

# Topical Dexamethasone-Cyclodextrin Microparticle Eye Drops for Diabetic Macular Edema

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**PURPOSE.** To test the safety and efficacy of topical 1.5% dexamethasone aqueous eye drops with cyclodextrin microparticles for diabetic macular edema (DME).

**METHODS.** Nineteen eyes of 19 consecutive patients with DME were administered dexamethasone-cyclodextrin eye drops three or six times a day for 4 weeks and then observed for 4 weeks without treatment. Visual acuity, intraocular pressure, and spectral domain optical coherent tomography-measured central macular thickness recordings at weeks 0 (baseline), 4, and 8. These parameters were compared using Bonferroni-corrected paired *t*-tests.

**RESULTS.** At weeks 0, 4, and 8, logMAR visual acuity (mean  $\pm$  SD) was  $0.52 \pm 0.41$ ,  $0.37 \pm 0.40$  ( $P = 0.0025$  vs. baseline), and  $0.45 \pm 0.41$ , respectively; central macular thickness ( $\mu\text{m}$ ) was  $512 \pm 164$ ,  $399 \pm 154$  ( $P = 0.0016$  vs. baseline), and  $488 \pm 172$  ( $P = 0.0116$  versus week 4), respectively; and intraocular pressure (mm Hg) was  $15.2 \pm 3.1$ ,  $17.4 \pm 4.2$  ( $P = 0.0015$  vs. baseline) and  $15.8 \pm 4.0$ , respectively. At week 4, in 12 (63%) of 19 eyes, central macular thickness had decreased more than 10%, and the mean change was  $-20\%$  ( $-65\%$  to  $+10\%$ ). In 14 of 19 eyes (74%) visual acuity (logMAR) had improved more than 0.1 at week 4. No subjects showed severe adverse effects related to the eye drops.

**CONCLUSIONS.** Based on this short pilot study, topical dexamethasone-cyclodextrin eye drops are well tolerated, decrease central macular thickness, and improve visual acuity in DME. The results encourage comparative studies between dexamethasone cyclodextrin microparticle eye drops and other treatments for DME. (<http://www.umin.ac.jp/ctr> number, UMIN000001790.) (*Invest Ophthalmol Vis Sci.* 2011;52:7944–7948) DOI:10.1167/iovs.11.8178

Drugs play an ever-increasing role in the treatment of diabetic macular edema (DME) in addition to retinal photocoagulation. To reach the retina, corticosteroids and/or vascular endothelial growth factor antibodies must be injected into the vitreous cavity, or slow-release drug capsules must be surgically implanted into the eye.<sup>1–5</sup> Intravitreal injections and

intravitreal implantation are a surgical approach in drug delivery, and therefore run the risk of surgical complications, including infection, hemorrhages, and cataract and increased burden on eye care resources. A noninvasive drug-delivery platform would circumvent most of these problems.

We have developed a drug-delivery platform for ocular pharmacology. It is based on cyclodextrin microparticles that dissolve in the tear fluid to form water-soluble drug/cyclodextrin complex microparticles.<sup>6</sup> Microparticulate 1.5% (wt/vol) dexamethasone/ $\gamma$ -cyclodextrin eye drops have been shown to effectively deliver the drug to the retina and vitreous humor in rabbits.<sup>7–10</sup> Other cyclodextrin-based dexamethasone eye drop solutions have been tested in patients and shown excellent penetration into the anterior segment of the eye.<sup>11,12</sup>

Our earlier pharmacology studies in rabbits and humans suggested that the cyclodextrin microparticle dexamethasone eye drops may reach the human retina and thus be therapeutically effective for retinal disease such as DME. We therefore embarked on the first clinical trial of dexamethasone eye drops for topical treatment of DME.

