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Nepafenac 0.3% after Cataract Surgery in Patients with Diabetic Retinopathy

Results of 2 Randomized Phase 3 Studies

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Purpose: To demonstrate the efficacy and safety of once-daily nepafenac 0.3% ophthalmic suspension versus vehicle, based on clinical outcomes, after cataract surgery in patients with diabetes.

Design: Two prospective, randomized, multicenter, double-masked, vehicle-controlled phase 3 studies.

Participants: Total, 615 patients in study 1 and 605 patients in study 2.

Methods: Patients were randomized (1:1) to topical nepafenac 0.3% or vehicle once-daily starting the day before surgery and continuing for 90 days thereafter.

Main Outcome Measures: Key efficacy variables were: patients (%) in whom macular edema (ME) developed (≥30% increase from preoperative baseline central subfield macular thickness) within 90 days after cataract surgery and the patients (%) with a best-corrected visual acuity (BCVA) improvement of ≥15 letters from preoperative baseline through day 14 maintained through day 90. Secondary end points included: patients (%) with a BCVA improvement of ≥15 letters from preoperative baseline through days 90 and 60 and safety over 3 months.

Results: A significantly lower percentage of patients demonstrated ME within 90 days after surgery with nepafenac 0.3% versus vehicle (study 1: 2.3% vs. 17.3%; $P < 0.001$; study 2: 5.9% vs. 14.3%; $P = 0.001$; pooled: 4.1% vs. 15.9%; $P < 0.001$). The percentage of patients achieving a ≥15-letter improvement from baseline through day 14 maintained through day 90 with nepafenac 0.3% versus vehicle was 61.7% versus 43.0% ($P < 0.001$) in study 1, 48.8% versus 50.5% ($P = 0.671$) in study 2, and 55.4% versus 46.7% ($P = 0.003$) in the pooled analysis. A greater percentage of patients treated with nepafenac 0.3% versus vehicle in study 1 and similar percentage in study 2 had a BCVA improvement of ≥15 letters from preoperative baseline through day 90 (77.2% vs. 67.7% [$P = 0.009$] and 65.4% vs. 65.9% [$P = 0.888$]) and through day 60 (76.2% vs. 64.7% [$P = 0.002$] and 68.9% vs. 62.1% [$P = 0.092$]). No unanticipated adverse events were observed.

Conclusions: These studies demonstrated the clinical benefits of nepafenac 0.3% over vehicle in reducing the risk of postoperative ME, with the integrated analysis showing improved BCVA after cataract surgery in patients with diabetic retinopathy, with no unanticipated safety events. *Ophthalmology 2017;124:776-785 © 2017 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.

Cataract is the leading cause of blindness, affecting 47.8% of patients worldwide.[1] Patients with diabetes are at an increased risk of developing cataract compared with those without diabetes, and the rising global prevalence of diabetes further increases the risk for cataract development.[2,3] Macular edema (ME) is a common cause of poor visual outcome after uneventful cataract surgery by phacoemulsification.[4–6] Approximately 30% of patients may experience some magnitude of postoperative ME, although many cases are not associated with impaired vision.[7] Although ME associated with visual acuity (VA) loss after uneventful cataract surgery has been reported in up to 2% of patients,[4,8] the incidence may be as high as 20% when cataract extraction is complicated by posterior capsule rupture with vitreous loss or severe iris trauma.[4,6] Cataract development occurs at a higher rate and at an earlier age in patients who have diabetes compared with those who do not have diabetes.[9,10] In addition, macular changes are more likely to occur after cataract surgery in patients with diabetes, especially in those with pre-existing retinopathies, compared with those without diabetes.[3]

Over the years, optical coherence tomography (OCT) has emerged as a reliable tool to diagnose and quantitatively follow changes in retinal pathology.[11] Optical coherence tomography better detects morphologic changes at an early stage.[12] Recent studies using OCT have reported higher rates of ME after cataract surgery in patients with diabetes with or without retinopathy (18%–28.6%) than in

http://dx.doi.org/10.1016/j.ophtha.2017.01.036
ISSN 0161-6420/17

those without diabetes (1%−5.5%).[3,13−17] Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are beneficial for treating ME after cataract surgery.[18,19] Nonsteroidal anti-inflammatory drugs block cyclooxygenase enzymes responsible for prostaglandin production.[18,19] Very few prospective studies have evaluated the role of NSAIDs to reduce the risk of ME and to improve VA outcomes after cataract surgery in eyes with diabetic retinopathy.

Nepafenac (Alcon Research, Ltd., Fort Worth, TX), an NSAID, rapidly permeates into the cornea and sclera and is converted to its active metabolite, amfenac, primarily in the retina−choroid and the iris−ciliary body.[20,21] Amfenac is a potent inhibitor of constitutive (cyclooxygenase-1) and inducible (cyclooxygenase-2) cyclooxygenases that catalyze the formation of proinflammatory prostaglandins.[22] Both nepafenac and amfenac block the inflammation-mediated breakdown of the blood−retinal barrier that contributes to plasma extravasation and edema.[22] Nonclinical and clinical studies have shown that nepafenac and amfenac reach the posterior segment of the eye after topical administration.[21,23−26]

Nepafenac 0.1% ophthalmic suspension, dosed 3 times daily, is approved in Europe to reduce the risk of postoperative ME associated with cataract surgery in adult patients with diabetes, based on 2 randomized, controlled, phase 3 trials.[23,24] In both trials, nepafenac 0.1% significantly reduced the incidence of ME compared with vehicle (study 1: 3.2% vs. 16.7%; $P < 0.001$; study 2: 5% vs. 17.5%; $P = 0.012$).[23,24] Furthermore, a higher percentage of patients in the nepafenac group compared with the vehicle group had improvements of ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from postoperative baseline through day 90 (Alcon data on file). Nepafenac 0.1% showed clinically relevant advantages compared with vehicle to prevent ME and to improve and maintain VA after cataract surgery in patients with diabetes (Alcon data on file). The hypothesis of the present studies was that 0.3% nepafenac formulation may achieve these aforementioned benefits with less frequent dosing. Thus, in 2 similarly designed randomized studies, the efficacy and safety of nepafenac 0.3% administered once-daily was assessed to reduce ME and to enhance VA after cataract surgery in eyes of patients with diabetes and nonproliferative diabetic retinopathy (NPDR).

