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A Collaborative Retrospective Study on the Efficacy and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema

The European DME Registry Study

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Purpose: To evaluate the efficacy, effect profile, and safety of dexamethasone implant on diabetic macular edema (DME) in a real-life setting, further comparing results by DME duration, previous treatment status, and diabetic control.

Design: A multicenter, retrospective cohort of 340 DME eyes of 287 patients from 25 clinical sites from 8 countries.

Methods: Data were analyzed in 2 perspectives: per injection, in which all measurements were grouped and baseline was defined as the day of injection, and thus the pharmacodynamics of single injections could be assessed; and injection series, defined as 2 or more injections with 3 to 6 months between injections analyzing the outcome 3 to 6 months after the last injection.

Main Outcome Measures: Primary outcome was improvement of 15 or more letters in best-corrected visual acuity (BCVA) from baseline. Secondary outcomes included improvement of 10 letters or more in BCVA, change in central macular thickness (CMT), and time to maximum improvement and safety.

Results: Overall, 762 injections were administered to 340 eyes of 287 patients. Injection series analysis included 171 series in 171 eyes of 150 patients, for a total of 444 injections, with a mean follow-up of 1.7±0.8 years. Of the 762 injections analyzed per injection, 22.7% achieved a 15-letter or more improvement, and 37.8% achieved a 10-letter or more improvement. Mean time to peak improvement was 81.9±39.7 days. Mean maximum change in CMT was −174±171 μm. Overall, 7.6% lost 15 or more letters. More eyes with early DME gained 10 or more letters and fewer eyes lost 10 or more letters compared with eyes with late DME (47.4% vs. 33.9% [$P = 0.001$] and 8.2% vs. 13.5% [$P = 0.029$], respectively). Patients with controlled diabetes showed greater CMT reduction ($P = 0.0002$). A higher percentage of treatment-naive patients gained 10 or 15 letter or more in BCVA ($P = 0.001$ and $P = 0.006$, respectively). Intraocular pressure elevation of more than 25 mmHg was found following 7.9% of injections; no endophthalmitis was reported.

Conclusions: Dexamethasone implant is an effective and safe treatment for DME. Peak improvement was achieved 3 months after injection and dissipated thereafter. Clinicians and providers may consider shortening treatment intervals. *Ophthalmology 2019;■:1−17 © 2019 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/4.0/).*

Supplemental material available at www.aaojournal.org.

Diabetic macular edema (DME) is one of the leading causes of visual loss among working-age patients (20−65 years) and the elderly.[1] It is estimated to affect 20% of patients with diabetic retinopathy,[2] and its prevalence increases with that of diabetes.[3,4] Diabetic macular edema is a multifactorial disease, driven by proinflammatory and proangiogenic elements.[5] It is characterized by macular thickening secondary to capillary leakage and fluid accumulation.[6] Anti−vascular endothelial growth factor (VEGF) therapies have been proven effective, leading to improved visual acuity and macular thickness reduction.[7] However, according to post hoc analysis of the Diabetic

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Retinopathy Clinical Research Network trials, a significant percentage of patients do not show a sufficient initial response to this treatment or do not reach complete anatomic resolution[8–10]; hence, a need for alternative therapy exists. In addition, current anti-VEGF treatments require frequent injections and monitoring, causing a significant burden on patients and health care systems, with a financial impact and reduction in patient quality of life.[11] Laser photocoagulation may prevent visual acuity loss in certain groups of patients; however, it typically cannot restore or improve visual acuity and is inferior to anti-VEGF treatments.[12]

Corticosteroids inhibit leukocytosis and expression of prostaglandins and proinflammatory cytokines, enhance the barrier function of vascular tight junctions, and reduce VEGF levels.[13] Therefore, intravitreal corticosteroids may play an important role as an alternative treatment for DME. Injections of triamcinolone have been used commonly; however, these treatments are associated with significant adverse events (AEs), primarily intraocular pressure (IOP) elevation and cataract formation.[12]

The dexamethasone intravitreal implant (Ozurdex; Allergan, Inc., Irvine, CA) is a sustained-release biodegradable implant injected into the vitreous that delivers 0.7 mg dexamethasone to the posterior segment of the eye. The biodegradable implant has dual-phase pharmacokinetics, initially releasing a burst of dexamethasone to achieve a rapidly therapeutic concentration followed by a lower sustained release.[14,15]

The results of the 3-year multicenter, phase 3 randomized clinical trials from the Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study group demonstrated that the dexamethasone intravitreal implant is an effective treatment method for DME, with approximately 20% of patients achieving a visual acuity improvement of 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters sustained with repeated injections over 3 years.[16] Although this study showed that the dexamethasone intravitreal implant is an effective and safe treatment, treated eyes demonstrated a distinct pendular effect of improvement and deterioration throughout the 6-month mandatory interval between injections. Based on these results, the dexamethasone intravitreal implant has been approved for treatment every 6 months by the Food and Drug Administration and European Medicine Agency for DME in pseudophakic eyes and as a second-line treatment to nonresponsive phakic eyes. Querques et al[17] emphasized the need for a study to evaluate the optimal dexamethasone treatment frequency in patients with DME. To date, several studies have been published on the use of the dexamethasone intravitreal implant in real-life settings, and although some were relatively small,[18–21] others included a large cohort and a good design. Nevertheless, these studies concentrated on its effect on the entire cohort or assessed the effect comparing a single subgroup.[22–24]

Because the real-life optimal treatment interval between the dexamethasone intravitreal implant injections is debatable and is heavily dependent on clinical response to each treatment rather than a preset interval, we recognized 2 unmet needs with regard to the study of the therapeutic effect of the dexamethasone intravitreal implant, the first of which is the lack of an in-depth analysis and depiction of the actual therapeutic profile of each implant within an injection series, allowing for a better understanding and planning of treatment frequency and follow-up protocols. The second is that previous studies allowed for the inclusion of patients treated at variable and relatively long intervals, thus introducing potential confounders for the treatment effect. Therefore, a need arose for a study to evaluate the effect an injection series with strict interval limitations. To the best of our knowledge, no study to date has examined and characterized the effect profile of the dexamethasone intravitreal implant injection. In addition, we aimed to address the difference in treatment effect between early and late DME, treatment-naive and previously treated eyes, and patients with controlled and uncontrolled diabetes in a large, international, multicenter, real-life study. The purpose of the current study was to evaluate the pharmacodynamics and clinical and anatomic effects over time of each dexamethasone intravitreal implant injection as well as the efficacy and safety of a dexamethasone intravitreal implant injection series with strict interval limitations within a real-life setting.

Methods

This study was approved by the independent ethics committee or institutional review board of the clinical sites where the study was conducted, or by another relevant ethics committee. No informed consent was needed. This study also was designed, implemented, and reported in accordance with the International Council for Harmonisation (ICH) Tripartite Guidelines for Good Clinical Practice, with applicable local regulations such as European Directive 2001/20/EC, and with the ethical principles laid down in the Declaration of Helsinki.

Study Design and Population

This multicenter retrospective cohort included DME patients from 25 European Vision Clinical Research Network clinical sites from 8 countries in Europe and Israel. Consecutive patients older than 18 years with type 1 or 2 diabetes and DME with central macular thickness (CMT) of 300 μm or more were included in the study. All patients demonstrated a minimum best-corrected visual acuity (BCVA) of 20/200 (35 ETDRS letters) at baseline. Patients with additional ophthalmic comorbidities that may affect BCVA, such as patients with any history of advanced age-related macular degeneration, retinal vein occlusion, proliferative diabetic retinopathy, glaucoma, or ocular hypertension (defined as IOP >23 mmHg without antiglaucoma medication, IOP >21 mmHg with 1 medication, or any use of 2 or more medications), optic neuropathy, or corneal opacity, were excluded. Also excluded were patients with previous ocular trauma or any surgery other than cataract extraction or steroid responders. Patients with DME who had undergone intravitreal triamcinolone 6 months or less before baseline or intravitreal bevacizumab, ranibizumab, or aflibercept 1 month or less before baseline were excluded as well.