## SUBJECTS AND METHODS

The institutional review board of Shimane University Hospital approved this prospective pilot study for topical dexamethasone-cyclodextrin microparticle eye drops for treatment of DME. All subjects signed an informed consent form that complied with the tenets of the Declaration of Helsinki. The study protocol was registered on the University Hospital Medical Information Network (UMIN) Clinical Trials Registry before the start of the study. Consecutive patients with DME were recruited for the study at Shimane University Hospital. The study eyes were required to have all the following inclusion criteria: (1) a previous diagnosis of diabetes and diabetic retinopathy, (2) best corrected visual acuity (BCVA) between 0.05 and 2.0 in logMAR (minimal angle of resolution), (3) definite retinal thickening resulting from DME based on clinical examination, (4) optical coherence tomography (OCT) central subfield thickness of 250  $\mu\text{m}$  or more, (5) no evidence of vitreomacular traction as the cause of DME, (6) intraocular pressure (IOP) of 21 mm Hg or less and no history of steroid glaucoma, (7) no history of retinopathy other than diabetic retinopathy, (8) absence of extra- and intraocular infections, (9) absence of hazy ocular media that obviously affects fundus examination and OCT measurement, and (10) no history of any intraocular surgery, laser therapy, intravitreal and periocular injections within the prior 3 months. If both eyes were eligible, the eye with greater central macular thickness (CMT) was used for the study.

## Preparation of Dexamethasone-Cyclodextrin Microparticle Eye Drops

The aqueous dexamethasone eye drop microsuspension was prepared by suspending 1.50 g dexamethasone and 14 g  $\gamma$ -cyclodextrin in 100 mL of an aqueous solution containing benzalkonium chloride (20 mg),

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Submitted for publication July 7, 2011; revised August 20, 2011; accepted August 24, 2011.

Disclosure: M. Tanito, None; K. Hara, None; Y. Takai, None; Y. Matsuoka, None; N. Nishimura, None; P. Jansook, Oculis ehf (E); T. Loftsson, Oculis ehf (I), P; E. Stefánsson, Oculis ehf (I), P; A. Ohira, None

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EDTA (100 mg), poloxamer 407 (2.5 g), and sodium chloride (570 mg). The suspension formed was heated in a sealed container in an autoclave (121°C for 20 minutes) and then allowed to cool to room temperature under constant agitation. The eye drops were analyzed as previously described.<sup>7,13</sup>

The amount of dissolved dexamethasone, as free dexamethasone or dexamethasone/ $\gamma$ -cyclodextrin microparticles, in the eye drop suspension was 2.3 mg/mL or approximately 15% of the total dexamethasone in the eye drops. Approximately 85% of the drug was present as dexamethasone/ $\gamma$ -cyclodextrin microparticles with a diameter between 1 and 3  $\mu$ m. The osmolarity of the eye drop suspension was determined to be 274 mOsm/kg, with a viscosity of 3.9 cP. The eye drops are chemically and physically stable at room temperature for at least 2 years.

### Treatment Protocols and Examination Procedures

After eligibility was confirmed, 19 eyes of 19 subjects were included. After the baseline examinations were performed, the subjects were treated with topical dexamethasone-cyclodextrin microparticle eye drops three times (6–8 AM, 4–6 PM, and 9–11 PM) or six times (6–8 AM, 9–11 AM, 12-noon–2 PM, 3–5 PM, 6–8 PM, and 9–11 PM) per day for 4 weeks, and then observed for 4 weeks without treatment. Cases 1 to 6 and 11 to 15 were consecutively treated by a 3-times/d regimen, and cases 7 to 10 and 16 to 19 were consecutively treated by a 6-times/d regimen. The subjects were prescribed one bottle of 10 mL dexamethasone-cyclodextrin microparticle eye drops for the 3-times/d regimen or two bottles of 7.5 mL for the 6-times/d regimen at the day of baseline examination. All subjects were instructed to stop any topical medication other than dexamethasone-cyclodextrin microparticle eye drops during the study periods for 8 weeks. They were instructed to vigorously shake the eye drop bottle before instillation, instill one drop (~50  $\mu$ L volume) per each time and add additional drop(s) only when instillation failed. BCVA, macular OCT, and IOP were recorded at baseline, 4 weeks after the start of medication (week 4), and 4 weeks after the finish of medication (week 8). At the same schedule, slit lamp, and fundus examinations are performed for monitoring of any adverse events. BCVA was measured by using a decimal VA chart and converted into logMAR. macular OCT was performed as foveal cross scans (6 mm length, 512-pixel horizontal and vertical scans) and an area scan covering a 6  $\times$  6-mm macular region (512 pixels  $\times$  128 horizontal line scans; 3D-OCT 1000 Mark 2; Topcon,

Tokyo, Japan). Mean retinal thickness at the central 1-mm diameter subfield on the area scan was defined as CMT. The IOP was measured by Goldmann applanation tonometry. To confirm the appropriate use of the eye drops, the bottles were collected from the subjects at week 4.

