the risk of further vision loss and increase the chance of improvement in visual acuity in eyes with BRVO or CRVO. The results of this study further demonstrate that, when eyes with RVO are left untreated, a significant percentage will either fail to improve or experience further loss of visual acuity. The DEX implant was well tolerated, producing generally transient, moderate, and readily managed increases in IOP in less than 16% of eyes. Overall, this study suggests that DEX implant could be a valuable new

treatment option for eyes with visual loss due to ME associated with BRVO or CRVO.

Acknowledgments. The writing assistance and manuscript preparation services of Amy Lindsay, PhD (Lindsay Biomedical Communications, Inc.), were retained by Allergan, Inc., for the writing committee. Dr. Lindsay, who did not meet authorship criteria, attended all meetings and conference calls of the writing committee; collated committee drafts, comments, and references; compiled an outline for discussion and review; drafted a first manuscript iteration on the basis of committee discussion and reworking of the detailed outline; and subsequently compiled the editorial comments of the group and executed several rounds of revisions under writing committee guidance.

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Footnotes and Financial Disclosures

Originally received: November 18, 2009.

Final revision: March 10, 2010.

Accepted: March 11, 2010.

Available online: April 22, 2010. Manuscript no. 2009-1609.

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*GENEVA: Global Evaluation of implantable dExamethasone in retinal Vein occlusion with macular edema. A list of the members of the GENEVA study group is available at <http://aojournal.org>.

A preliminary report of this study was presented at: Retina Congress 2009, September 30 to October 4, 2009, New York.

This article contains online-only material. The following should appear online only: Figure 3 and The GENEVA Study Group.

Financial Disclosure(s):

The author(s) have made the following disclosure(s): Dr. Haller is a consultant with Genentech and Allergan and an equity owner with Macusight and OptiMedica. Dr. Bandello is a consultant and lecturer with Allergan and Novartis. Dr. Belfort is a consultant and lecturer with Allergan and Alcon. Dr. Blumenkranz is a consultant with Allergan, Macusight, and Genentech, an equity owner with Macusight and Optimedica, a lecturer with Allergan, and a patent holder with Optimedica. Dr. Gillies is a consultant with Allergan, Novartis, and Pfizer. Dr. Heier is a consultant for and received financial support from Alimera, Allergan, Genentech, and Regeneron, and is a lecturer for Regeneron. Dr. Lowenstein is a consultant for Allergan and Notal Vision and a lecturer for Novartis and Alcon. Dr. Yoon is a consultant for Allergan and a lecturer for Alcon. Drs. Jacques, Jiao, Li, and Whitcup are employees of Allergan, Inc.

Sponsored by Allergan, Inc., which participated in the design of the study, data analysis, and interpretation, and supervised the preparation of the manuscript and approved the final version.

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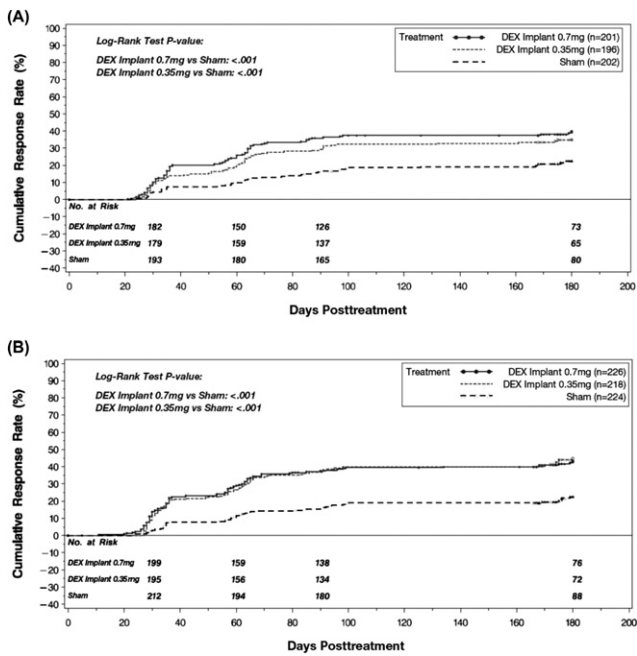


Figure 3. Time to achieve 15 letters of improvement from baseline BCVA for the 2 phase III studies separately. **A**, First study. **B**, Second study. BCVA = best corrected visual acuity; DEX implant = dexamethasone intravitreal implant.