Data Collection

Data were collected by retrospective review of the patients' medical charts and entered using electronic case report forms. Collected

Table 1. Baseline Characteristics of Patients and Study Eyes for All Injections

	Overall (287 Patients; 340 Eyes)	Injection Series (150 Patients; 171 Eyes)
Age (yrs)		
Mean ± SD	66.29±9.33	65.26±8.58
Range	24.00–89.00	24.00–89.00
Male gender, no. (%)	183 (63.8)	94 (62.7)
ETDRS letter score, mean ± SD	61.9±13.5	57.46±13.11
CMT (μm), mean ± SD	498±139	519.2±152.7
IOP (mmHg), mean ± SD	15.65±2.78	15.68±2.77
Use of IOP-lowering medication, no. (%)	53 (18.5)	31 (20.7)
Mean duration of diabetes (yrs), mean ± SD	14.16±9.54	14.43±9.04
Mean HbA1c (%), mean ± SD*	7.69±1.18	7.67±1.21
≤8%, no. (%)	151 (52.6)	83 (55.3)
>8%, no. (%)	88 (30.7)	44 (29.3)
Not available, no. (%)	48 (16.7)	23 (15.3)
Mean duration of DME (mos), mean ± SD	24.3±28.8	27.0±32.1
Range (mos)	0–163	0–163
Less than 6 mos, no. (%)	100 (29.4)	40 (23.4)
More than 6 mos, no. (%)	201 (59.1)	114 (66.7)
Unknown	39 (11.5)	17 (9.9)
Previous treatment for DME, no. (%)†	221 (65.0)	118 (69.0)
Focal/grid laser	185 (83.7)	98 (83.1)
Intravitreal steroid	39 (17.6)	18 (15.3)
Anti-VEGF	208 (94.1)	96 (81.4)
None	119 (35.0)	53 (31.0)
DME perfusion status, no. (%)		
Ischemic	84 (24.7)	52 (30.4)
Nonischemic	256 (75.3)	119 (69.6)
Lens status, no. (%)		
Phakic	205 (60.3)	109 (63.7)
Pseudophakic	135 (39.7)	62 (36.3)

CMT = central macular thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = hemoglobin A1c; IOP = intraocular pressure; SD = standard deviation; VEGF = vascular endothelial growth factor.
*Based on number of patients.
†Patients could have multiple treatment types.

parameters included demographic information, previous ocular history, type of DME, number and dates of the dexamethasone intravitreal implant injections, additional treatments for DME (before and after dexamethasone intravitreal implant administration), BCVA and IOP throughout the study period, cataract progression throughout the study period, and the occurrence of any complications. All IOP measurements were measured by Goldman applanator tonometer. All visual acuity measurements were measured using Snellen charts and later were converted into logarithm of the minimum angle of resolution for statistical analysis. Data regarding CMT and presence of intraretinal fluid from OCT scans were collected. The electronic case report form was designed with built-in edit checks that prompted the users for immediate data verification before committing data to the database. This measure was introduced to reduce typos and data entry errors.

Data Analysis

Analysis by Series. All patients included in the analysis received a minimum of 2 dexamethasone intravitreal implants with an interval of 3 to 6 months (±2 weeks) between injections and at least 3 months of follow-up after the last injection that met the inclusion criteria. Treatment outcome was defined as the change from the day of first injection to the result of last injection up to 6 months after the last injection.

Analysis by Injection. This analysis included all visual and anatomic observations of each study patient in the 6 months after each injection received (including those who were not included in the analysis per series because of injection intervals of more than 6 months or a single injection being received). The data were analyzed and displayed to depict the change over time in study outcomes up to 6 months after any injection. All analyses were performed for the entire cohort and by predefined subgroups (Fig S1, available at www.aaojournal.org). Contrary to the per-series analysis, in which the effect of a series of injections was analyzed for patients treated at defined intervals, the purpose of the analysis per injection was to study the effect of any injection on the visual and anatomic outcomes and to characterize the pharmacodynamics of the dexamethasone intravitreal implant. The summation of data from all study patients at all follow-up points allows better definition of the response over time to any injection (and later conclusions regarding optimal dosing intervals) while avoiding underrepresentation of eyes treated with a single injection because of poor response or loss to follow-up.

Predefined Subgroup Analysis. Three comparisons were made between subgroups: previous treatment status, comparing treatment-naive patients with previously treated patients conditioned on the patients meeting the inclusion criteria regarding interval from previous treatment: duration of DME, comparing early DME (defined as less than 6 months documented DME) and late DME (defined as 6 months or more of documented DME); and measure of diabetic control, defined similarly to the MEAD tables, that is, comparing controlled diabetes (defined as a blood level of hemoglobin A1c [HbA1c] lower than 8 mg/100) versus uncontrolled diabetes (defined as blood level of HbA1c of 8 mg/100 or more).[16]

Table 2. Number of Study Treatments Received

Treatments	Injection Series Analysis (171 Eyes; 444 Injections)	All Injections (340 Eyes; 762 Injections)
No. of treatments (%)		
1		85 (25.0)
2	106 (62.0)	147 (43.2)
3	45 (26.3)	70 (20.6)
4	12 (7.0)	26 (7.6)
5	3 (1.8)	7 (2.1)
6	2 (1.2)	2 (0.6)
7	2 (1.2)	2 (0.6)
8	1 (0.6)	1 (0.3)
Mean ± SD no. of injections in the first year	2.39±0.5	1.83±0.85
Mean ± SD no. of injections in the second year	0.18±0.6	0.31±0.58
Mean ± SD no. of injections in the third year	0.03±0.2	0.11±0.46
Mean ± SD interval between injections	145±24.5	218±167
Range	90–195	21–1354
Overall mean ± SD no. of injections	2.60±1.0	2.24±1.11
Overall median no. of injections	2.00	2.00

SD = standard deviation.

Outcomes

The primary outcome was defined as percentage of patients with improvement of 15 or more ETDRS letters of BCVA from baseline 3 to 6 months after the dexamethasone intravitreal implant injection or after the last injection. The secondary outcomes were improvement of 10 or more ETDRS letters of BCVA from baseline, time to BCVA improvement of 15 or more or 10 ETDRS letters or more, change in CMT from baseline during the study, and the percentage of patients with BCVA reduction of 10 or more ETDRS letters or more than 15 ETDRS letters from baseline and safety. Decrease in visual acuity was defined as a decrease in BCVA without a prior increase of at least 5 ETDRS letters after an injection. Safety measures included description of the percent of patients demonstrating cataract formation or progression, cataract operation, absolute IOP and IOP elevation of more than 10 mmHg, use of IOP-lowering medications, and other AEs.

Statistical Analysis

The data were analyzed using SAS software version 9.3 (SAS Institute, Cary, NC). All measured variables and derived parameters were tabulated by descriptive statistics. For categorical variables, summary tables were provided, giving sample size and absolute and relative frequency by individual treatment groups. For continuous variables, summary tables were provided giving sample size, arithmetic mean, standard deviation, minimum, median, and maximum by individual treatment groups. Analyzed groups for the tables included HbA1c status, DME duration, and DME status. Changes from baseline for ETDRS and CMT were tabulated per group. Differences were tested using independent sample t tests. The number of injections resulting in an increase of 10 or 15 ETDRS letters or a decrease of 10 or 15 ETDRS letters was tabulated by the number of frequency of participants. The difference between groups was analyzed using the chi-square test. Snellen values were converted to ETDRS letters. A 2-sided P value of less than 0.05 was considered statistically significant.

Results

The study included 340 eyes of 287 patients who received a total of 762 injections. Thirty-six percent of patients were women, and the mean age was 66.3±9.3 years. Of the 340 eyes, 171 (50.2%) received multiple injections meeting the criteria for an injection series. No eyes met the criteria twice; thus, no sequential injection series was included in the analysis.

Baseline Characteristics

Table 1 depicts the baseline characteristics of the per-injection and per-series analyses, respectively. In the per-injection analysis, mean baseline BCVA was 58.1 ETDRS letters (Snellen equivalent, approximately 20/80), mean CMT was 495.2±137.4 μm, and mean duration of DME before study entry was 24.3 months. For the per-series analysis, 171 eyes of 150 patients met the criteria of a continuous injection series, mean BCVA was 56.5 ETDRS letters (Snellen equivalent, approximately 20/80), mean CMT was 533±154 μm, and mean duration of DME before study entry was 24.3 months.

Per-Injection Analysis

Entire Cohort. Overall, this analysis includes the data from 2192 observation points of 762 injections per eye in 340 eyes throughout the study; mean number of injections per eye was 2.24±1.11 injection per patient (range, 2–8; Table 2). Of the 762 injections administered, 173 (22.7%) and 288 (37.8%) resulted in improvement of 15 and 10 ETDRS letters or more of BCVA improvement from baseline, respectively, whereas 58 eyes (7.6%) experienced reduction of more than 15 ETDRS letters in BCVA, and 95 eyes (12.5%) experienced a reduction of 10 or more ETDRS letters. The mean time to peak improvement after an injection was 81.9±39.7 days, and the mean change in CMT was −174±171 μm. Immediately after the injection, a statistically significant anatomic improvement became evident that was maintained throughout the first 3 months, with the effect later diminishing but remaining significantly improved at 6 months (Fig 1). Similarly, a significant improvement in visual acuity (with a slight delay compared with reduction in CMT) became evident that diminished after 3 months yet remained significant at 6 months (Fig 2).