### Statistical Analysis

Statistical analyses were performed with commercial software (Macintosh; Apple Computer, Cupertino, CA; StatView software, ver. 5.0; SAS Institute Inc., Cary, NC). All statistical tests were two-sided. For detecting the changes in CMT, logMAR VA, and IOP during study periods, they were compared between each pair of three time points by paired *t*-test. For collection of multigroup comparisons,  $P < 0.0167$  and  $<0.0033$  were considered as statistically significant, with significance level of 5% and 1%, respectively, after Bonferroni correction. For detecting the possible association of demographic characteristics of subjects on efficacy of dexamethasone-cyclodextrin microparticle eye drops, the percentage of changes in CMT from baseline to week 4 (%CMT change) was calculated in each subject and compared between subgroups divided based on the age, sex, lens status, previous pars plana vitrectomy (PPV), duration of DME, and treatment regimen by using unpaired *t*-tests.

### RESULTS

The list of subjects and demographic characteristics are shown in Tables 1 and 2, respectively. Based on an interview and checking by volume of remaining eye drops of the collected bottles at week 4, all subjects were thought to have used the eye drops appropriately during the 4 weeks. No subjects reported an adverse reaction to the eye drops such as ocular pain, red eye, and blurred vision. All subjects completed the examinations at weeks 4 and 8, and no subjects left the study prematurely.

The CMT, logMAR VA, and IOP at each time point were summarized in Figure 1 and Table 3. The CMT was significantly thinner at week 4 than at baseline and week 8, and thinner at week 8 than at baseline (Table 3). The CMT change from baseline to week 4 in each subject is shown in Table 1 (right-most column). In the 19 eyes, the CMT change (mean  $\pm$  SD) was  $-20\% \pm 20\%$  (range;  $-65\%$  to  $+10\%$ ). From the baseline,

TABLE 1. Subject Data

Case No.	Age	Sex	Lens Status	Previous Treatment for DME/DMR	Duration of DME	Treatment Regimen	CMT at Baseline ( $\mu$ m)	VA at Baseline (LogMAR)	IOP at Baseline (mmHg)	%CMT Change*
1	71	M	Pseudophakic	PRP	>6 mo	3Times/d	473	0.05	9	-22.6
2	53	F	Phakic	PRP	$\leq$ 6 mo	3Times/d	463	0.22	16	-4.5
3	66	M	Phakic	PRP	$\leq$ 6 mo	3Times/d	649	0.40	18	-0.8
4	49	M	Pseudophakic	PRP, PPV	$\leq$ 6 mo	3Times/d	648	0.30	13	-46.1
5	53	M	Phakic	PRP	>6 mo	3Times/d	459	0.70	17	-26.8
6	61	M	Phakic	PRP	>6 mo	3Times/d	902	0.52	15	-16.6
7	74	F	Pseudophakic		$\leq$ 6 mo	6Times/d	337	0.22	14	-11.6
8	55	M	Phakic	PRP	$\leq$ 6 mo	6Times/d	455	0.52	19	-4.0
9	49	F	Pseudophakic	PRP, PPV, PTI	$\leq$ 6 mo	6Times/d	576	0.40	18	-61.6
10	74	M	Phakic		$\leq$ 6 mo	6Times/d	354	0.52	10	-32.5
11	62	M	Phakic	PRP, PTI	>6 mo	3Times/d	264	0.30	12	9.8
12	62	F	Phakic	PRP	>6 mo	3Times/d	423	0.15	19	-16.1
13	79	F	Phakic	PRP	>6 mo	3Times/d	498	1.15	16	-20.1
14	59	M	Phakic	PRP	>6 mo	3Times/d	301	0.40	10	-15.3
15	76	F	Phakic	PRP, PTI, IVBx2	>6 mo	3Times/d	637	1.52	18	-7.8
16	63	F	Phakic	IVBx2	>6 mo	6Times/d	758	1.00	17	-65.4
17	67	M	Phakic		>6 mo	6Times/d	477	0.30	16	-9.9
18	80	M	Pseudophakic	PRP, IVB	>6 mo	6Times/d	651	1.15	16	-2.5
19	58	M	Pseudophakic	PRP, PPV	>6 mo	6Times/d	406	0.05	15	-32.0

PRP, panretinal photocoagulation; PTI, periocular triamcinolone injection; IVB, intravitreal bevacizumab injection.

