

Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema

David S. Boyer, MD,¹ Young Hee Yoon, MD, PhD,² Rubens Belfort, Jr, MD, PhD,³ Francesco Bandello, MD,⁴ Raj K. Maturi, MD,⁵ Albert J. Augustin, MD,⁶ Xiao-Yan Li, MD,⁷ Harry Cui, MS,⁷ Yehia Hashad, MD,⁷ Scott M. Whitcup, MD,⁷ for the Ozurdex MEAD Study Group*

Purpose: To evaluate the safety and efficacy of dexamethasone intravitreal implant (Ozurdex, DEX implant) 0.7 and 0.35 mg in the treatment of patients with diabetic macular edema (DME).

Design: Two randomized, multicenter, masked, sham-controlled, phase III clinical trials with identical protocols were conducted. Data were pooled for analysis.

Participants: Patients (n = 1048) with DME, best-corrected visual acuity (BCVA) of 20/50 to 20/200 Snellen equivalent, and central retinal thickness (CRT) of ≥ 300 μm by optical coherence tomography.

Methods: Patients were randomized in a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or sham procedure and followed for 3 years (or 39 months for patients treated at month 36) at ≤ 40 scheduled visits. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months.

Main Outcome Measures: The predefined primary efficacy endpoint for the United States Food and Drug Administration was achievement of ≥ 15 -letter improvement in BCVA from baseline at study end. Safety measures included adverse events and intraocular pressure (IOP).

Results: Mean number of treatments received over 3 years was 4.1, 4.4, and 3.3 with DEX implant 0.7 mg, DEX implant 0.35 mg, and sham, respectively. The percentage of patients with ≥ 15 -letter improvement in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%; $P \leq 0.018$). Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg (-111.6 μm) and DEX implant 0.35 mg (-107.9 μm) than sham (-41.9 μm ; $P < 0.001$). Rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively. Increases in IOP were usually controlled with medication or no therapy; only 2 patients (0.6%) in the DEX implant 0.7 mg group and 1 (0.3%) in the DEX implant 0.35 mg group required trabeculectomy.

Conclusions: The DEX implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA. The safety profile was acceptable and consistent with previous reports. *Ophthalmology* 2014;121:1904-1914 © 2014 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).



Supplemental material is available at www.aaojournal.org.

Diabetic retinopathy (DR) is a leading cause of vision loss and blindness in adults ≥ 40 years of age in the United States.¹ The vision loss associated with DR most commonly results from diabetic macular edema (DME), which is estimated to affect 20% of patients with DR.² Diabetic macular edema is characterized by capillary leakage, fluid accumulation, and macular thickening following breakdown of the blood–retinal barrier.³ Inflammation has an important role in the pathogenesis of DME, because the breakdown of the blood–retinal barrier involves expression of inflammatory factors⁴ including vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1, interleukin-6, and monocyte chemoattractant protein-1, as well as leukostasis⁵ and alterations in endothelial tight junction proteins.⁶

For >25 years, standard care for DME has included medical control of diabetes (glycemic and blood pressure control, and lipid management) and focal/grid laser photocoagulation of leaking microaneurysms and areas of diffuse capillary bed leakage.⁷ Laser photocoagulation can reduce the risk of moderate vision loss in DME, but most patients do not regain visual acuity that has been lost.^{8–10} In 2012, the VEGF inhibitor ranibizumab became the first approved medical treatment for DME. In phase III clinical studies (RISE and RIDE),^{11,12} monthly injections of ranibizumab led to a 2- to 3-fold increase in the percentage of patients who met visual improvement endpoints compared with sham treatment. However, the need for frequent injections is a treatment burden for patients; not all patients would be able to present to the clinic on a monthly basis for 3 years. Furthermore, some patients are

partial or nonresponders to anti-VEGF treatment.^{11,13} In the RISE and RIDE studies, after 2 years of monthly ranibizumab injections, pronounced macular edema (evidenced by center-point thickness of >250 μm on optical coherence tomography [OCT]) persisted in approximately 23% of patients, and 40% of patients had not achieved a best-corrected visual acuity (BCVA) of $\geq 20/40$.¹¹ Therefore, there remains a need for additional treatment options for patients with DME.

Intravitreal corticosteroids may be useful in the treatment of DME because they block production of VEGF and other inflammatory mediators,¹⁴ inhibit leukostasis,¹⁵ and enhance the barrier function of vascular endothelial cell tight junctions.¹⁶ Off-label treatment with intravitreal triamcinolone acetonide (TA) has been shown to be more effective than placebo in improving vision in patients with refractory DME.¹⁷ The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study evaluating intravitreal TA or ranibizumab in combination with laser treatment reported similar efficacy of TA and ranibizumab in pseudophakic eyes, in which there is no confounding of cataract development associated with corticosteroid treatment.¹⁸

Sustained-release corticosteroids have been developed to reduce the need for frequent intraocular injections. Dexamethasone intravitreal implant (DEX implant; Ozurdex; Allergan, Inc, Irvine, CA) is a sustained-release biodegradable implant approved for treatment of macular edema related to retinal vein occlusion, as well as noninfectious posterior segment uveitis. The DEX implant releases the potent corticosteroid dexamethasone into the vitreous over a period of ≤ 6 months.¹⁹ Dexamethasone differs from TA in pharmacologic activity and lipid solubility, as well as delivery requirements.²⁰ In previous studies, the DEX implant has demonstrated efficacy in the treatment of persistent DME,^{21,22} DME resistant to anti-VEGF treatment,²³ and DME in difficult-to-treat vitrectomized eyes.²⁴

Two large, multicenter clinical trials evaluating the safety and efficacy of DEX implant 0.7 and 0.35 mg in patients with DME were designed and conducted to support regulatory approval of DEX implant for treatment of DME. We report here the 3-year results of those trials.

Methods

Study Design

Two randomized, multicenter, masked, sham-controlled, 3-year, phase III clinical trials (registered with the identifiers NCT00168337 and NCT00168389 at ClinicalTrials.gov) evaluated the efficacy and safety of the DEX implant for treatment of DME. The trials were conducted from February 2005 to June 2012 at 131 sites in 22 countries. Because the trials were identical in study design, the results were pooled for analysis. The study adhered to the tenets of the Declaration of Helsinki and was compliant with the Health Insurance Portability and Accountability Act of 1996. The study protocol was approved by an institutional review board or independent ethics committee at each site, and all patients provided written informed consent.

Study Population

Patients ≥ 18 years of age diagnosed with type 1 or 2 diabetes mellitus who had fovea-involved macular edema that was

associated with DR and had been previously treated with medical or laser therapy were enrolled in the study. Treatment-naïve patients who had refused laser treatment or who, in the opinion of the investigator, would not benefit from laser treatment were also enrolled. BCVA in the study eye, measured with the Early Treatment Diabetic Retinopathy Study method, was required to be between 34 and 68 letters (20/200–20/50), and central retinal thickness (CRT) in the 1-mm central macular subfield of the study eye was required to be ≥ 300 μm by time domain OCT using the OCT2 or OCT3 (Stratus OCT, Carl Zeiss Meditec Inc, Dublin, CA) system.