Treatment-Naive versus Previously Treated Patients. Of the 762 injections included in this analysis, 243 injections were administered to 119 treatment-naive eyes, and 519 injections were administered to 221 previously treated eyes. At baseline, mean BCVA was significantly better in the treatment-naive eyes compared with the previously treated eyes (66.8±11.3 ETDRS letters vs. 59.6±13.9 ETDRS letters, respectively; $P < 0.0001$), whereas there was no significant difference in CMT ($P = 0.101$). After an injection, a significantly greater percentage of treatment-naive eyes gained 15 or more ETDRS letters of BCVA (70 eyes [28.8%]) compared with previously treated eyes (103 eyes [19.8%]; $P = 0.006$). One hundred twelve injections (46.1%) to

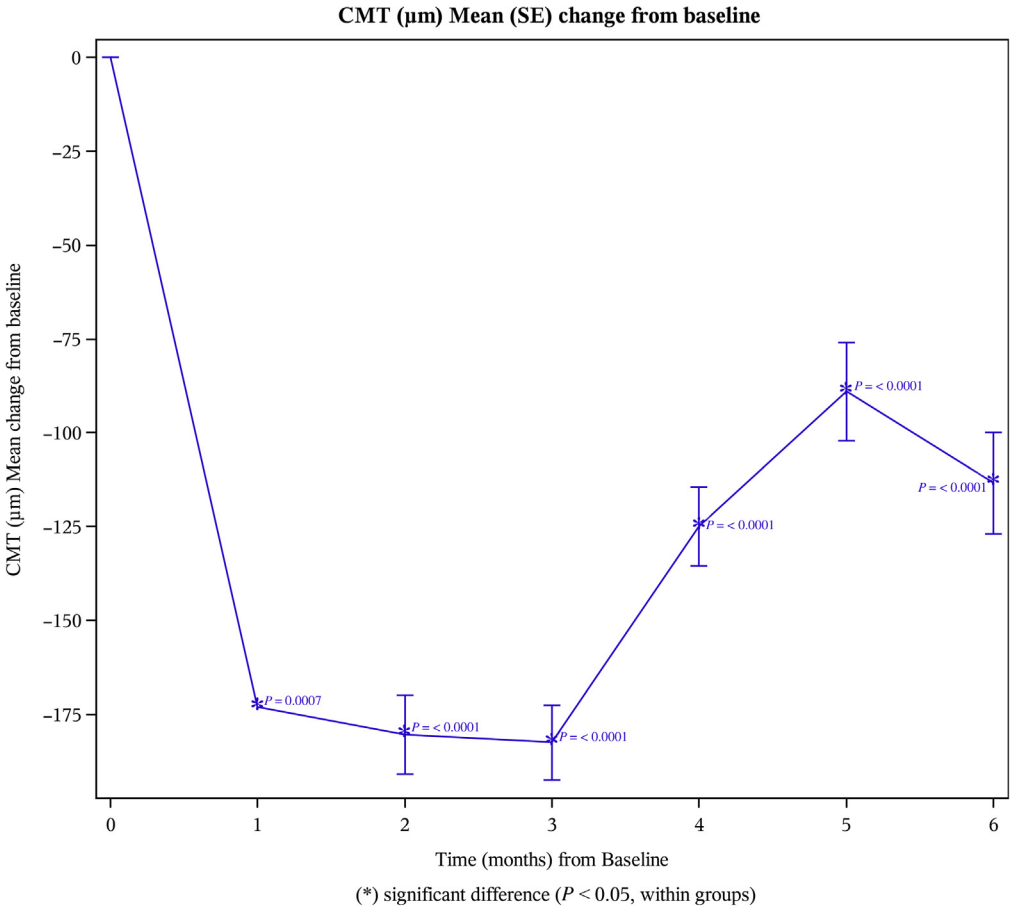

Figure 1. Graph showing anatomic changes after a dexamethasone implant injection, entire cohort (per-injection analysis). CMT = central macular thickness; SE = standard error.

treatment-naive eyes resulted in a gain of 10 ETDRS letters or more of BCVA compared with 176 injections (33.9%) in previously treated patients ($P = 0.001$). Overall, mean change in BCVA was slightly better in treatment-naive eyes compared with the previously treated patients (8.1±12.5 ETDRS letters vs. 6.2±10.4 ETDRS letters, respectively), yet this difference was not statistically significant ($P = 0.073$). Mean change in CMT did not differ between the 2 groups ($P = 0.620$). No statistically significant difference was found comparing the time to 15-letter improvement from baseline, time to 10-letter improvement from baseline, time to 10-letter reduction from baseline, time to 15-letter reduction from baseline, time to peak improvement in BCVA from baseline, time to peak improvement in CMT from baseline, number of injections, or duration in study. Further comparisons and details are described in Table 3. No significant anatomic differences emerged over time between treatment-naive and previously treated eyes (Fig 3); however, a lower amplitude of visual improvement was apparent in previously treated patients (Fig 4).

Early versus Late Diabetic Macular Edema (Duration <6 Months vs. ≥6 Months). The study included 196 injections given to 100 eyes of patients with early DME, 466 injections to 200 eyes of patients with late DME, and 100 injections to 39 patients with an unknown duration of DME. The mean baseline visual acuity was significantly lower for late DME patients compared with patients with an earlier onset of disease (65.0±12.6 ETDRS letters vs. 62.0±12.4 ETDRS letters, respectively; $P = 0.008$). There was a nonsignificant trend toward a higher proportion of 15-letter or more improvement in the early DME group (26.5% vs. 20.0%; $P = 0.06$), whereas the difference for 10-letter or more gain was significant (47.4% vs. 33.9%; $P = 0.001$). Significantly more eyes lost 10 ETDRS letters or more in the late DME group (13.4% vs. 8.2%; $P = 0.029$), and no difference was found in the percentage of injections resulting in a reduction of 15 ETDRS letters or more (5.6% vs. 7.1%; $P = 0.383$). Mean change in CMT after each injection was −151±171 µm versus −180±173 µm in the early and late DME patients, respectively ($P = 0.088$). Time from injection to peak improvement in CMT from baseline was slightly shorter in patients with late DME (76.5±34.8 days) than in patients with an early onset of disease (87.0±41.7 days; $P = 0.006$). Time to 15-letter improvement from baseline, time to 10-letter improvement from baseline, time to 10-letter reduction from baseline, time to 15-letter reduction from baseline, time to peak improvement in BCVA from baseline, baseline CMT, change in CMT from baseline, number of injections, and duration in study did not differ significantly between the groups (Table 4). There was no significant difference in CMT over time between early and late DME patients (Fig 5), with a similar delay in visual improvement as described previously (Fig 6), with the improvement in the late DME patients not as pronounced and maintained for a shorter time.

Controlled versus Uncontrolled Diabetes (Hemoglobin A1c <8 mg/100 vs. ≥8 mg/100). The study included 386 injections to 172 eyes of patients with controlled diabetes (HbA1c, ≤8%), 248

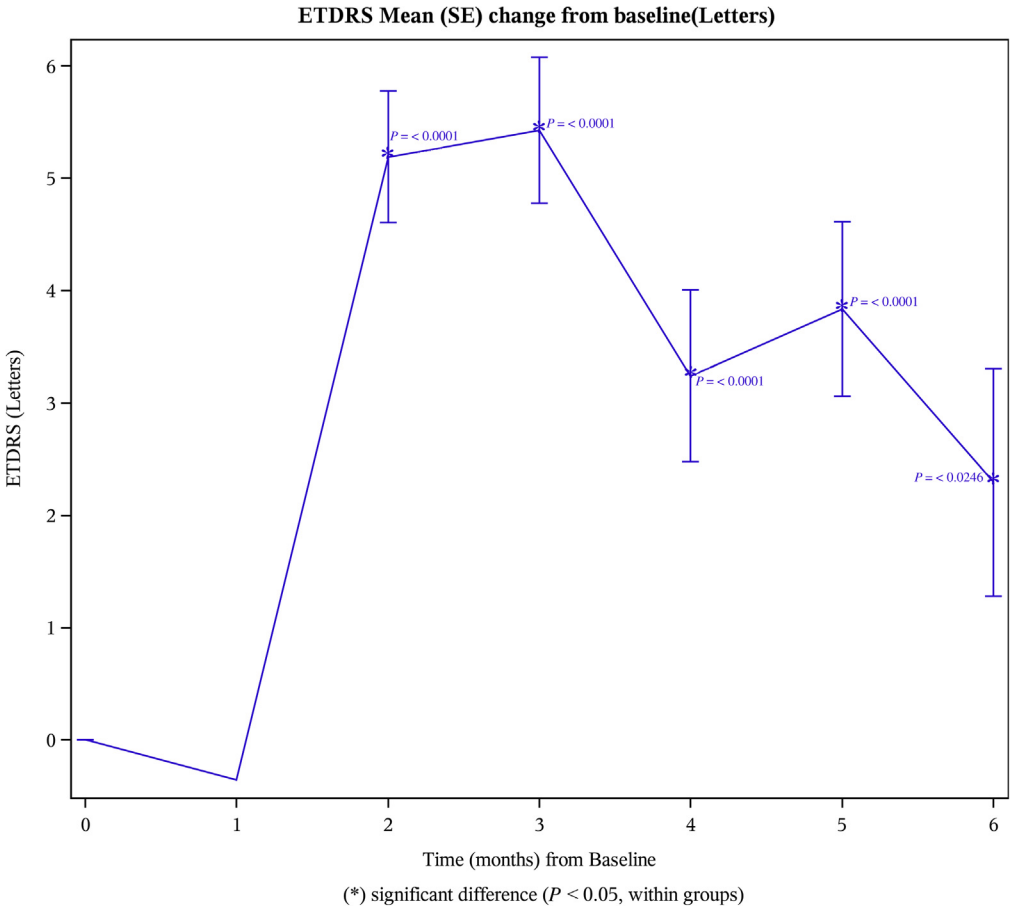

Figure 2. Graph showing functional changes after a dexamethasone implant injection, entire cohort (per-injection analysis). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