Methods

Study Design

Both studies were prospective, randomized, multicenter, vehicle-controlled, double-masked, parallel-group, phase 3 clinical trials. Study 1 was conducted at 66 centers in the United States, Latin America, and the Caribbean between March 2013 and May 2015. Study 2 was conducted at 73 centers across the United States, Europe, the Middle East, Africa, Latin America, Caribbean, and the Asia−Pacific region between June 2013 and May 2015.

The studies consisted of 9 visits as follows: a screening and randomization visit (performed within 2 days to 4 weeks before the surgery visit), the cataract surgery visit (day 0), and 6 postoperative follow-up visits (days 1, 7, 14, 30, 60, and 90 or early exit; Fig 1, available at www.aaojournal.org). Patients in whom ME was not resolved by day 90 were considered to be treatment failures; these patients were followed up until day 120.

In both the studies, all patients, investigators, and the study-related personnel were masked to the treatment assignment. The study was conducted in accordance with the Good Clinical Practice and the tenets of the Declaration of Helsinki. The study protocol was reviewed and approved by an independent ethics committee or an institutional review board for each contributing center. All patients provided written informed consent before entering the study. The studies are registered with clinicaltrials.gov (identifiers, NCT01853072 [study 1] and NCT01872611 [study 2]).

Patients

Both studies included patients 18 years of age or older with diabetes (types 1 or 2) and NPDR who required cataract extraction by phacoemulsification with planned posterior chamber intraocular lens (IOL) implantation, who had a best-corrected VA (BCVA) of 73 ETDRS letters or fewer (<20/63 Snellen equivalent) in the study eye at preoperative screening, and who had an expectation of improvement in BCVA after surgery, in the opinion of the investigator.

Patients with pre existing ME in the study eye as determined by spectral-domain (SD) OCT and confirmed by the reading center (central subfield macular thickness [CSMT], ≥320 μm [Spectralis; Heidelberg, Germany] or ≥300 μm [Cirrus; Zeiss, Germany]) or who had a history of retinal detachment, ischemic maculopathy, central or branch retinal vein occlusion, central or branch retinal artery occlusion, exudative age-related macular degeneration, or chronic or recurrent inflammatory eye disease were excluded. Additional exclusion criteria were use of intraocular or periocular corticosteroids or anti−vascular endothelial growth factor therapy within 6 months of surgery, systemic or topical ocular corticosteroids within 14 days of surgery, topical or systemic NSAIDs (except an allowed daily dose of 325 mg of aspirin) within 7 days of surgery, topical ophthalmic prostaglandins within 4 days of surgery, or topical ocular corticosteroids or NSAIDs 1 day before surgery. Patients allergic or hypersensitive to NSAIDs, corticosteroids, or any component of the investigational product also were excluded from the study. Detailed exclusion criteria are provided in Appendix 1 (available at www.aaojournal.org).

Treatment

Enrolled patients were randomized (1:1) to receive nepafenac 0.3% or vehicle once-daily in the study eye beginning 1 day before cataract surgery (day −1). Patients were randomized in a 1:1 manner to receive treatment with nepafenac 0.3% and control vehicle, respectively. Randomization was stratified by retinopathy severity (mild vs. moderate or severe) as defined by the International Clinical Diabetic Retinopathy Scale. Both the test articles (nepafenac 0.3% and vehicle) were provided in identical vials.

Dosing continued on the day of surgery (day 0) and for 90 days after surgery. On the day of the surgery (day 0), patients received an additional dose of assigned treatment 30 to 120 minutes before the surgery. All patients received prednisolone acetate (Omnipred; Alcon Laboratories Inc., Fort Worth, TX) [prednisolone acetate ophthalmic suspension] or similar alternate eye drops) in the operative eye 4 times daily for the first 2 weeks after surgery followed by twice-daily for the subsequent 2 weeks after surgery. This topical corticosteroid dosing regimen could be modified based on the investigator's judgment.

Study Objectives

The objective of both the studies was to determine the efficacy and safety of once-daily nepafenac 0.3% ophthalmic suspension versus

vehicle based on clinical outcomes after cataract surgery in patients with diabetes. The primary and secondary end points were as follows: (1) the percentage of patients who demonstrated ME (≥30% increase from the preoperative baseline in CSMT) within 90 days after cataract surgery (primary end point for the European Medicines Agency Committee for Medicinal Products for Human Use [EMA CHMP] and secondary end point for the United States Food and Drug Administration [FDA]); (2) the percentage of patients with a BCVA improvement of ≥15 letters from preoperative baseline through day 14 and maintained through day 90 (primary end point for the United States FDA and secondary end point for the EMA CHMP); (3) the percentage of patients with a BCVA loss of >5 and >10 letters from day 7 to any visit and safety over 90 days; and (4) the percentage of patients with a BCVA improvement of ≥15 letters from preoperative baseline through day 90 and day 60. The key supportive end points included mean changes in BCVA and CSMT from preoperative baseline to each postoperative visit. Given the identical nature of the protocols, pooled analyses were conducted to verify the study findings further.

Efficacy Assessments

The efficacy variables included measurements of BCVA, development of ME, macular thickness and volume, and the incidence of treatment failure. Macular edema was defined as a ≥30% increase in CSMT from the preoperative baseline measurement. Macular thickness and volume were measured using SD OCT (Spectralis or Cirrus) at each investigational center. Optical coherence tomography was assessed on scans obtained from both eyes at screening and day 90 (or day 120, if applicable, or early exit) and from the study eye on days 7, 14, 30, and 60. The OCT scans were analyzed in a masked fashion at the Duke Reading Center (Duke University, Durham, NC) and included the use of standard segmentation methods. Thickness results were reported for the foveal center point, the foveal central 1-mm subfield thickness, and the inner and outer rings, each of which were divided into 4 quadrants (temporal, superior, nasal, and inferior). The total macular volume was also reported.