Key exclusion criteria included uncontrolled diabetes (glycosylated hemoglobin [HbA1c] >10%) or other systemic disease, treatment with intravitreal anti-VEGF within 3 months of study entry, treatment with intravitreal triamcinolone within 6 months of study entry, current use or anticipated use of systemic steroids during the study, glaucoma or optic nerve head or visual field damage consistent with glaucoma, history of marked steroid-induced intraocular pressure (IOP) increase, and ocular hypertension in the study eye characterized by IOP >23 mmHg without antiglaucoma medication, IOP >21 mmHg treated with 1 antiglaucoma medication, or use of ≥ 2 antiglaucoma medications. Patients with aphakia or an anterior chamber intraocular lens in the study eye, a history of intraocular laser or incisional surgery in the study eye within 90 days before study entry, a history of pars plana vitrectomy in the study eye, or active iris or retinal neovascularization in the study eye were excluded.

If both eyes were eligible for the study, the eye with the shorter duration of macular edema was selected as the study eye at the screening visit, and only the study eye received study treatment.

Randomization, Intervention, and Masking

At the baseline day 0 visit (4–14 days after screening), patients were randomized in a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or a sham procedure. Each site used an interactive voice-response or web-response system to assign randomization numbers to patients. Treatment assignment was based on enrollment order and a computer-generated randomization scheme provided by the sponsor. Study treatment was administered after all baseline evaluations. An applicator system was used to insert DEX implant into the vitreous of the study eye through the pars plana as described previously.²⁵ In the sham procedure, a needleless applicator was pressed against the conjunctiva of the study eye.²⁵

Each site had a treating investigator who administered the study treatment and performed postinjection safety evaluations up to day 21 after each treatment. The study personnel who collected efficacy data, and a follow-up investigator who performed safety evaluations at other study visits, were masked to the treatment assignment, and patients were also masked.

Visit Schedule

Patients were seen at ≤ 40 scheduled visits (Fig 1). Study visits were scheduled every 1.5 months during the first year and every 3 months during years 2 and 3. In addition, patients were seen at safety visits 1, 7, and 21 days after study treatment or retreatment. After a study protocol amendment in May 2010, patients who had not yet completed the study and who met retreatment eligibility criteria were retreated at month 36 and followed at an additional study visit at month 39. Over 50% of patients had completed or discontinued the study before the protocol amendment.

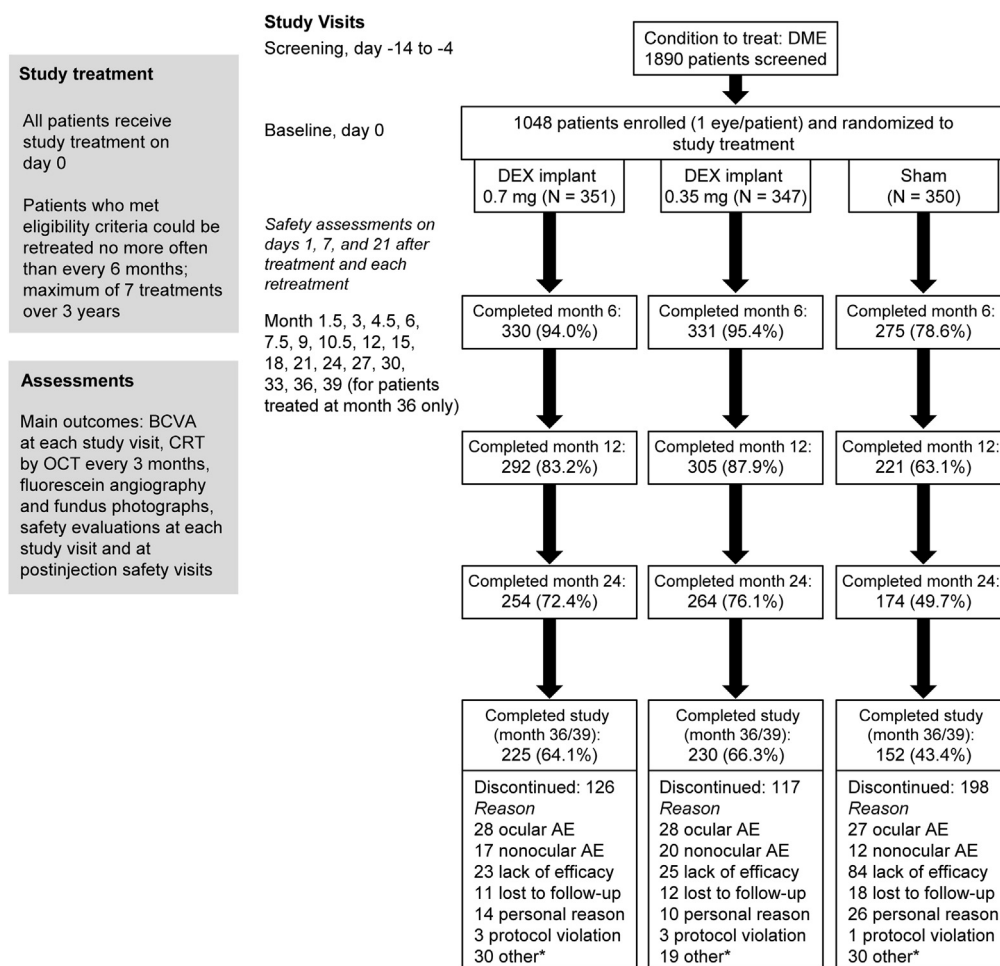


Figure 1. Study design and patient flow through the study. *Other reasons for discontinuation included site closure, patient withdrawal of consent, poor compliance from patient, sponsor request, patient relocation, and patient participation in another trial. AE = adverse event; BCVA = best-corrected visual acuity; CRT = central retinal thickness; DEX implant = dexamethasone intravitreal implant; DME = diabetic macular edema; OCT = optical coherence tomography.

Nonstudy Treatments and Procedures

Panretinal photocoagulation for proliferative DR and cataract surgery were allowed at the discretion of the investigator and patient. All other procedures in the study eye, and all treatments for macular edema in the study eye with the exception of study treatment, were prohibited. Systemic treatment with steroids and immunosuppressants also was prohibited.

Exit Criteria

A patient could be withdrawn from the study at the patient's or investigator's discretion at any time for any reason. Patients who received escape therapy (any treatment for macular edema other than the study treatment) in the study eye were required to be withdrawn from the study before its administration. Patients who had a loss of ≥ 15 letters in BCVA from baseline in the study eye, which was confirmed at 2 consecutive visits ≥ 4 weeks apart and was attributed to macular edema, were exited from the study at the investigator's discretion.

Retreatment Criteria

Patients were eligible for retreatment with DEX implant only if there had been ≥ 6 months since the most recent study treatment

and there was evidence of residual edema. For most of the study (95% of treatments), retreatment eligibility required CRT (retinal thickness in the 1 mm central macular subfield) of $>225 \mu\text{m}$ by OCT (as determined by the site), as well as judgment by the investigator that the treatment would not put the patient at significant risk. A study protocol amendment in May 2010 revised the anatomic criterion such that patients with CRT of $>175 \mu\text{m}$ by OCT or evidence of residual edema on OCT, seen as intraretinal cysts or regions of retinal thickening within or outside the central subfield, were eligible for retreatment.