injections to 110 eyes of patients with uncontrolled diabetes (HbA1c, >8%), and 128 injections to 58 eyes of patients with an unknown HbA1c level. At baseline, a significantly better BCVA was found in the controlled disease group compared with the uncontrolled diabetes (63.6±12.1 ETDRS letters vs. 60.6±15.2 ETDRS letters, respectively; $P = 0.014$). The percentage of eyes with BCVA improvement of 15 or more ETDRS letters at the end of the dexamethasone intravitreal implant injection and the percentage of BCVA improvement of 10 or more ETDRS letters did not differ significantly (24.4% vs. 20.2% [$P = 0.219$] and 39.4% vs. 35.5% [$P = 0.324$], respectively). In contrast, the percentage of eyes experiencing a reduction in visual acuity after the dexamethasone intravitreal implant injection was significantly larger in patients with uncontrolled diabetes for both 10 ETDRS letters or more (16.1% vs. 10.1%; $P = 0.023$) and 15 ETDRS letters or more (10.5% vs. 5.7%; $P = 0.025$). The baseline CMT did not differ significantly between the groups ($P = 0.182$), yet there was a greater reduction in controlled disease patients (−190±178 μm vs. −135±145 μm; $P = 0.0002$). Time to 15-letter improvement from baseline, time to 10-letter improvement from baseline, time to 10-letter reduction from baseline, time to 15-letter reduction from baseline, time to peak improvement in BCVA from baseline, time to peak improvement in CMT from baseline, number of injections, and duration in study did not differ significantly between controlled and uncontrolled diabetes patients. Further comparisons and details are described in Table 5. No significant anatomic differences were evident over time between controlled and uncontrolled patients (Fig 7); however, a lower amplitude of visual improvement was evident in uncontrolled patients (Fig 8).

Per-*Series* Analysis

Entire Cohort. In this analysis, we reviewed 171 eyes of 150 patients meeting the defined criteria for an injection series who received a total of 444 injections with a mean of 2.60±1.0 injections per series (range, 2–8; Table 2). An improvement of 15 and 10 ETDRS letters occurred in 20.5% (n = 35) and 35.7% (n = 61), respectively, whereas 7.0% (n = 12) lost more than 15 ETDRS letters in BCVA, and 12.3% (n = 21) lost 10 ETDRS letters in BCVA. Mean change in CMT was −151±197 μm. The dynamic in BCVA (Fig S2, available at www.aaojournal.org) and CMT (Fig S3, available at www.aaojournal.org) seen in the per-injection analysis clearly is visible during the first 5 months; past this point, a smoothing effect attributed to the variable interval allowed between injections is apparent.

Treatment-Naive versus Previously Treated Patients. Of the 171 included in this analysis, 53 eyes had not been treated previously (i.e., were treatment naive), and 118 had been treated previously (Table S1A, available at www.aaojournal.org). At baseline, mean BCVA was significantly better in the treatment-naive eyes (59.4±13.2 ETDRS letters vs. 55.2±13.2 ETDRS letters;

Table 3. Summary by Diabetic Macular Edema Status for All Injections

	Overall (762 Injections; 340 Eyes)	Treatment Naïve (243 Injections; 340 119 Eyes	Previously Treated (519 Injections; 221 Eyes)	Odds Ratio (Mean Difference)	95% Confidence Interval	*P* Value*
Baseline BCVA (ETDRS letters), mean ± SD	61.9±13.5	66.8±11.3	59.6±13.9	7.1694	5.2281 to 9.1108	<0.0001
Injections with 15-letter BCVA improvement from baseline, no. (%)	173 (22.7)	70 (28.8)	103 (19.8)	0.6119	0.4305 to 0.8697	0.0059
Time to 15-letter improvement in BCVA from baseline (days), mean ± SD	81.3±39.2	77.7±36.0	83.8±41.3	−6.0241	−18.0195 to 5.9712	0.3229
Injections with 10-letter BCVA improvement from baseline, no. (%)	288 (37.8)	112 (46.1)	176 (33.9)	0.6002	0.4398 to 0.8190	0.0012
Time to 10-letter improvement in BCVA from baseline (days), mean ± SD	66.1±11.3	68.8±9.8	64.4±11.8	0.7240	−8.4596 to 9.9076	0.8768
Injections with 10-letter BCVA reduction from baseline, no. (%)	95 (12.5)	25 (10.3)	70 (13.5)	1.4171	0.8714 to 2.3046	0.1585
Time to 10-letter reduction in BCVA change from baseline (days), mean ± SD	96.6±44.3	91.0±42.1	98.6±45.1	−7.5600	−28.0868 to 12.9668	0.4664
Injections with 15-letter BCVA reduction from baseline at study end, no. (%)	58 (7.6)	18 (7.4)	40 (7.7)	1.0833	0.6067 to 1.9343	0.7868
Time to 15-letter reduction in BCVA change from baseline, mean ± SD	96.5±45.3	92.4±46.8	98.3±45.1	−5.9361	−31.8891 to 20.0169	0.6486
Change in BCVA from baseline (ETDRS letters), mean ± SD	6.8±11.1	8.1±12.5	6.2±10.4	1.8948	−0.1745 to 3.9640	0.0726
Time to peak improvement in BCVA from baseline (days)	81.9±39.7	82.8±40.1	81.5±39.6	1.2213	−5.6768 to 8.1194	0.7282
Baseline CMT (μm), mean ± SD	498±139	479±128	508±144	−28.7211	−63.0974 to 5.6553	0.1012
Change in CMT from baseline at study end (μm), mean ± SD	−174±171	−157±180	−182±167	25.8578	−4.2757 to 55.9913	0.0925
Time to peak improvement in CMT from baseline (days), mean ± SD	79.6±38.1	83.1±39.2	78.1±37.5	5.3053	−1.3418 to 11.9523	0.1175
No. of injections, mean ± SD	2.1±1.2	2.1 ± 1.1	2.2 ± 1.2	−0.1004	−0.2831 to 0.0824	0.2813
Duration (yrs) in study, mean ± SD	1.8±0.8	1.9 ± 0.9	1.8 ± 0.8	0.1469	−0.0624 to 0.3562	0.1681

BCVA = best-corrected visual acuity; CMT = central macular thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
**t* test or chi-square test for association.

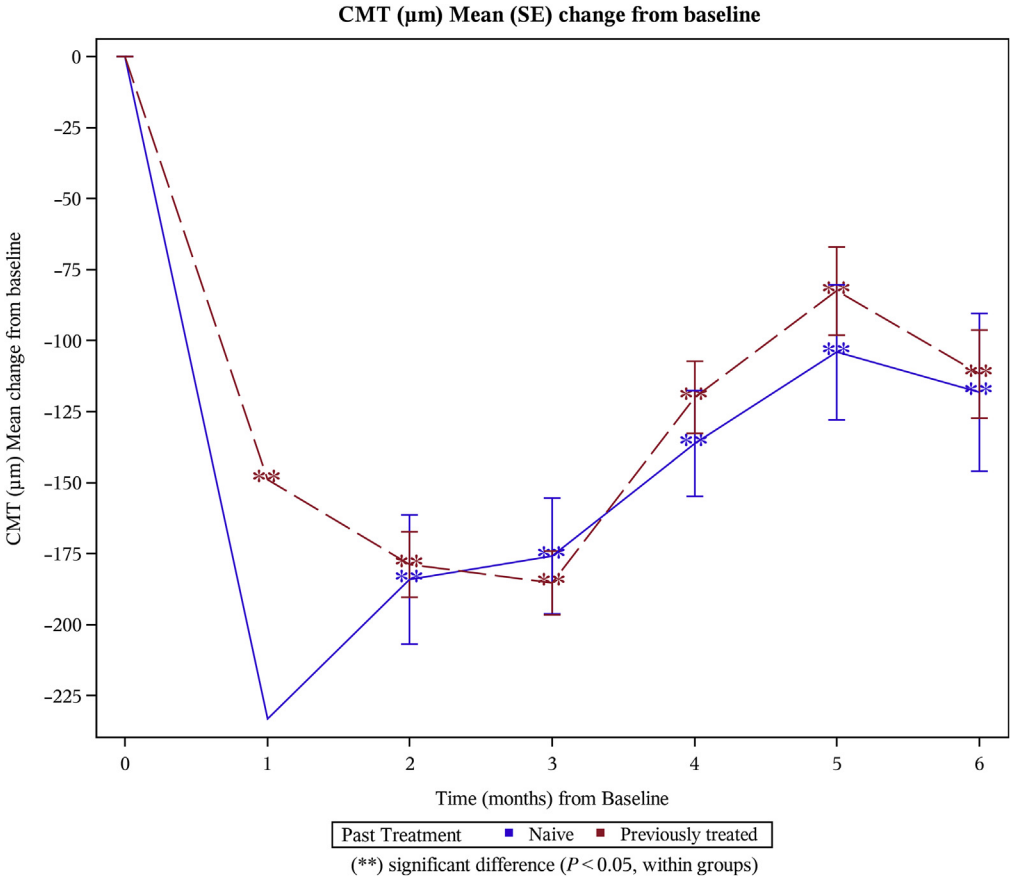

Figure 3. Graph showing anatomic changes after a dexamethasone implant injection, stratified by treatment status (per-injection analysis). CMT = central macular thickness; SE = standard error.