\* Percent changes in central macular thickness from baseline to week 4.

TABLE 2. Demographic Characteristics

Age, y	
Mean $\pm$ SD	63.7 $\pm$ 9.8
Range	49-80
Sex, n (%)	
Male	12 (63)
Female	7 (37)
Lens status, n (%)	
Phakic	13 (68)
Pseudophakic	6 (32)
Previous treatment for DME/DMR, n (%)	
PRP	15 (79)
PPV	3 (16)
PTI	3 (16)
IVB	3 (16)
Duration of DME, n (%)	
$\leq$ 6 mo	7 (37)
$>$ 6 mo	12 (62)
Treatment regimen	
3 Times/d	11 (58)
6 Times/d	8 (42)

PRP, panretinal photocoagulation; PTI, periocular triamcinolone injection; IVB, intravitreal bevacizumab injection.

CMT decreased more than 10% in 12 (63%) of 19 eyes. Only 1 (5%) of 19 eyes had increased CMT from baseline at week 4 (case 11, 264–290  $\mu$ m CMT).

LogMAR VA was significantly better at week 4 than at baseline and week 8 (Table 3). At week 4, 14 (74%) of 19 eyes had improvement in logMAR VA of more than 0.1. In one eye (5%), logMAR VA worsened more than 0.1 from baseline to week 4 (case 10, from 0.52 to 0.7). IOP was approximately 2 mm Hg higher at week 4 than at baseline and week 8, and IOP returned to baseline level at week 8 (Table 3). The single greatest IOP increase was 8 mm Hg from baseline to week 4 (case 16, from 17 to 25 mm Hg). No subjects required anti-glaucoma medications during the study periods for 8 weeks. Other than increase of IOP, no extra- and intraocular adverse

events related to dexamethasone-cyclodextrin microparticle eye drops were observed by the slit lamp and fundus examinations.

To assess the possible factors associated with efficacy of topical dexamethasone-cyclodextrin microparticle eye drops, difference in the %CMT change was compared between subgroups divided by subjects' demographic characteristics (Table 4). The decrease in CMT was significantly larger in eyes that had a history of pars plana vitrectomy than in other eyes, whereas other parameters including age ( $\leq$ 65 or  $>$ 65 years), sex (male or female), lens status (phakia or pseudophakia), duration of DME ( $\leq$ 6M or  $>$ 6M), and regimen of treatment (3 or 6 times/d) did not reach statistical significance. Representative OCT from vitrectomized eye during study period is shown in Figure 1.

## DISCUSSION

DME can be treated with topical eye drops. The dexamethasone-cyclodextrin microparticle eye drops significantly reduced retinal thickness and improved visual acuity in DME. Earlier studies suggested that macular edema could be treated with topical eye drops with other drug molecules. Campochiaro et al.<sup>14</sup> showed that administration of topical mecamlamine, a nonspecific nicotinic acetylcholine receptor blocker, has positive effects in patients with DME. Genead and Fishman<sup>15</sup> reported that topical therapy with dorzolamide hydrochloride 2%, improved visual acuity and macular edema in patients with retinitis pigmentosa and Usher syndrome. Nakano et al.<sup>16</sup> showed that treatment of refractory DME with difluprednate ophthalmic emulsion 0.05% is effective in vitrectomized eyes. In our study, we found more effect in (albeit few) vitrectomized eyes, probably due to the easier drug transport through the eye after removal of the viscous vitreous gel.<sup>17</sup> These studies all agree that topical eye drops influence macular edema. The old dogma that drugs in eye drops cannot reach the retina and are therefore useless in treatment of retinal disease is wrong. Eye drops can play a role in drug