Fundus photographs were obtained at the screening visit and were submitted to the reading center for grading of retinopathy severity (no apparent retinopathy, mild NPDR, moderate NPDR, severe NPDR, and proliferative diabetic retinopathy) as defined by the International Clinical Diabetic Retinopathy Scale before randomization. The BCVA was assessed by a certified VA technician and refractionist using a standard ETDRS chart at a distance of 4 m (and 1 m as necessary) in both eyes at baseline and at day 90 (or day 120, if applicable, or early exit) as well as in the study eye on days 1, 7, 14, 30, and 60. The BCVA was calculated at 4 m as the number of letters read correctly +30, whereas BCVA was calculated at 1 m as the number of letters read correctly. Regardless of distance, if no letters were read correctly, the BCVA was reported as 0 and the patient was to have been tested, in respective order, for the following levels of acuity: counting fingers, hand movements, and light perception. The BCVA assessment was standardized across all investigational centers. Treatment failure was defined as any eye with a ≥30% or more increase in CSMT from the preoperative baseline assessment as measured by SD OCT.

Safety Assessments

Information on adverse events (AEs) in all patients was collected from screening and at all visits through day 90 (or day 120, if applicable, or early exit). In addition to the AE assessments, the safety of nepafenac 0.3% was assessed by routine ocular examinations, which included intraocular pressure (IOP) measurements, slit-lamp parameters (inflammatory cells, aqueous flare, corneal edema, bulbar redness, and corneal epithelium integrity), dilated fundus parameters (peripheral retina, macula, choroid, and optic nerve), and the extent of exposure.

Statistical Analysis

A sample size of 590 patients was planned to achieve an evaluable sample size of 560 patients that was expected to provide approximately 90% power to detect a 14% difference between the nepafenac 0.3% and vehicle groups for the BCVA end point (assuming 45% in the vehicle group) and a more than 99% power to detect at least a 13% difference for the incidence of ME (assuming 18% in the vehicle group).

The efficacy analyses were performed using the full analysis set (FAS), which included all randomized patients who completed implant surgery and had at least 1 on-therapy postoperative visit. The BCVA end point (primary end point for the United States FDA and secondary end point for the EMA CHMP) was based on a binary outcome (positive or negative). A positive outcome required an improvement from the preoperative baseline BCVA of ≥15 letters at all 4 time points (days 14, 30, 60, and 90); any other outcome was considered negative. A logistic regression model for treatment and retinopathy severity was performed to assess the treatment group difference in BCVA. The primary inference was based on the odds ratio of a positive outcome. An estimate of the odds ratio, the associated 95% confidence interval (CI), and *P* value were provided, along with the difference in proportions and associated CIs. A similar model was used to analyze the percentage of patients who demonstrated ME within 90 days (primary end point for EMA CHMP and secondary end point for United States FDA) and the other secondary efficacy end points associated with changes in BCVA. The analyses of the supportive end points were descriptive. The primary and secondary analyses were repeated using the per-protocol (PP) analysis set, which included all patients in the FAS who had no major protocol violations, to investigate the sensitivity of the results to major protocol violations.

A gatekeeping strategy was used to ensure overall control of the type I error rate at a 5% level of significance (2 sided). The secondary efficacy hypotheses were relevant only if the primary efficacy null hypothesis was first rejected. The order of hypothesis testing was region specific. After the rejection of the primary null hypothesis, each secondary hypothesis was tested following the order of the hypotheses as listed for each region. For the European Union, the order of the hypotheses was consistent with the listing under study objectives. For the United States, the end point of maintained improvement in BCVA was considered as the primary end point and the ME end point was considered as the first secondary end point. The data presented in the manuscript follow the testing order of the European Union.

A pooled analysis of the 2 studies also was performed to gain better precision in estimating the treatment effects in patients with NPDR and to assess the consistency of the findings of the individual studies. The efficacy outcomes of pooled analysis were to be considered as only supportive of the individual study findings, and thus no formal multiplicity adjustment were used.

The safety analysis set included all patients who were exposed or were deemed exposed (i.e., discontinued the study before surgery, but either returned an opened bottle of the study drug or failed to return the study drug) to treatment. Descriptive statistics were used to summarize all safety parameters by visit and treatment group.

Results

Patient Demographics and Baseline Characteristics

In study 1, 615 patients (615 eyes) were randomized 1:1 to receive nepafenac 0.3% (n = 308) or vehicle (n = 307). Of these 615 patients, 12 (7 in the nepafenac 0.3% group and 5 in the vehicle group) did not receive treatment and were excluded from the analysis sets. All 603 patients who received treatment were included in the safety analysis set; 598 were included in the FAS and 557 were included in the PP analysis set. Overall, 12 patients in the nepafenac 0.3% group and 21 patients in the vehicle group discontinued the study. The reasons for study discontinuation are provided in Figure 2A (available at www.aaojournal.org).

In study 2, 605 patients (605 eyes) were randomized 1:1 to receive nepafenac 0.3% (n = 301) or vehicle (n = 304). Of the 605 patients, 17 (8 in the nepafenac 0.3% group and 9 in the vehicle group) did not receive treatment and were excluded from the analysis. All 588 patients who received treatment were included in the safety analysis set; 582 were included in the FAS and 552 were included in the PP analysis set. Overall, 24 patients in the nepafenac 0.3% group and 12 patients in the vehicle group discontinued the study. The reasons for study discontinuation are provided in Figure 2B (available at www.aaojournal.org).

Overall in both the studies, the patient demographics and baseline characteristics were well balanced, with no clinically relevant between-group differences (Table 1). Most patients were 65 years of age or older, female, and white.

Efficacy

For simplicity of reporting, the end points reported below are presented in the order of nominal statistical significance. For multiplicity considerations, please refer to the description in methods under statistical analysis.

Macular Edema

In both the studies, a significantly lower percentage of eyes in the nepafenac 0.3% versus the vehicle group developed ME within 90 days after cataract surgery (study 1: 2.3% vs. 17.3%; $P < 0.001$; study 2: 5.9% vs. 14.3%; $P = 0.001$; Fig 3). The results of the analysis using the PP analysis set were consistent with those from the primary analysis (study 1: 2.2% vs. 16.2%; $P < 0.001$; study 2: 4.4% vs. 13.0%; $P < 0.001$; Table 2, available at www.aaojournal.org).