Outcome Measures

Efficacy evaluations included BCVA by the Early Treatment Diabetic Retinopathy Study method at every study visit, Stratus OCT2 or OCT3 every 3 months, fundus photography, and fluorescein angiography. The OCT, fundus photography, and fluorescein angiography images were evaluated at a central reading center (University of Wisconsin Fundus Photograph Reading Center, Madison, WI).

The predefined primary efficacy endpoint for the United States Food and Drug Administration was the percentage of patients with BCVA improvement of ≥ 15 letters from baseline in the study eye at the end of the study, with missing values imputed using last

Table 1. Baseline Characteristics of Patients and Study Eyes

Characteristic	DEX Implant 0.7 mg (n = 351)	DEX Implant 0.35 mg (n = 347)	Sham (n = 350)
Mean age (SD), y	62.5 (8.3)	62.3 (9.2)	62.5 (9.5)
Range (y)	33–85	25–84	26–88
Male, n (%)	213 (60.7)	206 (59.4)	217 (62.0)
Mean duration of diabetes (SD), y	16.5 (9.0)	15.8 (9.4)	15.9 (9.1)
Mean HbA1c (SD), %	7.6 (1.2)	7.5 (1.1)	7.5 (1.1)
≤8%, n (%)	233 (66.4)	237 (68.3)	249 (71.1)
>8%, n (%)	114 (32.5)	108 (31.1)	100 (28.6)
Not available	4 (1.1)	2 (0.6)	1 (0.3)
Mean ETDRS letter score (SD)	56.1 (9.9)	55.5 (9.7)	56.9 (8.7)
Mean CRT (SD), μm	463.0 (157.1)	466.8 (159.5)	460.9 (132.6)
Mean duration of DME (SD), mo	23.6 (26.0)	25.2 (31.4)	25.9 (27.3)
Range (mo)	0–163	0–299	0–187
Previous treatment for DME, n (%)			
Focal/grid laser	231 (65.8)	224 (64.6)	243 (69.4)
Intravitreal steroid	58 (16.5)	69 (19.9)	61 (17.4)
Anti-VEGF	25 (7.1)	39 (11.2)	26 (7.4)
None	104 (29.6)	98 (28.2)	89 (25.4)
Severity of NPDR, n (%)			
Moderate or better	173 (49.3)	170 (49.0)	174 (49.7)
Severe or worse	151 (43.0)	151 (43.5)	149 (42.6)
Not available	27 (7.7)	26 (7.5)	27 (7.7)
DME perfusion status, n (%)			
Ischemic	43 (12.3)	31 (8.9)	27 (7.7)
Nonischemic	257 (73.2)	260 (74.9)	284 (81.1)
Not available	51 (14.5)	56 (16.1)	39 (11.1)
Lens status, n (%)			
Phakic	265 (75.5)	259 (74.6)	249 (71.1)
Pseudophakic	86 (24.5)	88 (25.4)	101 (28.9)
Mean IOP (SD), mmHg	15.3 (2.6)	15.6 (2.8)	15.3 (3.1)
Using IOP-lowering medication, n (%)	12 (3.5)	26 (7.6)	14 (4.0)

CRT = central retinal thickness; DEX implant = dexamethasone intravitreal implant; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated hemoglobin; IOP = intraocular pressure; NPDR = nonproliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor.

observation carried forward. Secondary efficacy outcomes for the study eye included average change in BCVA from baseline during the study determined with the area under the curve (AUC) method, mean change in BCVA from baseline at each study visit, time to ≥15-letter improvement in BCVA from baseline, percentage of patients with BCVA of ≥20/40 at each study visit, and average change in CRT from baseline during the study by OCT (AUC approach).

Safety parameters included adverse events (AEs), IOP, bi-microscopic and ophthalmoscopic findings, and measures of diabetes control (HbA1c and glomerular filtration rate).

Data Analysis and Statistical Methods

Efficacy outcomes were evaluated in the intent-to-treat population of all randomized patients. The last-observation-carried-forward method was used for imputation of missing values, except in the analyses of average change in BCVA and CRT from baseline during the study (AUC approach) and time-to-event data, which used observed data. Analysis of the proportion of patients with BCVA improvement of ≥15 letters from baseline and the proportion of patients with BCVA of ≥20/40 used the Cochran-Mantel-Haenszel general association test stratified by study. Analysis of the average change in BCVA or CRT from baseline during the study (AUC approach) used an analysis of covariance model with treatment and study as fixed effects and baseline BCVA or CRT as the covariate. Time-to-event data were analyzed

with the Kaplan-Meier method and log-rank tests. Predetermined subgroup analysis of selected outcome measures was performed in subgroups of patients defined by demographics, duration of diabetes, duration of DME, baseline HbA1c, prior laser treatment, treatment-naïve status, lens status at baseline, and nonproliferative DR severity at baseline. Safety outcomes were evaluated in the safety population of all patients who were treated during the study.

Statistical analysis was performed with SAS version 9.3 (SAS Inc, Cary, NC) and a 2-sided alpha level of 0.05. The planned sample size of 510 patients in each trial (170 in each treatment arm) was estimated to provide 80% power to detect a difference of 10% between the DEX implant 0.7 mg group and the sham group in the proportion of patients with ≥15-letter improvement in BCVA from baseline, assuming a 5% rate for sham and a 2-sided alpha level of 0.025.

Results

A total of 1048 patients were enrolled from February 2005 to June 2009 and randomized to study treatment. There were no differences in baseline demographic or study eye characteristics among the treatment groups (Table 1). The mean BCVA in study eyes was 56.2 letters (approximately 20/80 Snellen). The mean duration of DME before study entry was 24.9 months (median, 16). Overall, 66.6% of patients had received previous laser treatment for

Table 2. Number of Study Treatments Received (Safety Population)

Number of Study Treatments	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n = 350)
1, n (%)	44 (12.7)	34 (9.9)	106 (30.3)
2, n (%)	54 (15.6)	45 (13.1)	63 (18.0)
3, n (%)	39 (11.2)	41 (12.0)	41 (11.7)
4, n (%)	42 (12.1)	40 (11.7)	26 (7.4)
5, n (%)	49 (14.1)	41 (12.0)	29 (8.3)
6, n (%)	88 (25.4)	105 (30.6)	50 (14.3)
7, n (%)	31 (8.9)	37 (10.8)	35 (10.0)
Mean (SD)	4.1 (2.0)	4.4 (1.9)	3.3 (2.2)
Median	4	5	3

DEX implant = dexamethasone intravitreal implant; SD = standard deviation.

DME, 17.9% had been treated with intravitreal steroid, 8.6% had been treated with intravitreal anti-VEGF, and 27.8% had received no previous treatment for DME.

The 3-year study was completed by 607 (57.9%) patients (Fig 1). Study completion rates were higher in the DEX implant 0.7 mg (64.1%) and 0.35 mg (66.3%) groups than in the sham group (43.4%) because of a >3-fold higher rate of discontinuations owing to lack of efficacy in the sham group. The rate of discontinuations owing to AEs was <14% and similar among groups. The median number of study treatments received by patients was 4 in the DEX implant 0.7 mg group, 5 in the DEX implant 0.35 mg group, and 3 in the sham group (Table 2). Among patients who completed the study, the mean number of study treatments received was 5.0, 5.2, and 5.1 in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively.