$P = 0.026$), and baseline CMT was similar ($P = 0.570$). At the end of an injection series, the treatment-naïve eyes showed a significantly greater percentage with BCVA improvement of 15 ETDRS letters or more (34.0% vs. 14.4%, respectively; $P = 0.003$) and 10 ETDRS letters or more (49.1% vs. 29.7%, respectively; $P = 0.003$), as well as mean change in BCVA (8.5±11.9 vs. 3.5±12.4, respectively; $P = 0.017$). Statistically significant differences also were found in the time to 15-letter improvement from baseline (293±92.4 days vs. 451±242 days, respectively; $P = 0.012$), time to 10-letter improvement from baseline (304±96 days vs. 415±211 days, respectively; $P = 0.004$), and time to peak change in BCVA (320±104 days vs. 363±163 days, respectively; $P = 0.044$). The mean change in CMT did not differ between the 2 groups ($P = 0.620$. Similarly, no statistically significant difference was found in the time to 10-letter reduction from baseline, time to 15-letter reduction from baseline, baseline CMT, number of injections, or duration in study.

Early versus Late Diabetic Macular Edema (Duration <6 Months vs. ≥6 Months). The study included 40 patients with early DME, 114 eyes with late DME, and 17 eyes with an unknown duration of DME. Baseline mean BCVA was similar in both eyes with early and late DME (58.6±14.0 ETDRS letters vs. 57.1±12.1 ETDRS letters, respectively; $P = 0.470$). Significantly fewer early DME eyes showed a reduction of 15 ETDRS letters (0% vs. 8.8%, respectively). No significant difference was evident in early versus later DME in terms of percentage of eyes with improvement of 15 ETDRS letters (27.5% vs. 17.5%, respectively; $P = 0.177$), of 10 ETDRS letters (47.5% vs. 31.6%, respectively; $P = 0.07$), or reduction of 15 ETDRS letters and reduction of 10 ETDRS letters (4.7% vs. 13.9%, respectively; $P = 0.09$). Mean change in CMT was −182±196 µm versus −144±204 µm in the early and late DME patients, respectively ($P = 0.354$). Time to 15-letter improvement from baseline, time to 10-letter improvement from baseline, time to 10-letter reduction from baseline, eyes with 15-letter reduction from baseline, time to 15-letter reduction from baseline, time to peak improvement in BCVA from baseline, baseline CMT, change in CMT from baseline, time to peak improvement in CMT from baseline, number of injections, and duration in study did not differ significantly between the groups. Further comparisons and details are described in Table S1B (available at www.aaojournal.org).

Controlled versus Uncontrolled Diabetes (Hemoglobin A1c <8 mg/100 vs. ≥8 mg/100). The study included 93 eyes of patients with controlled diabetes (HbA1c, ≤8%), 49 with eyes of patients with uncontrolled diabetes (HbA1c, >8%), and 29 eyes of patients with an unknown HbA1c level. At baseline, BCVA did not defer significantly between the controlled and uncontrolled disease groups ($P = 0.500$). No significant difference was found in percentage of eyes with 15-letter or more improvement (20.4% vs. 20.4%, respectively; $P = 0.997$), 10-letter or more improvement (34.4% vs. 32.7%, respectively; $P = 0.833$), reduction of 15

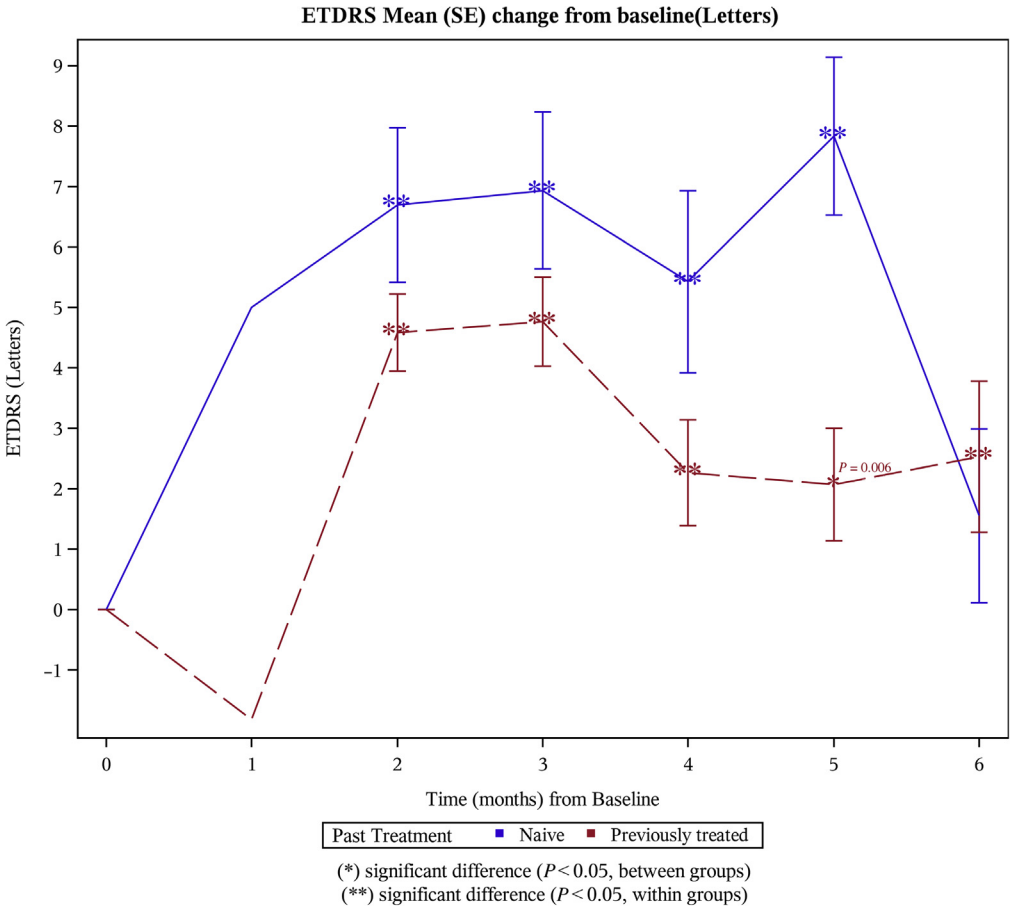

Figure 4. Graph showing functional changes after a dexamethasone implant injection, stratified by treatment status (per-injection analysis). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

ETDRS letters ($P = 0.607$), and reduction of 10 ETDRS letters ($P = 0.803$). Baseline CMT was significantly thicker in the controlled disease group (549±151 μm vs. 491±167 μm; $P = 0.01$), and the respective mean change in CMT was similar (−168±215 μm vs. -110±171 μm; $P = 0.132$). Time to 15-letter improvement from baseline, time to 10-letter improvement from baseline, time to 10-letter reduction from baseline, time to 15-letter reduction from baseline, time to peak improvement in BCVA from baseline, time to peak improvement in CMT from baseline, number of injections, and duration in study did not differ significantly between controlled and uncontrolled diabetes patients. Further comparisons and details are described in Table S1C (available at www.aaojournal.org).

Rescue Therapy

Our study permitted rescue therapy to be given at the physician's discretion. In the per-injection analysis, rescue therapy was given within 6 months of follow-up in 61 (8.0%) of the 762 injections. This treatment was administered, on average, 83.9±39.4 days after the dexamethasone intravitreal implant injection. No eye received more than 1 rescue treatment within the 6 months after an injection. In the injection series analysis, of 171 eyes, 32 (18.7%) received rescue therapy at 1 or more points throughout the entire series, with an overall of 44 treatments administered. This treatment was administered on average 86.8±44.5 days after the dexamethasone intravitreal implant injection. Further description of the different rescue treatments given is presented in Table S2 (available at www.aaojournal.org).

Safety Outcomes

Throughout the study, no cases of endophthalmitis or retinal detachment were reported, and the percentage of IOP-related AE was relatively low, with 52 injections (6.8%) resulting in an increase of IOP of more than 10 mmHg and 7 injections (0.9%) resulting in a final IOP of more than 35 mmHg. No serious AEs were reported (Table 6).

Discussion

In this large, multicenter, real-life study, multiple anatomic and functional parameters measuring the efficacy of dexamethasone implant in 2 different perspectives were assessed. The response to each injection was assessed, and pharmacodynamics, efficacy, and safety were analyzed. In addition, the final outcome after a series of injections was assessed in a similar fashion to that in the pivotal MEAD trial.[16] However, rather than limiting the interval to a strict 6-month period, all intervals ranging from 3 to 6 months were included. The