Best-Corrected Visual Acuity

BCVA Improvement of ≥15 Letters from Preoperative Baseline to Day 14 and Maintained through Day 90. In study 1, a significantly higher percentage of eyes in the nepafenac 0.3% versus the vehicle group (61.7% vs. 43.0%; $P < 0.001$) achieved a clinically relevant improvement of ≥15 letters from preoperative baseline through day 14, that was maintained through day 90 (Fig 4). In study 2, similar percentages of eyes in both the treatment groups achieved this end point (nepafenac 0.3%, 48.8%; vehicle, 50.5%; $P = 0.671$; Fig 4). The results of the PP analysis set were consistent with those from the primary analysis (study 1: 56.6% vs. 35.6%; $P < 0.001$; study 2: 46.5% vs. 43.0%; $P = 0.400$; Table 2, available at www.aaojournal.org).

Percentage of Eyes with a BCVA Loss of >5 and >10 Letters from Day 7 to Any visit. A lower percentage of eyes receiving nepafenac 0.3% in study 1 compared with those receiving vehicle lost >5 letters from day 7 to any visit (study 1: 15.4% vs. 27.3%; $P < 0.001$; Fig 5A, available at www.aaojournal.org). This effect was not observed in study 2, where similar percentages of eyes had BCVA loss of >5 letters in either group (18.7% vs. 16.7%; $P = 0.540$). Fewer eyes in the nepafenac 0.3% group than in the vehicle group had a >10-letter loss in BCVA from day 7 to any visit in study 1 (study 1: 9.1% vs. 15.3%; $P = 0.02$); however, the percentages of eyes were similar between treatment groups in study 2 (10.7% vs. 8.9%; $P = 0.458$; Fig 5B, available at www.aaojournal.org).

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Study 1		Study 2		Pooled	
	Nepafenac (n = 289)	*Vehicle (n= 300)*	*Nepafenac (n = 289)*	*Vehicle (n = 293)*	*Nepafenac (n = 587)*	*Vehicle (n = 593)*
Mean age (SD), years	66.8 (8.5)	66.8 (8.3)	67.7 (8.5)	68.1 (8.4)	67.2 (8.5)	67.4 (8.3)
18–64	100 (33.6)	110 (36.7)	101 (34.9)	84 (28.7)	201 (34.2)	194 (32.7)
≥65	198 (66.4)	190 (63.3)	188 (65.1)	209 (71.3)	386 (65.8)	399 (67.3)
Female gender, n (%)	158 (53.0)	166 (55.3)	149 (51.6)	149 (50.9)	307 (52.3)	315 (53.1)
Race, n (%)						
White	220 (73.8)	231 (77.0)	174 (60.2)	169 (57.7)	394 (67.1)	400 (67.5)
Black	50 (16.8)	44 (14.7)	13 (4.5)	11 (3.8)	63 (10.7)	55 (9.3)
Alaska native	0	0	1 (0.3)	0	1 (0.2)	0
Asian	5 (1.7)	5 (1.7)	26 (9.0)	34 (11.6)	31 (5.3)	39 (6.6)
Native Hawaiian/Pacific Islander	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Multiracial	0	0	2 (0.7)	0	2 (03)	0
Other	23 (7.7)	19 (6.3)	73 (25.3)	78 (26.6)	96 (16.4)	97 (16.4)
Mean CSMT (SD), µm	245.4 (24.2)	247.6 (25.0)	246 (25.0)	247.8 (23.4)	245.7 (24.6)	247.7 (24.2)
Mean BCVA (SD), letters	62.0 (12.1)	63.0 (11.0)	59.6 (14.0)	59.8 (12.4)	60.8 (13.1)	61.4 (11.8)
Retinopathy severity, n (%)						
Mild	40 (13.4)	44 (14.7)	29 (10.0)	33 (11.3)	69 (11.8)	77 (13.0)
Moderate	255 (85.6)	253 (84.3)	260 (90.0)	257 (87.7)	515 (87.7)	510 (86.0)
Severe	3 (1.0)	3 (1.0)	0 (0)	3 (1.0)	3 (0.5)	6 (1.0)

BCVA = best-corrected visual acuity; CSMT = central subfield macular thickness; SD = standard deviation.

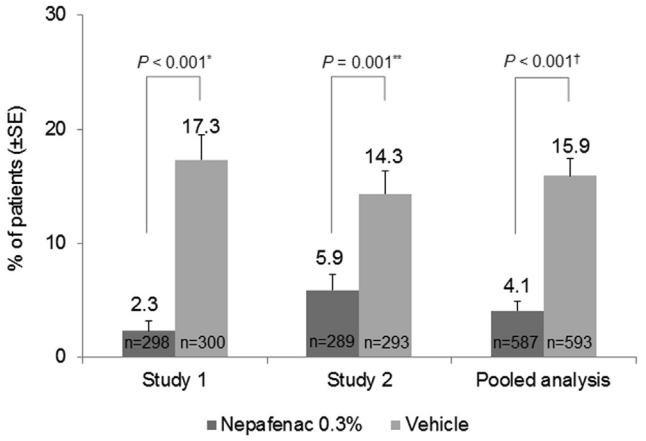

Figure 3. Bar graph showing the incidence of macular edema within 90 days after cataract surgery in patients treated with nepafenac 0.3% and vehicle and the associated odds ratio (OR; 95% confidence interval [CI]) in each study and in the pooled analysis (full analysis set). *P* value for pooled analysis is for descriptive purposes only. *OR, 0.1 (95% CI, 0.1−0.3). **OR, 0.4 (95% CI, 0.2−0.7). †OR, 0.2 (95% CI, 0.1−0.4). SE = standard error.

BCVA Improvement of ≥15 Letters from Preoperative Baseline to Day 60 and to Day 90. In study 1, a significant improvement of ≥15 letters was observed with nepafenac 0.3% versus vehicle from preoperative baseline through day 90 (77.2% vs. 67.7%; $P = 0.009$) and day 60 (76.2% vs. 64.7%; $P = 0.002$; Fig 6A and B). In study 2, the between-group difference was not significant; numerical difference in favor of nepafenac 0.3% was observed for a BCVA improvement of ≥15 letters from preoperative baseline through day 60 (68.9% vs. 62.1%; $P = 0.092$), whereas the outcomes were similar for a BCVA improvement of ≥15 letters from preoperative baseline through day 90 (65.4% vs. 65.9%; $P = 0.888$; Fig 6A and B).