Efficacy Analyses

The DEX implant 0.7 mg and 0.35 mg demonstrated statistical superiority to sham in the primary efficacy endpoint (Fig 2). The percentage of patients with a ≥ 15 -letter improvement in BCVA from baseline at the year 3 or final study visit was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than with sham (12.0%; $P \leq 0.018$). The interaction of treatment effect and study was not significant ($P = 0.853$) in the pooled data analysis, suggesting a consistent effect of treatment across the individual clinical trials.

A rapid onset of treatment effect compared with sham was observed in both DEX implant treatment groups. Survival analysis showed significantly earlier gain of ≥ 15 letters in BCVA with both DEX implant 0.7 mg ($P < 0.001$) and 0.35 mg ($P = 0.005$) compared with sham (Fig 3, available at www.aaojournal.org). Significant differences in the proportion of patients with a ≥ 15 -letter improvement from baseline were observed between each DEX implant group and sham as early as day 21 ($P \leq 0.003$).

The percentage of patients with a ≥ 15 -letter improvement in BCVA from baseline, as well as the percentage of patients with $\geq 20/40$ BCVA, was significantly greater in both DEX implant treatment groups compared with the sham group at the majority of visits (Fig 4, available at www.aaojournal.org). The mean (standard deviation) average change in BCVA from baseline during the study was 3.5 (8.4) letters with DEX implant 0.7 mg, 3.6 (8.1) letters with DEX implant 0.35 mg, and 2.0 (8.0) letters with sham. The between-group difference in average change in BCVA from baseline during the study was significant for the

comparison of both DEX implant 0.7 mg ($P = 0.023$) and DEX implant 0.35 mg ($P = 0.019$) with sham.

Analysis of mean change in BCVA from baseline at each study visit showed greater BCVA improvement in both DEX implant groups compared with sham at most timepoints during the first 15 months. However, the improvement in BCVA provided by DEX implant relative to sham was reduced after month 15, with a trend for it to increase and the benefit of DEX implant treatment to resume in year 3 (Fig 5A). During the second year of the study, an increase in cataract AE reports correlated with the reduced effect of treatment.

Because these results suggested that the treatment effect on vision improvement might be confounded after the first year by cataract formation or progression, additional analyses were performed to take into account the effects of cataract AEs and cataract surgery on visual acuity. In subgroup analysis, mean improvement in BCVA provided by DEX implant relative to sham in pseudophakic eyes was consistent across time in the 3-year study, and there was no reduction in treatment benefit observed in year 2 (Fig 5B). A gain of ≥ 15 letters in BCVA from baseline was seen at the end of the study in 23.3%, 15.9%, and 10.9% of pseudophakic eyes in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively (Table 3). In phakic eyes with an AE report of cataract, the mean average BCVA improvement from baseline with DEX implant 0.7 mg was substantial until the time of a cataract AE report (Fig 6A). Vision loss was observed after an AE report of cataract until the time of cataract surgery, and improvement in vision from baseline was restored after cataract surgery. By the end of the study, treatment with DEX implant resulted in clinically meaningful improvement in BCVA independent of the lens status at baseline. The percentage of patients who gained ≥ 15 letters from baseline at study end was similar in the phakic and pseudophakic subgroups (Fig 7, available at www.aaojournal.org) and reflected the results in the total study population.

The mean (standard deviation) average reduction in CRT from baseline during the study was -111.6 (134.1) μm with DEX implant 0.7 mg, -107.9 (135.8) μm with DEX implant 0.35 mg, and -41.9 (116.0) μm with sham, and was significantly greater

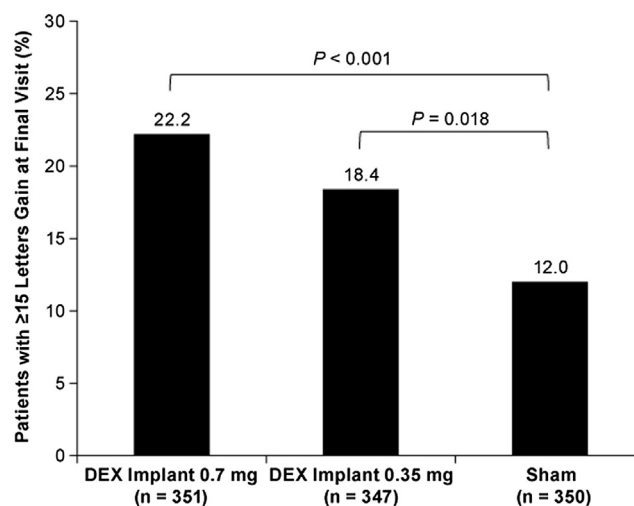


Figure 2. Primary efficacy endpoint. Percentage of patients with a ≥ 15 -letter improvement in best-corrected visual acuity from baseline at the year 3 or final study visit in the intent-to-treat population with last observation carried forward for missing values. DEX implant = dexamethasone intravitreal implant.

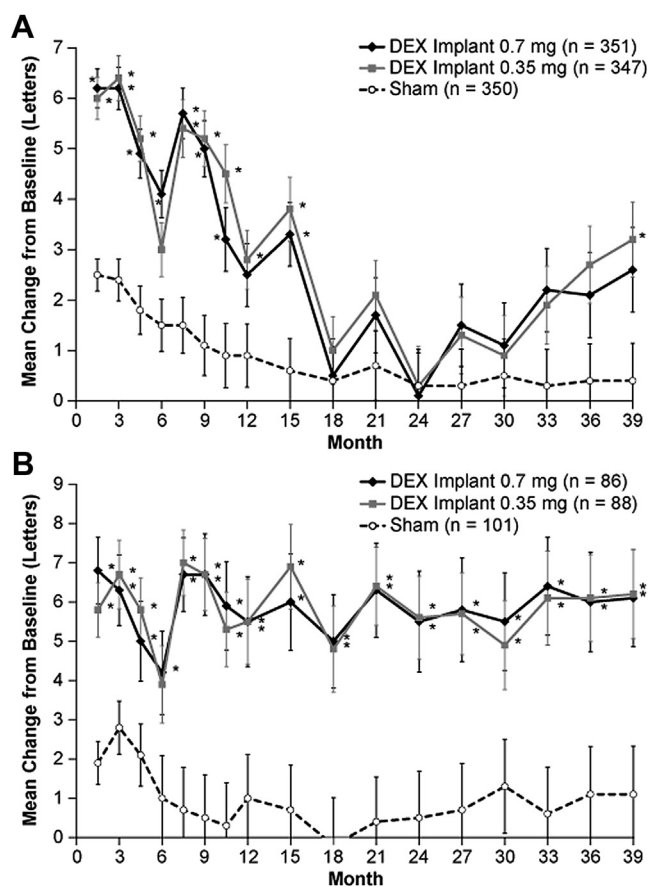


Figure 5. Mean change in best-corrected visual acuity from baseline in (A) the total study population and (B) the subgroup of patients with pseudophakic study eyes at baseline. Vertical bars indicate the standard error of the mean. * $P \leq 0.046$ versus sham (analysis of covariance in the intent-to-treat population with last-observation-carried-forward imputation of missing values). DEX implant = dexamethasone intravitreal implant.

with DEX implant 0.7 mg and 0.35 mg than with sham ($P < 0.001$). Decreases in CRT were seen in eyes that had cataract AEs leading to cataract surgery, despite the vision loss in those eyes (Fig 6B). Notably, an increase in CRT after cataract surgery was observed in the sham group but not in the DEX implant groups (Fig 6B), suggesting a protective effect of DEX implant following cataract surgery.