Table 4. Summary by Diabetic Macular Edema Duration for All Injections

	Overall (762 Injections; 340 Eyes)	<6 Months (196 Injections; 100 Eyes)	≥6 Months (201 Injections; 466 Eyes)	Unknown (100 Injections; 39 Eyes)	Odds Ratio (Mean Difference)	95% Confidence Interval	P Value*
Baseline BCVA (ETDRS letters), mean ± SD	61.9±13.5	65.0±12.6	62.0±12.4	55.1±17.6	2.9519	0.7798 to 5.1240	0.0078
Injections with 15-letter BCVA improvement from baseline, no. (%)	173 (22.7)	52 (26.5)	93 (20.0)	28 (28.0)	0.6905	0.4674 to 1.0199	0.0619
Time to 15-letter improvement in BCVA from baseline (days), mean ± SD	81.3±39.2	86.8±38.0	79.2±38.6	78.4±43.8	7.5780	−5.5629 to 20.7188	0.2562
Injections with 10-letter BCVA improvement from baseline, no. (%)	288 (37.8)	93 (47.4)	158 (33.9)	37 (37.0)	0.5681	0.4045 to 0.7980	0.0010
Time to 10-letter improvement in BCVA from baseline (days), mean ± SD	79.9±38.5	84.1±37.2	77.9±38.6	78.0±41.6	6.2366	−3.5703 to 16.0436	0.2116
Injections with 10-letter BCVA reduction from baseline, no. (%)	95 (12.5)	16 (8.2)	63 (13.5)	16 (16.0)	1.8878	1.0596 to 3.3634	0.0289
Time to 10-letter reduction in BCVA change from baseline (days), letters, mean ± SD	96.6±44.3	88.1±47.5	101±43.2	89.1±45.9	−12.5575	−37.1090 to 11.9940	0.3116
Injections with 15-letter BCVA reduction from baseline at study end, no. (%)	58 (7.6)	11 (5.6)	33 (7.1)	14 (14.0)	1.3671	0.6756 to 2.7661	0.3829
Time to 15-letter reduction in BCVA change from baseline (days), letters, mean ± SD	96.5±45.3	83.9±53.0	104±41.5	87.7±47.2	−20.4848	−51.7798 to 10.8101	0.1937
Change in BCVA from baseline (ETDRS letters), mean ± SD	6.8±11.1	7.4±11.1	6.6±11.0	6.7±11.7	0.8265	−1.2664 to 2.9194	0.4382
Time to peak improvement in BCVA from baseline (ETDRS letters), mean ± SD	81.9±39.7	85.1±40.7	80.9±38.7	80.4±42.5	4.2340	−3.1974 to 11.6653	0.2635
Baseline CMT (μm), mean ± SD	498±139	494±147	502±141	490±116	−8.6163	−46.6244 to 29.3917	0.6556
Change in CMT from baseline at study end (μm), mean ± SD	−174±171	−151±171	−180±173	−193±158	29.0965	−4.4305 to 62.6235	0.0888
Time to peak improvement in CMT from baseline (days), mean ± SD	79.6±38.1	87.0±41.7	76.5±34.8	79.9±43.8	10.5026	2.9670−18.0382	0.0065
No. of injections, mean ± SD	2.1±1.2	2.1±1.3	2.1±1.2	2.1±1.1	−0.0213	−0.2247 to 0.1820	0.8369
Duration (yrs) in study, mean ± SD	1.8±0.8	1.9±0.8	1.7±0.8	2.0±0.9	0.1469	−0.0624 to 0.3562	0.1681

BCVA = best-corrected visual acuity; CMT = central macular thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
*t Test or chi-square test for association, <6 months vs. ≥6 months.

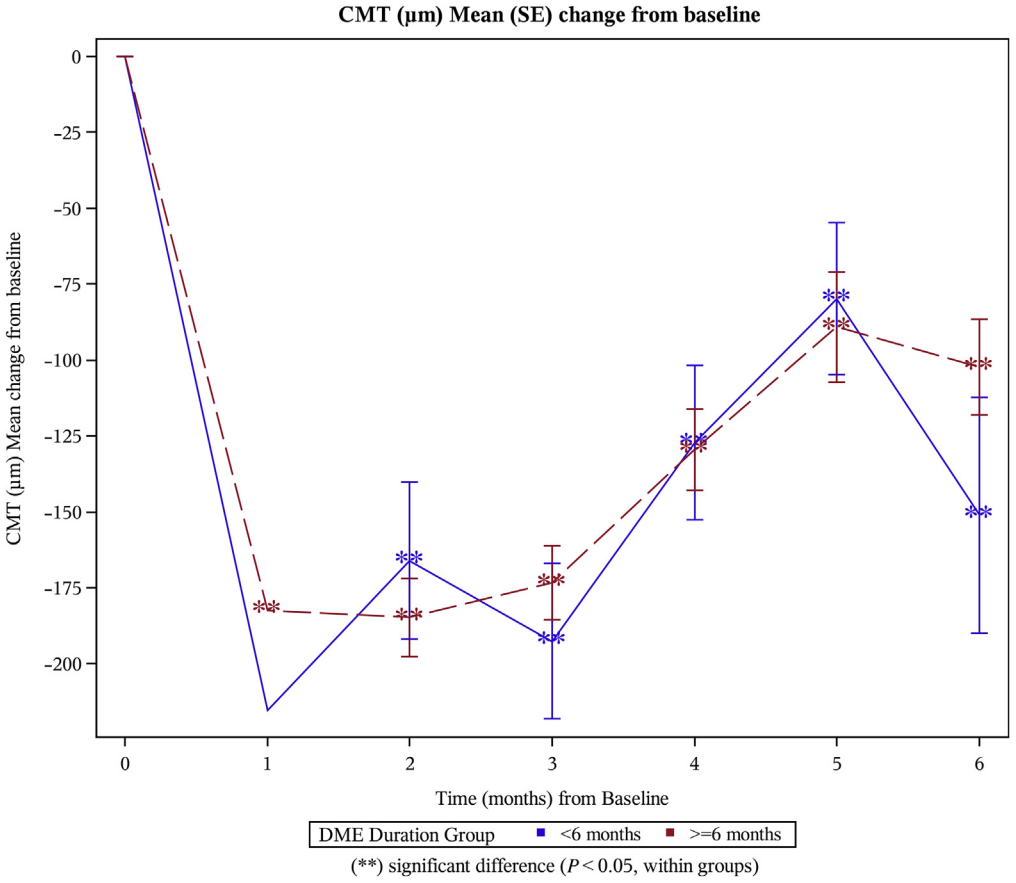

Figure 5. Graph showing anatomic changes after a dexamethasone implant injection, stratified by diabetic macular edema (DME) duration (per-injection analysis). CMT = central macular thickness; SE = standard error.

outcome was compared within the entire cohort and between treatment-naive and previously treated eyes, patients with early and late duration of DME, and patients with controlled and uncontrolled diabetes. To the best of our knowledge, this is one of the largest and more comprehensive real-life study assessing the efficacy of the dexamethasone intravitreal implant in a defined injection series setting across multiple subgroups and the only study applying the per-injection analysis to understand better the pharmacodynamics of the dexamethasone intravitreal implant.

This study showed that one quarter of injections in the per-injection analysis and one fifth of the injection series resulted in BCVA improvement of 15 ETDRS letters or more. More than one third of the injections in both the per-injection analysis and in the injection series analysis resulted in BCVA improvement of 10 ETDRS letters or more. The similar outcome of the per-injection and the injection series analysis highlights the repeatability of the dexamethasone intravitreal implant effect.

These results are in concordance with the MEAD 3-year results,[16] in which 22.2% of patients in the dexamethasone intravitreal implant 0.7-mg group gained 15 ETDRS letters or more. Other real-life postmarketing studies evaluating the outcome of an injection series demonstrated variable results with 15-letter gains occurring in 14% to 36% of patients.[24–27] This may be attributed to the variability in the definition of both the outcomes and the actual series. Unlike the current study, in which the interval between injections was set to 3 to 6 months, most real-life studies did not limit the interval between injections, with reported treatment intervals ranging up to 23 months.[17,24,26,28] Thus, the actual effect of the drug may be hindered by additional rescue treatments and the cumulative effect potentially lost, in turn rendering the definition of a series somewhat obsolete. Looking at the treatment effect over time within an injection series, this study demonstrated a pendular effect profile of improvement and deterioration in both visual acuity and anatomic outcome. This was expected and demonstrated previously in the MEAD trials.[16] The MEAD study protocol dictated a dexamethasone injection every 6 months with 3 months between observations. This may have hindered the ability to characterize the pendular effect accurately and to evaluate the time frame of the drugs' effectiveness. In a real-life setting, this effect also is difficult to characterize because of the variable interval between injections, hence, the significance of applying the per-injection analysis implemented in this study, which allowed better understanding of the effect after each injection, regardless of previous or subsequent injections, overlapping treatment intervals, or both. The per-injection