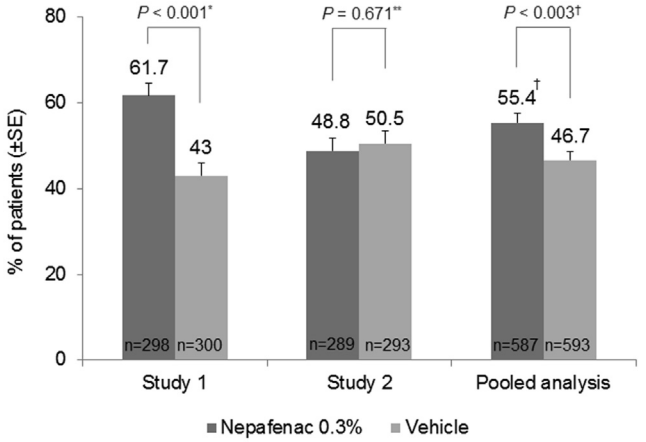

Figure 4. Bar graph showing the percentage of patients with best-corrected visual acuity improvement of 15 letters or more from preoperative baseline through day 14 and maintained through day 90 in patients treated with nepafenac 0.3% and vehicle and the associated odds ratio (OR; 95% confidence interval [CI]) in each study and in the pooled analysis (full analysis set). *P* value for pooled analysis is for descriptive purposes only. *OR, 2.1 (95% CI, 1.5−3.0). **OR, 0.9 (95% CI, 0.7−1.3). †OR, 1.4 (95% CI, 1.1−1.8). SE = standard error.

Mean Change in BCVA and CSMT from Preoperative Baseline to Each Visit. In both the studies, an overall BCVA improvement was observed based on the mean change in BCVA from baseline to each postoperative study visit. The improvement was higher in the nepafenac 0.3% group than in the vehicle group at all postoperative visits from days 7 to 90 in both studies ($P < 0.05$), except on the day 7 visit in study 2 ($P = 0.088$; Fig 7). In both studies, the increase in CSMT from preoperative baseline was smaller in the nepafenac 0.3% group than in the vehicle group at all postoperative visits from days 7 through 90 ($P < 0.05$ at all visits in both studies; Fig 8).

Pooled Analysis

A notable difference was observed with nepafenac 0.3% versus vehicle in the incidence of ME (4.1% vs. 15.9%; $P < 0.001$; Fig 3) and in BCVA improvement of ≥15 letters from preoperative baseline through day 14 and maintained through day 90 (55.4% vs. 46.7%; $P = 0.003$). A lower proportion of eyes in the nepafenac 0.3% group showed a BCVA loss of >5 letters (17.0% vs. 22.1%; $P = 0.029$) or >10 letters (9.9% vs. 12.1%; $P = 0.211$) from day 7 compared with the vehicle group (Fig 5A and B, available at www.aaojournal.org). More eyes in the nepafenac 0.3% group versus the vehicle group had a BCVA improvement of ≥15 letters from preoperative baseline through day 60 (72.6% vs. 63.4%; $P < 0.001$) and day 90 (71.4% vs. 66.8%; $P = 0.088$; Fig 6A and B).

Safety

Overall in study 1, 108 patients (35.9%) in the nepafenac 0.3% group and 125 patients (41.4%) in the vehicle group experienced at least 1 treatment-emergent AE (TEAE). Of these, 8 patients (2.7%) in the nepafenac 0.3% group and 7 patients (2.3%) in the vehicle group reported treatment-related TEAEs. In addition, 4 patients experienced treatment-related AEs during the posttreatment period, which included keratitis (1 patient in the nepafenac 0.3% group and 2 patients in the vehicle group) and punctate keratitis (1 patient in the vehicle group). One patient in the vehicle group died during the treatment-period because of a serious TEAE (sepsis). In addition, 1 patient in the nepafenac 0.3% group and 3 patients in the vehicle group died because of serious TEAEs during the posttreatment period. Thirteen (4.3%) patients in each treatment group experienced at least 1 nonfatal serious TEAE. Four patients (1.3%) in the vehicle group discontinued the study because of a TEAE; there was no discontinuation due to TEAE in nepafenac 0.3% group (Table 3).

In study 2, overall 102 patients (34.8%) in the nepafenac 0.3% group and 136 patients (46.1%) in the vehicle group experienced at least 1 TEAE. Of these, 6 patients (2.0%) in the nepafenac 0.3% group and 8 patients (2.7%) in the vehicle group reported treatment-related TEAEs. In addition, 3 patients experienced treatment-related TEAEs during the posttreatment period, which included punctate keratitis (1 patient in the vehicle group), retinal detachment (1 patient in the nepafenac 0.3% group), and diabetic retinal edema (1 patient in the vehicle group). One patient in the vehicle group died during the treatment-period because of a serious TEAE (cardiac failure). One patient who never received the study treatment died because of a serious AE during the pretreatment period. No deaths were reported in the nepafenac 0.3% group. Fourteen patients (4.8%) in the nepafenac 0.3% group and 13 patients (4.4%) in the vehicle group experienced at least 1 nonfatal serious TEAE. One patient in the nepafenac 0.3% group and 1 patient in the vehicle group discontinued the study because of a TEAE (Table 3).