Prespecified analysis of patient subgroups defined by demographics, diabetes status, duration of diabetes and DME, and prior treatment, showed effects of DEX implant relative to sham similar to those in the total study population.

Safety Analyses

The overall incidence of AEs at any time during the study was 96.0% in the DEX implant 0.7 mg group, 97.4% in the DEX implant 0.35 mg group, and 80.3% in the sham group. These rates are influenced by the period of patient exposure to study treatment (patient years), which was approximately 22% to 24% shorter in the sham group compared with the DEX implant groups (853.9 with DEX implant 0.7 mg, 880.2 with DEX implant 0.35 mg, and 665.5 with sham) because of the high rate of discontinuations in the sham group during the first year of the study (Fig 1). The overall incidence of AEs adjusted for treatment exposure time was similar among treatment groups. Almost all AEs that were considered by the investigator to be possibly caused by the study treatment occurred in the study eye. Table 4 (available at www.aaojournal.org) lists ocular AEs reported in $\geq 2\%$ of the study eyes in any treatment group. The most common ocular AEs in study eyes were cataract and increased IOP related to DEX implant.

On biomicroscopy, 85.0% of patients (651/766) with a phakic study eye had cortical, nuclear, or posterior subcapsular opacities at baseline. Among patients with a phakic study eye at baseline, the overall incidence of cataract-related AEs (cataract, cataract cortical, cataract nuclear, cataract subcapsular, and lenticular opacities) was 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively, and the rate of cataract surgery during the study was 59.2%, 52.3%, and 7.2%, respectively. The incidence of cataract-related AEs increased after

Table 3. Efficacy Outcomes in Pseudophakic Eyes, Intent-to-Treat Population

Parameter	DEX Implant 0.7 mg (n = 86)	DEX Implant 0.35 mg (n = 88)	Sham (n = 101)	P Value DEX Implant 0.7 mg vs Sham	P Value DEX Implant 0.35 mg vs Sham
Patients with ≥ 15 letters BCVA improvement from baseline at study end, %*	23.3	15.9	10.9	0.024 [†]	0.329 [†]
Time to ≥ 15 -letter improvement in BCVA from baseline					
Cumulative response rate at study end for ≥ 15 -letter improvement in BCVA from baseline, %	57.4	43.7	26.3	<0.001 [‡]	0.005 [‡]
Patients with $\geq 20/40$ BCVA at study end, %*	29.1	30.7	17.8	0.072	0.042
Mean (SD) average change in BCVA from baseline across the study, letters	6.5 (8.1)	5.9 (7.1)	1.7 (7.1)	<0.001 [§]	<0.001 [§]
Mean (SD) change in BCVA from baseline at study end, letters*	6.1 (11.5)	6.2 (10.6)	1.1 (12.3)	0.004	0.003
Mean (SD) average change in central retinal thickness [¶] from baseline across the study, μm	-131.8 (140.2)	-117.1 (127.1)	-50.8 (93.6)	<0.001 [§]	<0.001 [§]

BCVA = best-corrected visual acuity; DEX implant = dexamethasone intravitreal implant; SD = standard deviation.

*Analysis used the last-observation-carried-forward method for imputation of missing values.

[†]Based on the Cochran-Mantel-Haenszel general association test stratified by study.

[‡]Based on the log-rank test of cumulative response.

[§]Based on an analysis of covariance model with treatment and study as factors and the baseline value as a covariate.

^{||}Based on an analysis of covariance model with treatment as factor and the baseline value as a covariate.

[¶]Retinal thickness in the central retinal subfield by optical coherence tomography.