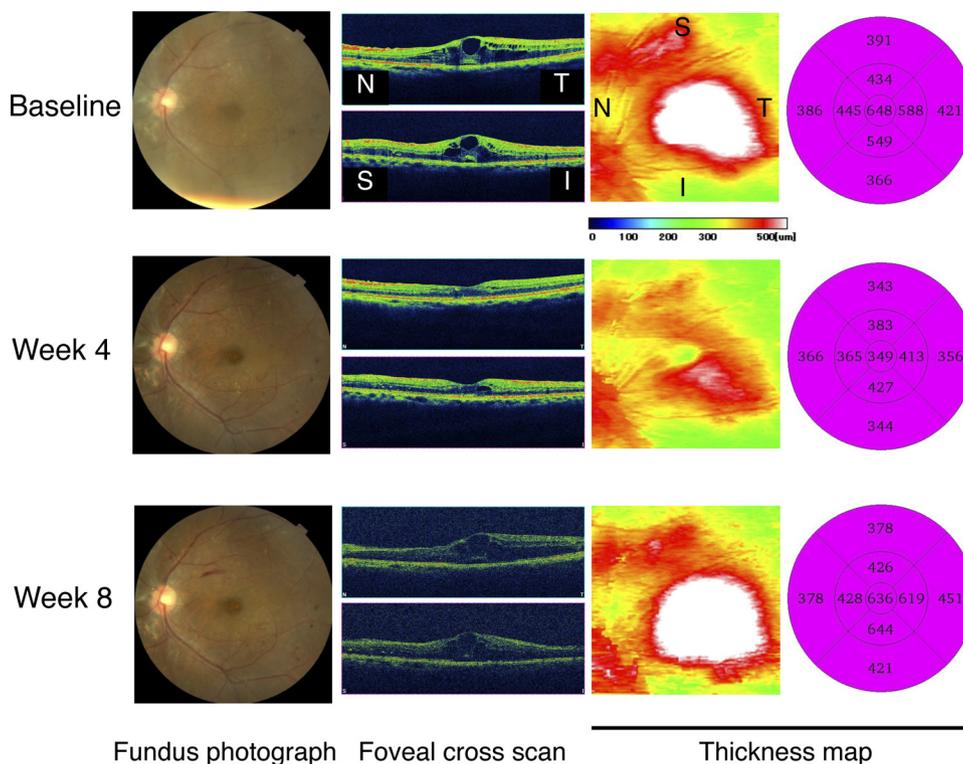


FIGURE 1. Representative optical coherence tomographs from vitrectomized eye: color fundus photographs (left column), foveal cross scans (6 mm length; second left column) and macular thickness maps (6  $\times$  6 mm area; second right and right columns) before treatment (top row), after 4 weeks of treatment with dexamethasone-cyclodextrin microparticle eye drops 3 times a day (middle row), and after 4 weeks of follow-up without treatment (lower row) are shown. The percentage of CMT change from baseline to week 4 in this pseudophakic and vitrectomized eye was  $-46\%$ . The best corrected visual acuity (logMAR) in this case was 0.30, 0.10, and 0.30 at baseline, week 4, and week 8, respectively. N, nasal, T, temporal, S, superior, I, inferior.

TABLE 3. Changes in Central Macular Thickness, Visual Acuity, and Intraocular Pressure

	Baseline	Week 4	Week 8
Central macular thickness, $\mu\text{m}$			
Mean $\pm$ SD	512 $\pm$ 164	399 $\pm$ 154	488 $\pm$ 172
Range	264-902	221-752	238-951
<i>P</i> vs. baseline	—	0.0016*	0.2196
<i>P</i> vs. week 4	—	—	0.0116†
VA, LogMAR			
Mean $\pm$ SD	0.52 $\pm$ 0.41	0.37 $\pm$ 0.40	0.45 $\pm$ 0.41
Range	0.05-1.52	-0.08-1.30	0.05-1.22
<i>P</i> vs. baseline	—	0.0025*	0.1092
<i>P</i> vs. week 4	—	—	0.1736
Intraocular pressure, mm Hg			
Mean $\pm$ SD	15.2 $\pm$ 3.1	17.4 $\pm$ 4.2	15.8 $\pm$ 4.0
Range	9-19	9-25	9-22
<i>P</i> vs. baseline	—	0.0015*	0.3440
<i>P</i> vs. week 4	—	—	0.0175

*P* values are calculated by paired *t*-test between each pair of groups, with Bonferroni correction for multigroup comparisons.