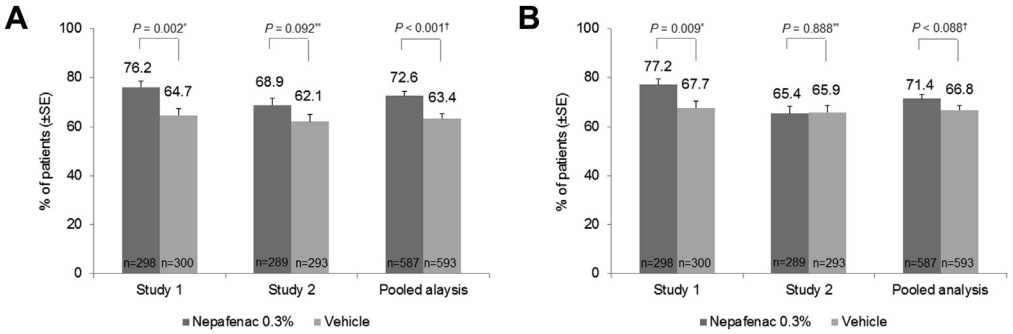

Figure 6. Bar graph showing the best-corrected visual acuity improvement of 15 letters or more from preoperative baseline to (**A**) day 60 and (**B**) day 90 in patients treated with nepafenac 0.3% and vehicle and the associated odds ratio (OR; 95% confidence interval [CI]) in each study and in the pooled analysis (full analysis set). *P* value for pooled analysis is for descriptive purposes only. **A**, *OR, 1.8 (95% CI, 1.2−2.5). **OR, 1.3 (95% CI, 1.0−1.9). †OR, 1.5 (95% CI, 1.2−2.0). **B**, *OR, 1.6 (95% CI, 1.1−2.3). **OR, 1.0 (95% CI, 0.7−1.4). †OR, 1.2 (95% CI, 1.0−1.6). SE = standard error.

In both the studies, none of the deaths were considered by the investigator to be related to the study treatment; none of the serious TEAEs or TEAEs that led to study discontinuation were considered by the investigator to be treatment-related. In both studies, a review of ocular examination results (IOP, slit-lamp biomicroscopy, and dilated fundus examination) revealed no meaningful treatment differences between the nepafenac 0.3% and vehicle groups.

Discussion

The 2 randomized, vehicle-controlled phase 3 studies demonstrated that nepafenac 0.3%, when given once-daily beginning 1 day before surgery and continued for 90 days, was superior to vehicle in reducing the risk of ME after cataract surgery in patients with diabetes. In study 1, clinically relevant differences between nepafenac 0.3% and vehicle were observed for all the BCVA end points, whereas in study 2, the outcomes were similar between the nepafenac 0.3% and vehicle groups. The BCVA outcomes in the pooled analysis were similar to the results observed in study 1 (Fig 9, available at www.aaojournal.org).

In the current studies, the primary analysis was conducted on the FAS. The BCVA end point was not met using the FAS in study 2, which remains a potential limitation of these findings. However, results based on the PP analysis were in favor of nepafenac 0.3% for several of the BCVA end points. Notable differences in favor of nepafenac 0.3% (at the nominal 5% significance level) were observed for >5-letter and >10-letter loss from day 7 end points and for the 15-letter or more gain from preoperative baseline to the day 60 end point (Table 2, available at www.aaojournal.org). Numerous post hoc subgroup analyses were conducted in study 2 to understand the reasons for the similar BCVA outcomes between treatments. These included subgroup analyses by the geographic location of the participating patients (by region, country, and investigational center), by patient demographics and baseline characteristics (e.g., age, gender, race, retinopathy severity, and VA), and by factors related to the medical history or concomitant medications (type and duration of diabetes, type of concomitant steroid, and others; Alcon data on file). These additional analyses did not reveal any single factor that could explain the similar

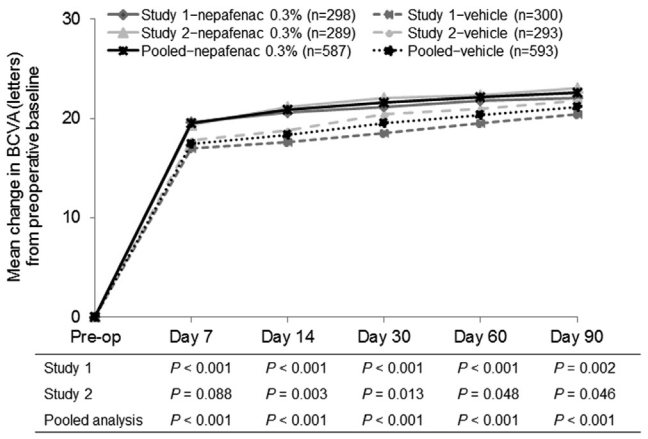

Figure 7. Graph showing the mean change in best-corrected visual acuity (BCVA) from preoperative baseline to each visit in patients treated with nepafenac 0.3% and vehicle in each study and in the pooled analysis (full analysis set). *P* value for pooled analysis is for descriptive purposes only. Pre-op = before surgery.

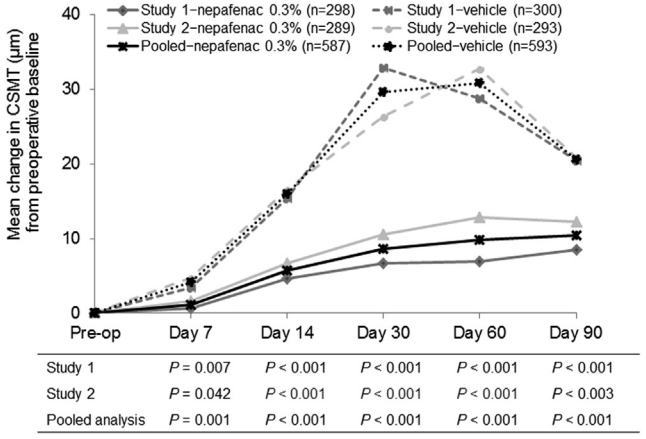

Figure 8. Graph showing the mean change in central subfield macular thickness (CSMT) from preoperative baseline to each visit in patients treated with nepafenac 0.3% and vehicle in each study and in the pooled analysis (full analysis set). *P* value for pooled analysis is for descriptive purposes only. Pre-op = before surgery.