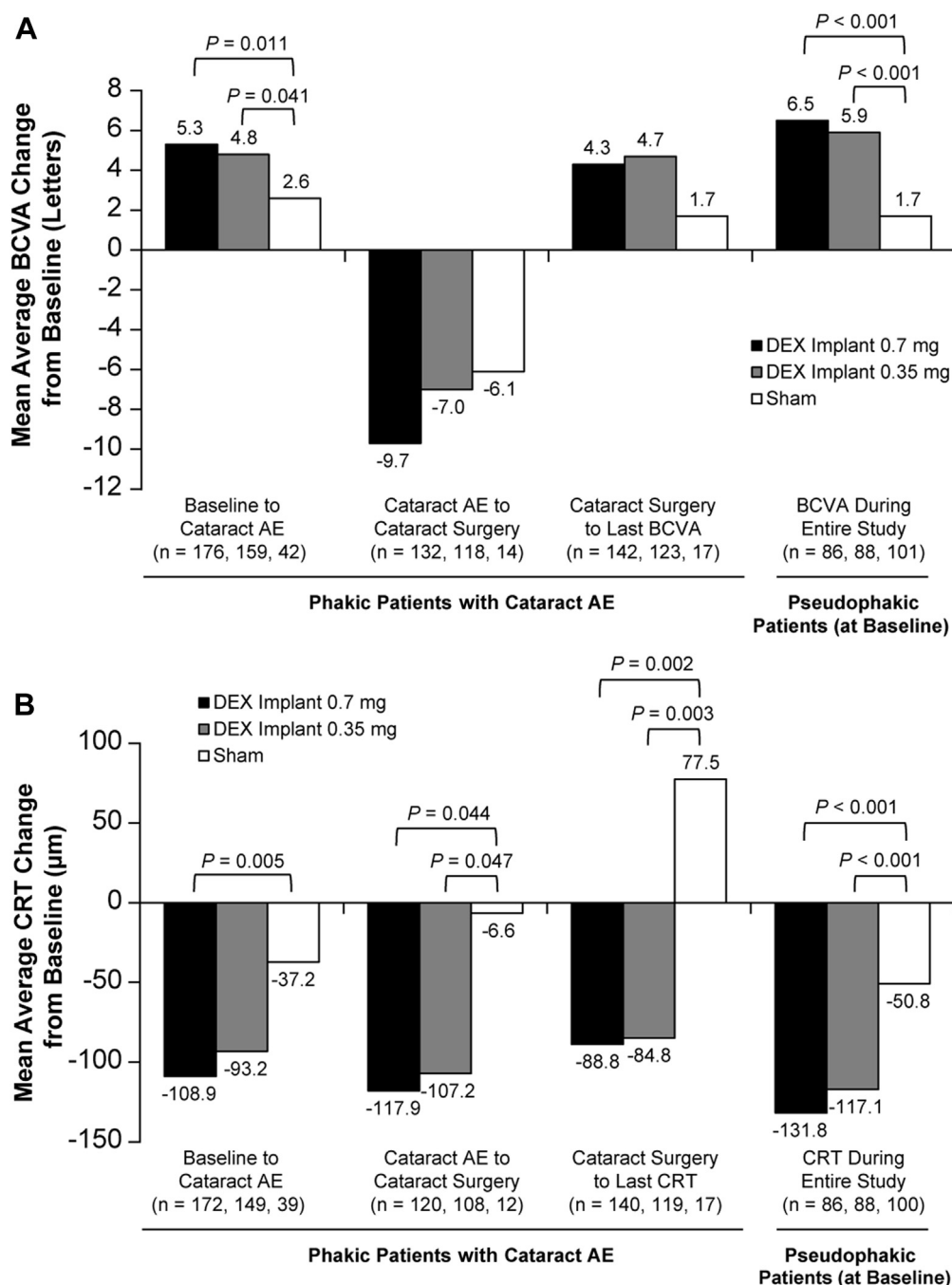


Figure 6. Mean average change in (A) best-corrected visual acuity (BCVA) and (B) central retinal thickness (CRT) during the study by lens status. Results were analyzed in phakic patients with a cataract adverse event (AE) as well as in pseudophakic patients using an area-under-the-curve approach and observed values in the intent-to-treat population. DEX implant = dexamethasone intravitreal implant.

the first year of the study, and over three-fourths of the cataract surgeries in the DEX implant groups were performed between 18 and 30 months.

Approximately one-third of patients in each DEX implant treatment group had a clinically significant increase in IOP requiring treatment during the study (Table 5). No patient underwent removal of the implant to control IOP, and only 1 patient (0.3%) in each DEX implant treatment group underwent glaucoma incisional surgery for steroid-induced increases in IOP (Table 5). Mean IOP

peaked at a similar level and returned to baseline levels by 6 months after each DEX implant injection (Fig 8, available at www.aaojournal.org). Furthermore, in comparison with the incidence of IOP AEs after the first treatment and during the first year of the study, the incidence of IOP AEs did not increase after subsequent treatments or in year 2 or 3, and the proportion of patients using IOP-lowering medications in the study eye remained similar from year to year. Together these results indicate that there was no cumulative effect of DEX implant on IOP.

Table 5. Intraocular Pressure Safety Parameters in Study Eyes

Parameter	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n = 350)
AE, n (%)*	125 (36.0)	117 (34.1)	18 (5.1)
IOP at any visit during the study, n (%)			
≥25 mmHg	111 (32.0)	94 (27.4)	15 (4.3)
≥35 mmHg	23 (6.6)	18 (5.2)	3 (0.9)
Increase of ≥10 mmHg from baseline	96 (27.7)	85 (24.8)	13 (3.7)
Use of IOP-lowering medication, n (%)	144 (41.5)	129 (37.6)	32 (9.1)
Procedure for IOP control, n (%) [†]			
Trabeculectomy	2 (0.6) [†]	1 (0.3)	0
Iridectomy	1 (0.3)	0	1 (0.3)
Iridotomy	2 (0.6) [†]	0	0
Trabeculectomy	0	2 (0.6)	0

AE = adverse event; DEX implant = dexamethasone intravitreal implant; IOP = intraocular pressure.

*Any AE related to elevated IOP or glaucoma.

[†]One patient in the DEX implant 0.7 mg group underwent both trabeculectomy and iridotomy; this patient had rubeosis of the anterior chamber angle and iris and marked anterior chamber fibrin in the study eye that was considered to be the primary cause of the increased IOP.

Vitreous hemorrhage in the study eye was reported in 6.9%, 13.1%, and 7.1% of patients in the DEX 0.7 mg, DEX 0.35 mg, and sham groups, respectively. Vitreous hemorrhage was considered to be possibly related to treatment in 3.5%, 4.1%, and 0.0% of patients, respectively (rates unadjusted for exposure), but in each case, the vitreous hemorrhage did not require vitrectomy, and most cleared spontaneously in a short period of time. Other ocular AEs of interest, including retinal tear, retinal detachment, vitreous loss, endophthalmitis, hypotony, and complication of device insertion (implant misplacement), were reported in <2% of patients in each group (Table 6). There were a total of 2928 DEX implant injections during the study and 2 reports of endophthalmitis in the study eye. One case occurred after cataract surgery and was considered unrelated to study treatment, and the other occurred after a DEX implant 0.7 mg injection. There were 2 cases of implant misplacement; there was no decrease in vision in either case.

The overall incidence of serious AEs was higher in the DEX implant groups than in the sham group (Table 7), but was similar among groups when the data were adjusted for treatment exposure time. All serious AEs possibly caused by treatment were ocular AEs in the study eye, and most were related to cataract (Table 7).

Table 6. Ocular Adverse Events of Interest

AE, n (%)*	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n = 350)
Retinal tear	5 (1.4)	3 (0.9)	3 (0.9)
Retinal detachment	2 (0.6)	0	2 (0.6)
Endophthalmitis	2 (0.6)	0	0
Hypotony of eye	2 (0.6)	0	0
Vitreous loss	1 (0.3)	0	0
Necrotizing retinitis	1 (0.3) [†]	0	0
Complication of device insertion	1 (0.3)	1 (0.3)	0

AE = adverse event; DEX implant = dexamethasone intravitreal implant.

*AEs are categorized by Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 preferred terms.

[†]The patient had no known history of herpes or human immunodeficiency virus infection; however, the investigator considered herpes to be the most likely cause of the retinal necrosis.

The systemic serious AEs that occurred during the study are listed in Table 8 (available at www.aaojournal.org).

Analysis of mean HbA1c and glomerular filtration rate changes from baseline showed no statistically significant differences among groups during the study. HbA1c mean levels remained ≤8.1% in all groups (Fig 9A, available at www.aaojournal.org). Small decreases in glomerular filtration rate occurred in each group,

Table 7. Incidence of Serious Adverse Events

SAE, n (%)*	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n = 350)
Any SAE	115 (33.1)	120 (35.0)	83 (23.7)
Ocular SAE in study eye	24 (6.9)	14 (4.1)	4 (1.1)
Treatment-related SAE [†]	16 (4.6)	10 (2.9)	1 (0.3)
Cataract	8 (2.3)	8 (2.3)	1 (0.3)
Cataract subcapsular	2 (0.6)	2 (0.6)	0
Lens dislocation	1 (0.3)	0	0
Macular edema	1 (0.3)	0	0
Necrotizing retinitis	1 (0.3) [‡]	0	0
Retinal detachment	1 (0.3)	0	0
Vitreous adhesions	1 (0.3)	0	0
Endophthalmitis	1 (0.3)	0	0
Death [§]	9 (2.6)	15 (4.4)	5 (1.4)

DEX implant = dexamethasone intravitreal implant; SAE = serious adverse event.

*The SAEs are categorized by Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 preferred terms.

[†]In the judgment of the investigator, there was a reasonable possibility that the SAE was caused by the study drug, the applicator, or the insertion procedure.

[‡]The patient had no known history of herpes or human immunodeficiency virus infection; however, the investigator considered herpes to be the most likely cause of the retinal necrosis.

[§]All deaths were considered by the investigator to be unrelated to treatment.

consistent with aging²⁶ and progression of the underlying diabetes in some patients (Fig 9B, available at www.aajournal.org).