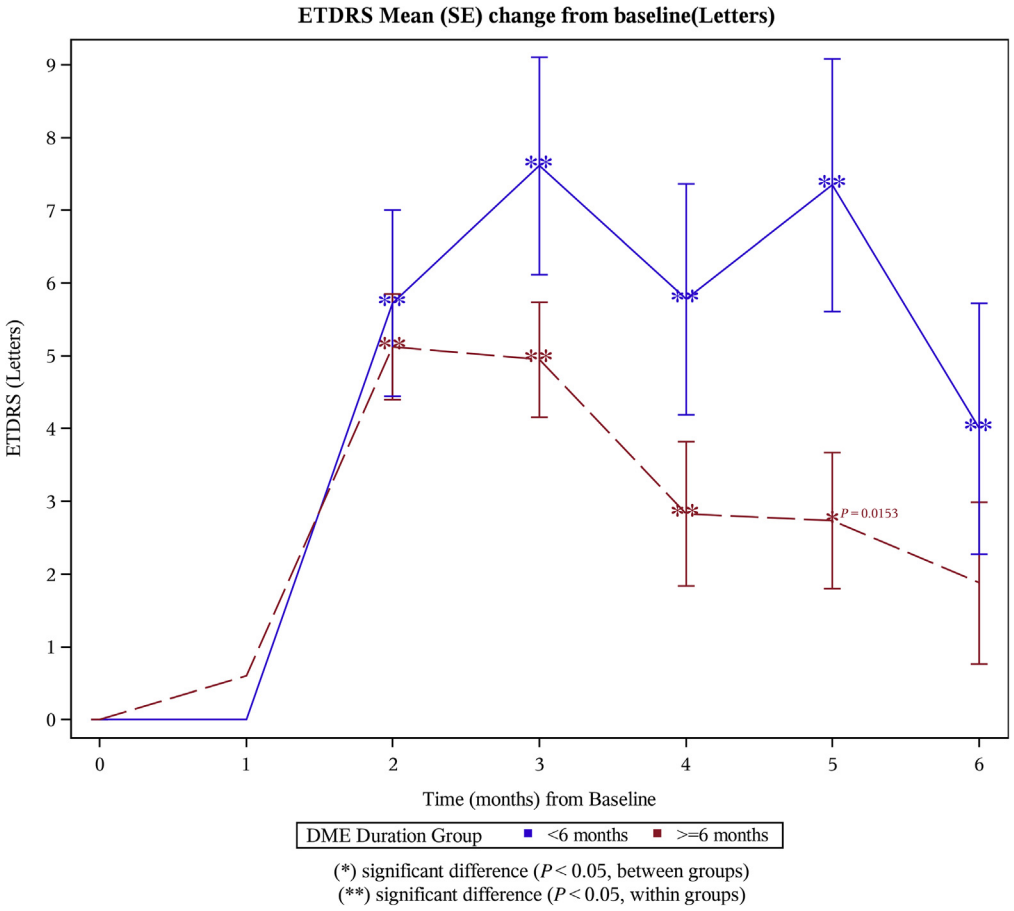

Figure 6. Graph showing functional changes after a dexamethasone implant injection, stratified by diabetic macular edema (DME) duration (per-injection analysis). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

analysis demonstrated a rapid anatomic improvement that was sustained until achieving a maximum effect 3 months after injection. Thereafter, the effect deteriorated but did not return to baseline. Change in visual acuity followed similar dynamics but lagged after the anatomic improvement. The PLACID,[29] Mozart,[30] and a few small real-life studies[17,31,32] analyzed the outcome of a single dexamethasone injection and demonstrated similar pendular characteristics with some lingering effect. Furthermore, it is interesting to note the similarities of the single-injection trial results with the per-injection analysis of the present study, validating this analysis and re-emphasizing the repeatability of the dexamethasone intravitreal implant effect. Therefore, contrary to trials advocating for reinjection of the dexamethasone intravitreal implant with 6-month intervals, it is safe to conclude that shorter treatment intervals are reasonable.

Throughout the current study, the percentage of patients experiencing BCVA deterioration was relatively small.[16,32] Safety-related outcomes and percentage of IOP-related AEs were lower than in the MEAD trial, with no endophthalmitis reported. Although the relatively small percentage of patients with elevated IOP is not surprising, the nature of this retrospective real-life study design always warrants some considerations as to the potential presence of report bias, mainly because real-life medical files may lack the detailed and strict follow-up of a randomized control trial.

In the current study, both treatment-naive and previously treated eyes showed a significant anatomic response and significant visual acuity improvement, as reported in the subgroup analysis of the MEAD trial.[33] Improvement was more pronounced in treatment-naive eyes compared with previously treated eyes. These results are in concordance with several other real-life studies,[26,28,32–34] indicating a more favorable visual outcome in treatment-naive compared with previously treated eyes. Iglicki et al[28] associated previously treated patients with longer and more refractory edema and consequently, a disruption in the inner segment–outer segment layer. Because this assumption seems valid, the analysis of these anatomic changes was not within the scope of this study. However, the present study did examine the difference between early and late DME, and in this analysis, both groups showed good functional and anatomic outcomes, and the differences between groups were even more pronounced than the differences between treatment-naive and previously treated patients. All visual outcomes were worse in eyes with longstanding DME, thus making the duration of DME an important predictor for

Table 5. Summary by Hemoglobin A1c Level for All Injections

	Overall (762 Injections; 340 Eyes)	Controlled Diabetes Mellitus (Hemoglobin A1c ≤8%; 386 Injections; 172 Eyes)	Noncontrolled Diabetes Mellitus (Hemoglobin A1c >8%; 248 Injections; 110 Eyes)	Missing Hemoglobin A1c Level (128 Injections; 58 Eyes)	Odds Ratio (Mean Difference)	95% Confidence Interval	*P* Value*
Baseline BCVA (ETDRS letters), mean ± SD	61.9±13.5	63.6±12.1	60.6±15.2	59.1±13.5	2.9436	0.5978 to 5.2894	0.0140
Injections with 15-letter BCVA improvement from baseline, no. (%)	173 (22.7)	94 (24.4)	50 (20.2)	29 (22.7)	0.7844	0.5324 to 1.1559	0.2190
Time to 15-letter improvement in BCVA from baseline (days), mean ± SD	81.3±39.2	77.0±36.1	86.5±43.1	86.3±41.7	−9.5187	−22.8918 to 3.8543	0.1616
Injections with 10-letter BCVA improvement from baseline, no. (%)	288 (37.8)	152 (39.4)	88 (35.5)	48 (37.5)	0.8467	0.6083 to 1.1786	0.3238
Time to 10-letter improvement in BCVA from baseline (days), mean ± SD	79.9±38.5	76.5±36.5	85.2±41.6	81.2±38.8	−8.7016	−18.8381 to 1.4349	0.0921
Injections with 10-letter BCVA reduction from baseline, no. (%)	95 (12.5)	39 (10.1)	40 (16.1)	16 (12.5)	1.7254	1.0721 to 2.7769	0.0235
Time to 10-letter reduction in BCVA change from baseline (days), letters, mean ± SD	96.6±44.3	95.8±41.2	95.1±44.0	102±53.8	0.6699	−18.4368 to 19.7766	0.9445
Injections with 15-letter BCVA reduction from baseline at study end, no. (%)	58 (7.6)	22 (5.7)	26 (10.5)	10 (7.8)	1.9506	1.0774 to 3.5313	0.0252
Time to 15-letter reduction in BCVA change from baseline (days), letters, mean ± SD	96.5±45.3	100±43.3	92.8±45.6	97.7±52.7	7.5490	−18.4406 to 33.5385	0.5616
Change in BCVA from baseline (ETDRS letters), mean ± SD	6.8±11.1	7.5±11.4	5.8±11.0	6.7±10.4	1.7119	−0.3330 to 3.7567	0.1006
Time to peak improvement in BCVA from baseline (days), mean ± SD	81.9±39.7	79.3±38.2	84.9±40.3	84.5±43.2	−5.5117	−12.5826 to 1.5593	0.1263
Baseline CMT (μm), mean ± SD	498±139	502±148	478±118	526±145	23.3925	−11.0365 to 57.8215	0.1819
Change in CMT from baseline at study end (μm), mean ± SD	−174±171	−190±178	−135±145	−204±183	−54.9981	−84.1418 to −25.8544	0.0002
Time to peak improvement in CMT from baseline (days), mean ± SD	79.6±38.1	79.9±37.7	79.7±37.9	78.3±39.8	0.2500	−6.5284 to 7.0285	0.9423
No. of injections, mean ± SD	2.1±1.2	2.1±1.2	2.2±1.3	2.2±1.2	−0.0890	−0.2801 to 0.1020	0.3605
Duration (yrs) in study, mean ± SD	1.8±0.8	1.8±0.8	1.9±0.9	1.7±0.8	0.1469	−0.0624 to 0.3562	0.1681

BCVA = best–corrected visual acuity; CMT = central macular thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
**t* test or chi-square test for association, controlled vs. noncontrolled disease.