Table 3. Treatment-Emergent Adverse Events (Safety Population)

Parameters	Study 1		Study 2	
	Nepafenac 0.3% (n = 301)	*Vehicle (n = 302)*	*Nepafenac 0.3% (n = 293)*	*Vehicle (n = 295)*
At least 1 TEAE	108 (35.9)	125 (41.4)	102 (34.8)	136 (46.1)
Related to treatment	8 (2.7)	7 (2.3)	6 (2.0)	8 (2.7)
Any serious TEAE	13 (4.3)	14 (4.6)	14 (4.8)	14 (4.7)
Deaths	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Nonfatal serious TEAE	13 (4.3)	13 (4.3)	14 (4.8)	13 (4.4)
Related to treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation because of TEAE	0 (0.0)	4 (1.3)	1 (0.3)	1 (0.3)
Related to treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most frequent TEAEs*				
Intraocular pressure increase	13 (4.3)	12 (4.0)	10 (3.4)	12 (4.1)
Dry eye	5 (1.7)	12 (4.0)	6 (2.0)	9 (3.1)
Corneal edema	2 (0.7)	2 (0.7)	4 (1.4)	12 (4.1)
Eye pain	5 (1.7)	10 (3.3)	1 (0.3)	8 (2.7)
Macular edema	2 (0.7)	5 (1.7)	2 (0.7)	10 (3.4)
Punctate keratitis	8 (2.7)	5 (1.7)	5 (1.7)	8 (2.7)
Foreign body sensation in eyes	3 (1.0)	8 (2.6)	4 (1.4)	2 (0.7)
Headache	3 (1.0)	8 (2.6)	4 (1.4)	6 (2.0)
Nasopharyngitis	4 (1.3)	4 (1.3)	3 (1.0)	7 (2.4)
Vitreous floaters	2 (0.7)	6 (2.0)	2 (0.7)	1 (0.3)
Eye irritation	3 (1.0)	6 (2.0)	2 (0.7)	1 (0.3)
Conjunctivitis	5 (1.7)	1 (0.3)	0 (0.0)	4 (1.4)
Diarrhea	2 (0.7)	4 (1.3)	0 (0.0)	0 (0.0)
Keratitis	3 (1.0)	3 (1.0)	0 (0.0)	1 (0.3)
Lacrimation increased	1 (0.3)	5 (1.7)	0 (0.0)	1 (0.3)
Nausea	4 (1.3)	1 (0.3)	1 (0.3)	0 (0.0)
Ocular discomfort	1 (0.3)	4 (1.3)	0 (0.0)	0 (0.0)
Urinary tract infection	2 (0.7)	3 (1.0)	2 (0.7)	2 (0.7)
Cardiac failure congestive	0 (0.0)	4 (1.3)	0 (0.0)	1 (0.3)
Hypokalemia	1 (0.3)	3 (1.0)	0 (0.0)	0 (0.0)
Iritis	1 (0.3)	3 (1.0)	0 (0.0)	1 (0.3)
Cellulitis	0 (0.0)	3 (1.0)	1 (0.3)	1 (0.3)
Noncardiac chest pain	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)
Vision blurred	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)
Upper respiratory tract infection	3 (1.0)	0 (0.0)	0 (0.0)	4 (1.4)
Visual acuity reduced	0 (0.0)	3 (1.0)	6 (2.0)	2 (0.7)
Diabetic retinal edema	2 (0.7)	2 (0.7)	1 (0.3)	6 (2.0)
Ocular hypertension	2 (0.7)	0 (0.0)	4 (1.4)	3 (1.0)
Conjunctival hemorrhage	2 (0.7)	4 (1.3)	1 (0.3)	5 (1.7)
Corneal epithelium defect	0 (0.0	0 (0.0)	3 (1.0)	3 (1.0)
Influenza	1 (0.3)	0 (0.0)	0 (0.0)	6 (2.0)
Corneal disorder	0 (0.0)	0 (0.0)	5 (1.7)	0 (0.0)
Anterior chamber cell	0 (0.0)	1 (0.3)	1 (0.3)	3 (1.0)
Blepharitis	2 (0.7)	0 (0.0)	1 (0.3)	3 (1.0)
Corneal abrasion	0 (0.0)	1 (0.3)	1 (0.3)	3 (1.0)
Eye injury	1 (0.3)	0 (0.0)	3 (1.0)	1 (0.3)
Posterior capsule opacification	2 (0.7)	1 (0.3)	1 (0.3)	3 (1.0)
Posterior capsule rupture	0 (0.0)	2 (0.7)	4 (1.4)	0 (0.0)
Bronchitis	2 (0.7)	2 (0.7)	3 (1.0)	0 (0.0)
Cystoid macular edema	1 (0.3)	1 (0.3)	0 (0.0)	3 (1.0)
Sinusitis	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.0)
Uveitis	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.0)
Viral infection	1 (0.3)	1 (0.3)	0 (0.0)	3 (1.0)
Vitreous hemorrhage	0 (0.0)	1 (0.3)	3 (1.0)	0 (0.0)

TEAE = treatment-emergent adverse event.
Data are no. (%).
*Incidence 1% or more of patients in any treatment group in any study.

BCVA outcomes between the nepafenac 0.3% and vehicle treatment groups, and the results were consistent with the BCVA results observed in the overall study population. Given the positive results of both studies with regard to ME and the BCVA results observed in study 1, which are consistent with the findings[23,24] reported previously for

nepafenac 0.1%, it is reasonable to assume that the more likely error is a type II error (false negative) in study 2 than a type I error (false positive) in study 1 for the BCVA end points. Furthermore, it is also reasonable to assume that the 2 studies were conducted on similar patient populations. However, regional differences in medical practices (e.g., cataract surgery technique) and compliance also may have played a role.

In the present studies, ME was defined as a ≥30% increase in CSMT from the preoperative baseline. This increase in CSMT is well above the 10% coefficient of variation associated with SD OCT repeat testing variability[3] and translates to an absolute change of at least 60 μm in CSMT.[27] Central subfield macular thickness, instead of center point thickness, was chosen in the present and previous studies of nepafenac because it has been shown to have greater reliability than center point macular thickness.[28]

Macular edema remains a common cause of suboptimal vision after cataract surgery. Patients with diabetes have an increased risk of experiencing postsurgical complications and associated poor visual outcomes after cataract surgery.[3] Thus, it is important to monitor macular changes in patients with diabetes after cataract surgery. The signs and symptoms of clinically significant ME develop within 4 to 12 weeks after surgery and peak approximately 4 to 6 weeks after surgery.[29] Even in this study, most incidences of ME in the vehicle group occurred on the day 14, day 30, and day 60 visits, and the incidence was the highest on day 30 (Fig 8). The incidence of ME in the vehicle group observed in this study is consistent with that observed in the 2 nepafenac 0.1% studies conducted of patients with diabetes.[23,24] This present study evaluated patients for occurrence of ME over a 3-month postoperative period only. Hence, the efficacy of nepafenac 0.3% in patients with chronic ME (lasting for ≥6 months) needs to be assessed in future studies.