Discussion

In this study, DEX implant 0.7 mg or 0.35 mg, with a mean of only 4 to 5 injections over 3 years, provided robust long-term improvement in vision and macular edema in patients with DME. The proportion of patients with a ≥ 15 -letter gain in BCVA at the end of the study was significantly greater with the DEX implant compared with sham. Mean changes in BCVA from baseline were confounded by cataract in phakic patients after the first year, yet significant improvement in BCVA over 3 years was still seen with DEX implant (AUC analysis). Moreover, analysis of the proportion of patients gaining 3 lines in BCVA or achieving $\geq 20/40$ vision showed separation of the DEX implant and sham curves in study year 3, when the influence of cataract was reduced because of cataract extractions. Visual outcomes were favorable and the benefit of DEX implant treatment was consistent over time in pseudophakic patients. In phakic patients who developed cataract, vision again improved with DEX implant after cataract extraction, and there was no increase in CRT after cataract surgery.

The safety profile of the DEX implant in this study was better than the reported safety profile of other intraocular corticosteroids in patients with DME.^{9,18,27} The incidence of pressure elevations was less than reported in studies using other steroids.²⁸ There were no unexpected AEs, and DEX implant demonstrated excellent systemic safety. The overall incidence of AEs and serious AEs was similar across treatment groups in exposure-adjusted analyses, and there was no evidence for incremental systemic AEs or increased risk of arterial thromboembolic events after repeat DEX implant treatment. There were no arterial thromboembolic events considered by the investigator to be related to treatment. Also, there was no evidence of local or systemic delayed wound healing.

Longer exposure to repeat DEX implant was associated with an increase in cataract development or progression in phakic eyes, and cataract surgery was performed in $\leq 59.2\%$ of phakic eyes. Lens opacities account for the reduced improvement in BCVA seen in the DEX implant groups after month 15 of the study. Vision improvement related to DEX implant treatment was consistent throughout the 3-year study in pseudophakic eyes. In phakic eyes that developed cataract, vision improvement related to DEX implant treatment was seen after cataract extraction, for the remainder of the study. Increases in IOP that occurred were typically manageable with topical medication. The timing of IOP rises was predictable, and the incidence and magnitude of IOP elevations did not increase upon repeated injection or from year to year in the study. Only 2 incisional surgeries to control steroid-induced IOP elevations were required.

Although cataract progression and IOP increases are expected complications of corticosteroid treatment, the incidence rates seem to differ among available intraocular corticosteroids. The DEX implant has been associated with a lesser incidence of increases in IOP compared with

the intravitreal fluocinolone acetonide implant or intravitreal TA.²⁸ In the 3-year phase III study of the fluocinolone acetonide implant in patients with DME (the FAME study), incisional IOP-lowering surgery was performed in 8.1% of patients in the high-dose group and 4.8% in the low-dose group compared with 0.5% in the sham group.²⁷ In comparison, in the present study, 0.6% of patients in the DEX implant 0.7 mg group and 0.3% in the DEX implant 0.35 mg group compared with none in the sham group required trabeculectomy during the study. Cataract surgery was also performed in more eyes treated with the fluocinolone acetonide implant in the FAME study: Rates in phakic eyes were 87.2%, 80.0%, and 27.3% in the high-dose, low-dose, and sham groups, respectively.²⁷

Differences in the pharmacologic and pharmacokinetic profiles of the available intravitreal steroid treatments may account for their differing safety profiles. Dexamethasone, fluocinolone acetonide, and TA have been shown to activate different patterns of gene expression in human trabecular meshwork cell lines.²⁹ In addition, dexamethasone is less lipophilic than TA or fluocinolone acetonide and does not accumulate to the same extent in the trabecular meshwork and lens; therefore, there may be reduced risk of IOP increases and cataract progression with dexamethasone.³⁰

The MEAD study began in 2004, and the high rate of patient discontinuations was a consequence of the study design requirement for patients to exit before receiving any escape treatment. The discontinuation rate was substantially higher and patients discontinued earlier in the sham group than in the DEX implant groups because of lack of efficacy. Long-term studies of medical treatment in DME that were designed more recently have permitted patients to receive escape treatment and remain in the study. For example, in the 2-year RISE/RIDE study¹¹ of DME patients treated with ranibizumab, which began in 2009, patients who met predefined criteria were treated with adjunctive macular laser as well as ranibizumab or sham. The significant percentage of patients (72% in the sham group, 38% in the ranibizumab 0.3 mg group, and 27% in the ranibizumab 0.5 mg group) who were treated with macular laser during RISE/RIDE would have been exited from the MEAD study. Also, anti-VEGF became available during the course of the MEAD study, allowing some patients a good escape. Because there was a bias for patients with poor outcomes in the sham group to drop out of the study, outcomes in the sham group were better than expected and better than is typically seen in clinical practice. Nonetheless, DEX implant 0.7 mg and 0.35 mg demonstrated improved visual acuity and CRT thickness compared with sham.

During the study, the protocol was modified as more information became available about DME treatment and DEX implant effects. One protocol amendment concerned the timing of cataract surgery. Timely diagnosis and treatment of cataracts minimizes loss of visual acuity during corticosteroid treatment. In most cases, there was a delay of 6 months between the initial AE report of cataract and the cataract surgery. A protocol amendment in May 2010 added the statement that the cataract surgery should take place within 3 months of the last retreatment, to gain the benefit of

DEX implant effect on reducing macular edema associated with the cataract surgery.

Evaluation of the comparative efficacy of DEX implant versus anti-VEGF treatment will require head-to-head studies, because of the influence of patient population characteristics (diabetes status, baseline BCVA) and study design (treatment frequency, use of escape therapy) on measured efficacy. Visual outcomes of ranibizumab treatment in DME have been most favorable in studies that used monthly injections (e.g., in RISE and RIDE).¹¹ In the RESTORE study, the BCVA stability-based retreatment criteria resulted in patients receiving a mean of 7 ranibizumab injections in year 1, and the mean average improvement in BCVA during the year was 6.1 letters.³¹ This improvement is similar to the mean average improvement seen in this study in pseudophakic eyes treated with a mean of 4 to 5 injections of DEX implant 0.7 mg (6.5 letters) or DEX implant 0.35 mg (5.9 letters) over 3 years.

This study had several limitations. An imbalance in ischemia status at baseline may have reduced the demonstrated efficacy of DEX implant 0.7 mg relative to sham in improving vision. The study provided no information about use of DEX implant in combination with laser or other treatment for DME. Also, the fixed dosing schedule used may have limited efficacy, and more frequent dosing may improve results. Patient dropout rates of approximately 20% to 30% have been reported previously in 3-year studies of medical treatment of DME.^{12,27} It is likely that the approximately 35% discontinuation rate from the DEX implant treatment groups in the present study was influenced by the study design requirement for patients who received escape treatment to exit the study.