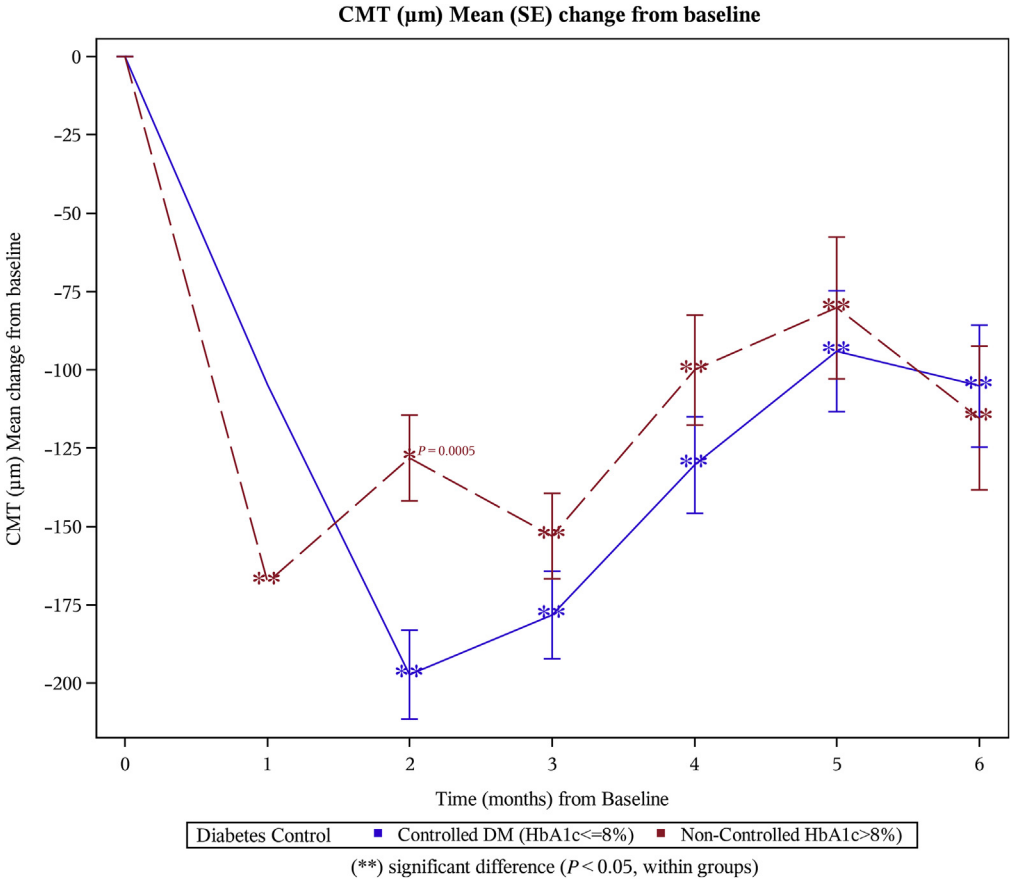

Figure 7. Graph showing anatomic changes after a dexamethasone implant injection, stratified by diabetic control (per-injection analysis). CMT = central macular thickness; DM = diabetes mellitus; HbA1c = hemoglobin A1c; SE = standard error.

visual outcomes. A subgroup analysis of the MEAD study published by Augustin et al[33] concluded that the dexamethasone intravitreal implant significantly improves visual and anatomic outcomes in patients who previously received intravitreal anti-VEGF or triamcinolone injections or laser treatment. Our study adds new data and emphasizes that results may be even better in early DME (of less than 6 months' duration) in both treatment-naive and previously treated eyes. Cunha-Vaz et al[35] showed the long-term benefit of sustained-delivery fluocinolone acetonide implants in patients with chronic DME (≥3 years), which was explained by the multifactorial pharmacologic profile of the drug. We hypothesize that the difference between the studies' results may be that a chronic prolonged DME may respond better to a low continuous dose of fluocinolone, whereas early DME may benefit from an ad hoc dosing.

Uncontrolled diabetes was defined in the current study similarly to how it was defined in the MEAD trial, as HbA1c of more than 8 mg/100, and these patients showed both worse baseline BCVA and a higher risk of losing visual acuity, but no difference was found in the percentage of patients gaining visual acuity or in anatomic outcomes. We hypothesize that this indicates that the dexamethasone intravitreal implant is efficient for all patients regardless of systemic diabetic control and that both initial and final lower BCVA may be associated with diabetes complications such as vitreous hemorrhage or recurrent DME, which are more common in uncontrolled diabetes.[36,37]

Our study was not without limitations, which derive mainly from its real-life retrospective multicenter aspect. As such, patients varied widely with different baseline characteristics and different ocular histories, contrary to randomized control trails. Visual acuity was extrapolated from Snellen VA to EDTRS letters; thus, mean letter gains and losses may not be as accurate as in clinical trials in which VA is measured in EDTRS letters initially. Additionally, our study applied certain exclusion criteria regarding glaucoma patients, as such allowing IOP elevation to be higher in a cohort that did not strictly exclude eyes with glaucoma or ocular hypertension.

Additionally, some patients with serious AEs and perhaps AEs may be unintentionally underrepresented in the injection series analysis because of discontinuation of sequential injections. However, the evaluation of serious AEs and AEs of these patients are represented in the per-injection analysis. Furthermore, unlike randomized control trials and single-injection studies, patients included in our study were treated in different centers with different follow-up schedules and different treatment strategies, giving a

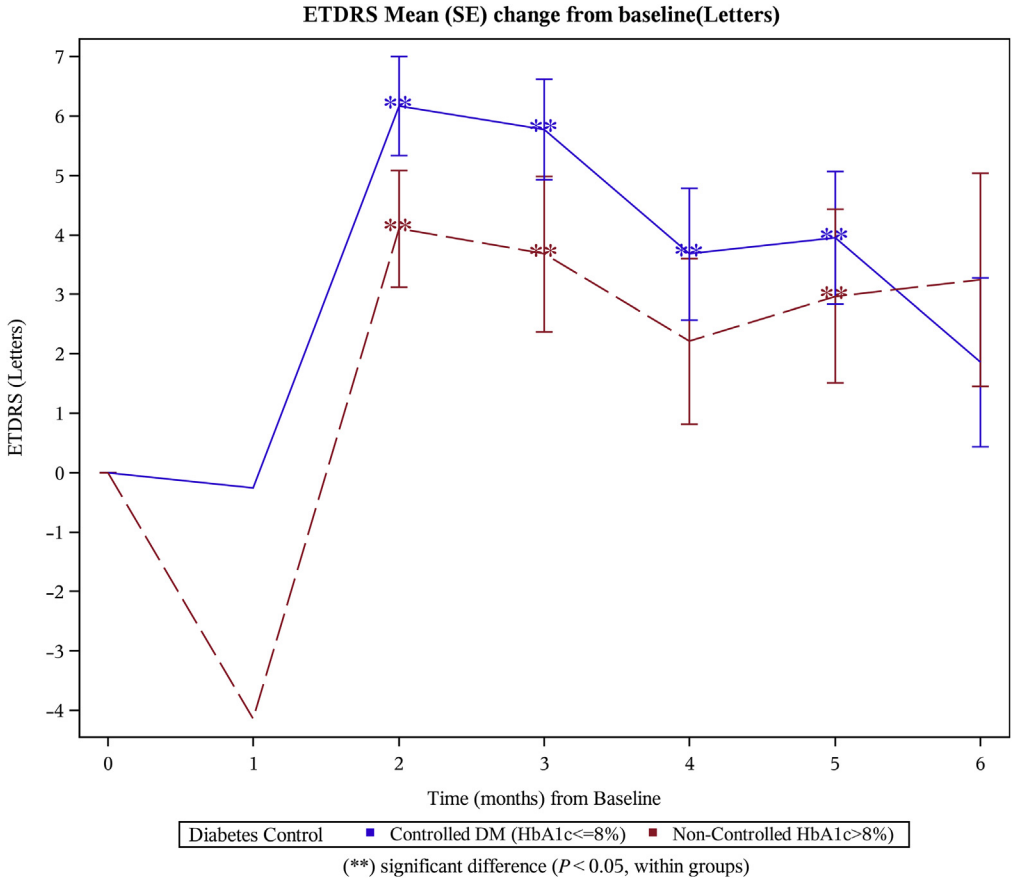

Figure 8. Graph showing functional changes after a dexamethasone implant injection, stratified by diabetic control (per-injection analysis). DM = diabetes mellitus; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = hemoglobin A1c; SE = standard error.

Table 6. Adverse Events

No. of Treatments	Injection Series Analysis (444 Injections; 171 Eyes)	All Injections (762 Injections; 340 Eyes)
IOP (mmHg)		
≥25	5 (2.9)	60 (7.9)
≥35	1 (0.6)	7 (0.9)
Increase of 10 mmHg from baseline	2 (1.2)	52 (6.8)
Use of IOP-lowering medication	28 (6.3)	48 (6.3)
Cataract*	32 (18.7)	44 (12.9)
Cataract operation*	31 (18.1)	42 (12.4)
Vitreous hemorrhage	3 (0.6)	3 (0.4)
Retinal detachments	0 (0)	0 (0)
Endophthalmitis	0 (0)	0 (0)
Other related adverse events	76 (17.1)	112 (14.7)

IOP = intraocular pressure.
Data are no. (%).
*Percentage is per eye, not per injection. All other percentages based on the number of injections.

more heterogenic population. Thus, some results could be masked by relatively large heterogenicity between patients, as seen in the injection series analysis, and the potential exists for the presence of unaccounted-for biases. Finally, anatomic outcome was limited to CMT, with no further analysis of the OCT images. Nevertheless, in this large, international multicenter real-life study, the intravitreal dexamethasone implant proved to be effective and safe in treatment-naive and previously treated eyes, eyes with early and late DME, and patients with controlled and uncontrolled diabetes. Peak improvement was achieved approximately 3 months after injection in all groups and dissipated thereafter.

In conclusion, our study demonstrates the benefit of dexamethasone intravitreal implant treatment in various subgroups of patients with DME with a relatively low incidence of AEs, including IOP elevation and cataract formation. It is our belief that the dexamethasone implant may be considered as a viable treatment option for a wide array of DME patients. Clinicians and providers should consider shortening treatment intervals or as-needed treatment regimens to maintain and maximize a beneficial clinical effect.

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Abbreviations and Acronyms:
AE = adverse events; **ARTES** = **A** Collaborative **R**etrospective s**T**udy on the **E**fficacy and **S**afety of intravitreal dexamethasone implant; **BCVA** = best-corrected visual acuity; **CMT** = central macular thickness; **DME** = diabetic macular edema; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HbA1c** = hemoglobin A1c; **ICH** = International Council for Harmonisation; **IOP** = intraocular pressure; **MEAD** = Macular Edema Assessment of Implantable Dexamethasone in Diabetes study; **EGF** = vascular endothelial growth factor.

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