Kim et al[30] suggest that the use of NSAIDs before surgery may speed up visual recovery in the first several weeks after cataract surgery; however, the evidence supporting long-term benefits to prevent vision loss from ME at 3 months or more is lacking. This study also provides evidence supporting the benefits of using NSAIDs—prophylactically beginning 1 day before surgery, on the day of surgery, and continued for the initial 3-month postoperative period, in high-risk patients with diabetes.

In both of the studies, relatively few patients experienced AEs that were considered by the investigator to be treatment related, and the percentages were similar between the groups. It is known that increases in IOP can occur during or after cataract surgery.[31,32] None of the TEAEs of IOP increase that occurred in this study were considered treatment related. The overall safety profile of nepafenac 0.3%, dosed once-daily beginning the day before surgery and continued for 90 days thereafter, was comparable with that of nepafenac 0.1% dosed thrice-daily for the same duration in patients with diabetic retinopathy.

In conclusion, nepafenac 0.3% given once-daily for 90 days after surgery was superior to vehicle in reducing the risk of postoperative ME associated with cataract surgery in both the studies and in the pooled analysis, whereas the VA was improved and maintained in study 1 and in the pooled analysis. The safety results were consistent with the established safety profile of nepafenac, and no new safety concerns were observed.

Acknowledgments. The authors thank Abhijit Narvekar (former employee of Alcon Research Ltd) for his contribution towards the conduct of the study and Usha Gutti (Product Life-cycle Services-Global Medical and Clinical Services, Novartis Healthcare Pvt. Ltd) for assistance in medical writing and editing toward the development of this article.

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Footnotes and Financial Disclosures

Originally received: September 23, 2016.
Final revision: January 6, 2017.
Accepted: January 20, 2017.
Available online: March 4, 2017. Manuscript no. 2016-401.

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Presented in part at: European Society of Retina Specialists Annual Meeting, 2015 (Nice, France) and 2016 (Copenhagen, Denmark); European Society of Cataract & Refractive Surgeons Annual Meeting, 2015 and 2016 (Copenhagen, Denmark); and American Society of Cataract and Refractive Surgery Annual Meeting, 2016 (New Orleans, Louisiana).

Financial Disclosure(s):
The author(s) have made the following disclosure(s): R.P.S.: Consultant − Alcon (Fort Worth, TX), Regeneron, Genentech, Zeiss, Shire; Financial support - Genentech/Roche, Regeneron, Apellis

R.L.: Consultant − Alcon (Fort Worth, TX); Financial support − Bausch & Lomb, AMO, WaveTech, Omerous, AVS

A.P.: Financial support − Alcon (Fort Worth, TX), Bayer, Neovista, Novartis, Ophthotech, Regeneron, Quark, Santen

G.S.: Financial support − Novartis, Alcon (Fort Worth, TX), Bayer, Allergan, Boehringer Ingelheim, Genentech, Roche, Zeiss Meditec, Heidelberg Engineering, Optos, Centervue

G.C.-C. Cervantes: Consultant − Alcon (Fort Worth, TX)

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The studies were funded and managed by Alcon Research, Ltd., Fort Worth, Texas. The sponsor participated in the design of the study, data management, data analysis and interpretation, and preparation, review and, approval of the manuscript. The investigational product nepafenac 0.3% ophthalmic suspension is an Alcon product. These studies were the confirmatory trials that supported the registration of nepafenac 0.3% for the reduction in risk of macular edema associated with cataract surgery in patients with diabetes in the European Union.

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Obtained funding: none

Overall responsibility: Singh, Lehmann, Martel, Jong, Pollack, Tsorbatzoglou, Staurenghi, Cervantes-Coste Cervantes, Alpern, Modi, Svoboda, Adewale, Jaffe

Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CME** = cystoid macular edema; **CSMT** = central subfield macular thickness; **EMA CHMP** = European Medicines Agency Committee for Medicinal Products for Human Use; **FAS** = full analysis set; **FDA** = Food and Drug Administration; **IOL** = intraocular lens; **IOP** = intraocular pressure; **ME** = macular edema; **NPDR** = nonproliferative diabetic retinopathy; **NSAID** = nonsteroidal anti-inflammatory drug; **OCT** = optical coherence tomography; **PP** = per protocol; **SD** = spectral-domain; **SE** = standard error; **TEAE** = treatment-emergent adverse event; **VA** = visual acuity.

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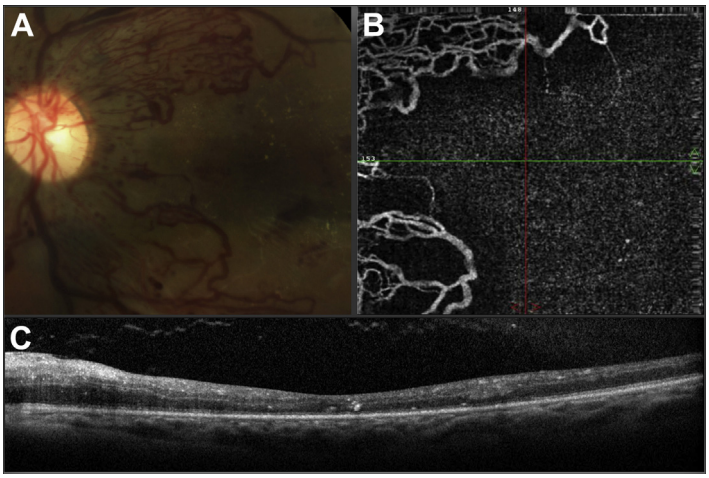
Pictures & Perspectives



Profound Macular Ischemia on Optical Coherence Tomography Angiography in Severe Diabetic Retinopathy

A 24-year-old woman with type I diabetes mellitus with significant macular ischemia in her left eye with a large net of neovascularization of the disc (Fig 1**A**). There is profound retinal capillary nonperfusion contrasting with perfusion of the neovascularization of the disc demonstrated on a full thickness 6×6-mm optical coherence tomography−angiography scan (Fig 1**B**), using Angiovue software (Optovue, Inc. Fremont, CA). On horizontal B-scan raster there is significant attenuation of the ellipsoid zone and outer retinal layers (Fig 1**C**).

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