The DEX implant demonstrated efficacy in the treatment of DME and had a favorable safety profile in this study. There is a need for efficacious treatments for DME in addition to anti-VEGF, because many patients do not achieve a dry macula even after frequently repeated treatment with anti-VEGF. The results suggest that up to one-third of patients treated with DEX implant for their DME achieve $\geq 20/40$ vision after their first implant, and treatment benefit is maintained over the long term when confounding effects of cataract are removed. The small number of injections of DEX implants associated with clinical benefit represents a substantial decrease in treatment burden for patients compared with anti-VEGF therapies. Cataract development or progression is probable in phakic eyes treated with DEX implant, but cataract removal is uneventful and is followed by clinically relevant improvement in vision compared with sham treatment. Prompt diagnosis and cataract extraction are needed for optimal visual outcomes with DEX implant.

In summary, with an average of only 4 to 5 injections over 3 years, patients treated with DEX implant achieved statistically significant and clinically meaningful visual improvements. These data support the use of DEX implant in the management of patients with DME.

Acknowledgments. The authors thank the study personnel and patients who participated in the study at each site. Allergan, Inc, (Irvine, CA) funded medical writing support for manuscript development. Kate Ivins, PhD, of Evidence Scientific Solutions

(Philadelphia, PA) prepared a draft of the manuscript under the direction of the authors; Diann Glickman, PharmD, CMPP, of Evidence Scientific Solutions (Southport, CT) provided editorial assistance.

References

1. Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol* 2004;122:552–63.
2. Yau JW, Rogers SL, Kawasaki R, et al; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556–64.
3. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol* 2009;54:1–32.
4. Funatsu H, Noma H, Mimura T, et al. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology* 2009;116:73–9.
5. Miyamoto K, Khosrof S, Bursell SE, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. *Proc Natl Acad Sci U S A* 1999;96:10836–41.
6. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Semin Ophthalmol* 1999;14:223–32.
7. American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care* 2009;32(suppl):S13–61.
8. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–806.
9. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447–59.
10. Aiello LP, Edwards AR, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2010;117:946–53.
11. Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789–801.
12. Brown DM, Nguyen QD, Marcus DM, et al; RISE and RIDE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;120:2013–22.
13. Bhisitkul RB, Campochiaro PA, Shapiro H, Rubio RG. Predictive value in retinal vein occlusions of early versus late or incomplete ranibizumab response defined by optical coherence tomography. *Ophthalmology* 2013;120:1057–63.
14. Wang K, Wang Y, Gao L, et al. Dexamethasone inhibits leukocyte accumulation and vascular permeability in retina of streptozotocin-induced diabetic rats via reducing vascular endothelial growth factor and intercellular adhesion molecule-1 expression. *Biol Pharm Bull* 2008;31:1541–6.
15. Tamura H, Miyamoto K, Kiryu J, et al. Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. *Invest Ophthalmol Vis Sci* 2005;46:1440–4.

16. Antonetti DA, Wolpert EB, DeMaio L, et al. Hydrocortisone decreases retinal endothelial cell water and solute flux coincident with increased content and decreased phosphorylation of occludin. *J Neurochem* 2002;80:667–77.
17. Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. *Ophthalmology* 2006;113:1533–8.
18. Diabetic Retinopathy Clinical Research Network, Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609–14.
19. Chang-Lin JE, Attar M, Acheampong AA, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest Ophthalmol Vis Sci* 2011;52:80–6.
20. Edelman JL. Differentiating intraocular glucocorticoids. *Ophthalmologica* 2010;224(suppl):25–30.
21. Haller JA, Kuppermann BD, Blumenkranz MS, et al; Dexamethasone DDS Phase II Study Group. Randomized controlled trial of an intravitreal dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol* 2010;128:289–96.
22. Pacella E, Vestri AR, Muscella R, et al. Preliminary results of an intravitreal dexamethasone implant (Ozurdex) in patients with persistent diabetic macular edema. *Clin Ophthalmol* 2013;7:1423–8.
23. Lazic R, Lukic M, Boras I, et al. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. *Retina* 2014;34:719–24.
24. Boyer DS, Faber D, Gupta S, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina* 2011;31:915–23.
25. Haller JA, Bandello F, Belfort R Jr, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134–46.
26. Glasscock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. *Trans Am Clin Climatol Assoc* 2009;120:419–28.
27. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 2012;119:2125–32.
28. Kiddee W, Trope GE, Sheng L, et al. Intraocular pressure monitoring post intravitreal steroids: a systematic review. *Surv Ophthalmol* 2013;58:291–310.
29. Nehmé A, Lobenhofer EK, Stamer WD, Edelman JL. Glucocorticoids with different chemical structures but similar glucocorticoid receptor potency regulate subsets of common and unique genes in human trabecular meshwork cells. *BMC Med Genomics* [serial online] 2009;2:58. Available at: <http://www.biomedcentral.com/1755-8794/2/58>. Accessed April 19, 2014.
30. Thakur A, Kadam R, Kompella UB. Trabecular meshwork and lens partitioning of corticosteroids: implications for elevated intraocular pressure and cataracts. *Arch Ophthalmol* 2011;129:914–20.
31. Mitchell P, Bandello F, Schmidt-Erfurth U, et al; RESTORE Study Group. The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615–25.

Footnotes and Financial Disclosures

Originally received: December 18, 2013.

Final revision: February 21, 2014.

Accepted: April 21, 2014.

Available online: June 4, 2014.

Manuscript no. 2013-2075.

¹ Retina-Vitreous Associates Medical Group, Los Angeles, California.

² Asan Medical Center, University of Ulsan, Seoul, South Korea.

³ Vision Institute, Federal University of São Paulo, São Paulo, Brazil.

⁴ University Vita-Salute, Hospital San Raffaele, Milan, Italy.

⁵ Midwest Eye Institute, Indianapolis, Indiana.

⁶ Department of Ophthalmology, Staedisches Klinikum Karlsruhe, Karlsruhe, Germany.

⁷ Allergan, Inc, Irvine, California.

*MEAD Study Group members listed online in [Appendix 1](#) (available at www.aaojournal.org).

Financial Disclosure(s):

Sponsored by Allergan, Inc. The sponsor participated in the design of the study, data management, data analysis, interpretation of the data, and preparation, review, and approval of the manuscript.

The authors have made the following disclosures:

David S. Boyer: Consultant—Allergan; Young Hee Yoon: Consultant—Allergan; Rubens Belfort, Jr: Consultant—Allergan; Francesco Bandello: Consultant—Allergan; Raj K. Maturi: Consultant—Allergan; Albert J. Augustin: Research Support, Speaker Fees — Allergan, Inc; Xiao-Yan Li: Employee — Allergan, Inc; Harry Cui: Employee — Allergan, Inc; Yehia Hashad: Employee — Allergan, Inc; Scott M. Whitcup: Employee — Allergan, Inc.

Abbreviations and Acronyms:

AE = adverse event; **AUC** = area under the curve; **BCVA** = best-corrected visual acuity; **CRT** = central retinal thickness; **DEX** = dexamethasone intravitreal implant; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **HbA1C** = glycosylated hemoglobin; **IOP** = intraocular pressure; **OCT** = optical coherence tomography; **TA** = triamcinolone acetonide; **VEGF** = vascular endothelial growth factor.

Correspondence:

David S. Boyer, MD, Retina-Vitreous Associates Medical Group, 1127 Wilshire Blvd, Suite 1620, Los Angeles, CA 90017. E-mail: vitdoc@aol.com.