\* *P* < 0.0033, with a significance level of 1%.

† *P* < 0.0167, with a significance level of 5%.

delivery to the retina and treatment of retinal disease, including DME.

The side effects of corticosteroids in the eye are well known and include cataract formation, increased IOP, and infections. The relatively short duration of treatment, 4 weeks, may be responsible for the lack of noticeable cataract formation on slit lamp examination and the absence of visual impairment due to cataract. A longer study and Scheimpflug photography of the crystalline lens is needed to fully evaluate the cataractous side effect of the eye drops. The IOP rose modestly during the study, and only one patient had an increase as high as 8 mm Hg. The pressure regressed after cessation of treatment, and no patient needed treatment for increased IOP. Again, in a longer term study, increased IOP may be more of an issue, but cessation of the eye drops should end the problem. We saw no infections in this clinical trial or other adverse events. Based on the observations, the eye drops do not provide a sustained

treatment effect; the effect stops once the treatment stops. This outcome is to be expected with eye drops. It may be an advantage, in that the side effects also stop (i.e., increased IOP).

Side effects of cyclodextrin in this formulation were not seen and are unlikely to occur. Cyclodextrins can be found in several marketed eye drops, as well as parenteral solutions.<sup>18</sup>  $\gamma$ -Cyclodextrin, the cyclodextrin used in this study, has GRAS (generally regarded as safe) status (<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=46>) and can also be found in the U.S. Food and Drug Administration's (FDA's) list of inactive pharmaceutical ingredients (<http://www.accessdata.fda.gov/scripts/cder/iig/>, search word "cyclodextrin").  $\gamma$ -Cyclodextrin, unlike  $\alpha$ - and  $\beta$ -cyclodextrin, is rapidly digested by salivary and pancreatic  $\alpha$ -amylase.<sup>19</sup> Our group has tested several cyclodextrin-containing eye drops in human subjects without any significant adverse effects.<sup>11,12,20</sup> The possibility of treating DME with noninvasive topical eye drops is an attractive option for patients and doctors alike. The cost, anxiety, and risk of invasive drug delivery are avoided by the patient, and the overwhelming burden of intravitreal injections, which is overwhelming many eye departments and clinics, is lessened. The effectiveness of the drug delivery platform in DME also suggests that it may be useful for other retinal and intraocular diseases and could be used with other drug molecules, as well.

The effectiveness of the dexamethasone-cyclodextrin microparticle eye drops in this small, short-term, prospective trial is promising. A larger trial with direct comparison with other treatment modalities and over a longer time period is needed to further substantiate the clinical efficiency and explore the side effect profile. The dexamethasone-cyclodextrin microparticle eye drops may have a role as monotherapy and also in combination with intravitreal injections, implants, and laser treatment.

### Acknowledgments

The authors thank Yusa Tane, Yasuou Koyama, Hiroko Yoshizako, and Tatsuo Kodama for their assistance in recruiting patients.

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TABLE 4. Subgroup Analysis of Macular Thickness Change

	<i>n</i>	%CMT change* (mean $\pm$ SD)	<i>P</i> †
Age, y			
≤65 ys	11	-25.3 $\pm$ 24.1	0.2129
>65 ys	8	-13.5 $\pm$ 10.8	
Sex			
Male	12	-16.6 $\pm$ 16.1	0.3223
Female	7	-26.7 $\pm$ 25.7	
Lens status			
Phakic	13	-16.2 $\pm$ 18.5	0.1888
Pseudophakic	6	-29.4 $\pm$ 22.0	
Previous PPV			
No	16	-15.4 $\pm$ 17.1	0.0090
Yes	3	-46.6 $\pm$ 14.8	
Duration of DME			
≤6 mo	7	-23.0 $\pm$ 23.9	0.6698
>6 mo	12	-18.8 $\pm$ 18.4	
Treatment regimen			
3 Times/d	11	-15.2 $\pm$ 14.7	0.1966
6 Times/d	8	-27.4 $\pm$ 25.0	

\* Percent change of central macular thickness at week 4 from baseline value.

† *P* values are calculated between subgroups by unpaired *t*-test.

CMT, central macular thickness; PPV, pars plana vitrectomy; DME, diabetic macular edema.

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