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## Topical Nepafenec in Eyes with Non-Central Diabetic Macular Edema

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### Abstract

**Purpose**—To evaluate the effect of a topical non-steroidal anti-inflammatory drug, nepafenac 0.1%, in eyes with non-central diabetic macular edema (DME).

**Methods**—Multi-center double-masked randomized trial. Individuals with good visual acuity and non-center involved DME were randomly assigned to nepafenac 0.1% (N = 61) or placebo (nepafenac vehicle, N = 64) three times a day for 12 months. The primary outcome was mean change in OCT retinal volume at 12 months.

**Results**—Mean baseline retinal volume was 7.8 mm<sup>3</sup>. At 12 months, in the nepafenac and placebo groups respectively, mean change in retinal volume was -0.03 mm<sup>3</sup> and -0.02 mm<sup>3</sup> (treatment group difference: -0.02, 95% CI: -0.27 to 0.23, P = 0.89). Central involved DME was present in 7 eyes (11%) and 9 eyes (14%) at the 12-month visit (P = 0.79), respectively. No differences in visual acuity outcomes were identified. One study participant developed a corneal

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\*Personnel that participated in this trial are listed in the Appendix

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melt after using nepafenac in the non-study eye, which had a history of severe dry eye. No additional safety concerns were evident.

**Conclusion**—In eyes with non-central DME and good visual acuity, topical nepafenac 0.1% three times daily for 1 year likely does not have a meaningful effect on OCT-measured retinal thickness.

### Keywords

Diabetic Retinopathy Clinical Research Network; Nepafenac; Non-central DME; Topical NSAID

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### Introduction

Recent population-based studies in the U.S. and elsewhere report diabetic macular edema (DME) as the most common cause of vision loss in patients with diabetes mellitus.<sup>1, 2</sup> Prevalence data from the Centers for Disease Control in the U.S. population over age 40 suggest that many cases of DME do not involve the central macula.<sup>3</sup> Data from the ETDRS and the Protein Kinase C  $\beta$  Inhibitor study indicate that 22% to 30% of these cases may have central-involved DME by 1 year.<sup>4, 5</sup> A common management of non-central DME is careful observation until either the center of the macula becomes thickened, or until it is perceived that the central subfield of the macula is threatened.<sup>6</sup> A relatively safe treatment that reduces the risk of eyes with non-central involved DME from developing center-involved DME might be beneficial.

Elevated inflammatory markers have been found in patients with diabetic retinopathy suggesting that inflammation may have a role in the pathogenesis of DME.<sup>7, 8</sup> Reports from animal models have shown that topical non-steroidal anti-inflammatory drops (NSAIDs) have the capability of reaching the posterior segment of the eye.<sup>9</sup> Nepafenac rapidly penetrates the cornea and is deaminated by intraocular hydrolases to form the active metabolite amfenac. Nepafenac and amfenac inhibit activity from both cyclooxygenase isoforms (COX-1 and COX-2) responsible for prostaglandin synthesis and are frequently used to treat post-surgical (Irvine-Gass) cystoid macular edema.<sup>10</sup> There is some evidence that NSAIDs penetrate to the retina which might affect resolution of macular edema.<sup>11, 12</sup> Nepafenac is approved for use in the United States and elsewhere for the treatment of post-operative pain and inflammation associated with cataract surgery. In addition, it recently has been approved by some regulatory agencies in Europe,<sup>13</sup> but not by the U.S. Food and Drug Administration, for macular edema associated with cataract surgery in adult diabetes patients.

Given the prevalence of non-central involved DME and frequency of worsening to central-involved DME, this Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol was designed to assess whether topical nepafenac 0.1% might prevent worsening of DME as manifested primarily by optical coherence tomography (OCT) retinal volume and secondarily by other OCT and visual acuity outcomes among eyes with non-central involved DME.

## Methods

This phase II, multicenter, double-masked randomized clinical trial was conducted by the DRCR.net at 43 clinical sites throughout the United States. The protocol and Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by the institutional review board for each participating site. Each participant gave written informed consent to participate in the study. The study protocol (named “A Phase II Evaluation of Topical NSAIDs in Eyes with Non Central Involved DME”) is available on the DRCR.net website ([www.drcr.net](http://www.drcr.net)) and registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01331005). Key aspects of the study are summarized below.

### Study Population

Eligible study participants were at least 18 years of age, with type 1 or type 2 diabetes mellitus and had at least one eye with DME that did not involve the center of the macula. Patients were excluded if they were receiving systemic corticosteroids or vascular endothelial growth factor (VEGF) inhibitors, were concurrently using systemic prescription NSAIDs, or had an auto-immune disease judged to increase the risk for corneal complications.

Study-eligible eyes had a best corrected visual acuity Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS) letter score  $\geq 74$  (approximate Snellen equivalent of 20/32 or better), with definite retinal thickening by clinical examination, due to DME within 3000  $\mu\text{m}$  of, but not involving, the center of the macula. In addition, eligible eyes had at least two of eight non-central macular subfields with OCT thickness above a threshold value, or at least one non-central macular subfield with OCT thickness  $\geq 15 \mu\text{m}$  above a threshold value in Zeiss Cirrus (Carl Zeiss Meditec, Inc., Dublin, CA) or Heidelberg Spectralis (Heidelberg, Carlsbad, CA) OCT. Threshold values were defined as the average machine-specific OCT thickness in normal eyes + 2 standard deviations (Figure 1 online). In addition, the central subfield thickness was required to be less than the gender-specific mean thickness from a normal cohort + 2 standard deviations. Exclusion criteria included history of focal/grid macular laser within the last 6 months or other treatment for DME within the prior 4 months, an anticipated need for DME treatment during the course of study, lipid in the center of the macula, a history of panretinal photocoagulation (PRP) within 4 months prior to enrollment or an anticipated need for PRP within 6 months following randomization, aphakia, history of vitrectomy, cataract surgery within 1 year prior to enrollment, and any other major ocular surgery within 4 months prior to enrollment.

### Study Design

Study participants were enrolled by investigators at participating DRCR.net clinical sites (Appendix 1). Only one eye of each participant was entered. If both eyes were eligible for the study, the study eye was chosen by the investigator. Enrollment procedures to screen for eligibility included blood pressure measurement; best corrected E-ETDRS visual acuity; ocular examination, including intraocular pressure assessment, slit lamp and fundus examination in each eye; and OCT scan of the study eye.

The study began with a 30- to 60-day run-in phase to assess compliance with daily drop placement, during which participants were required to apply one eye drop (artificial tears, Tears Naturale Forte® [Alcon Research Inc., Fort Worth, TX]) three times per day into the study eye. Participants were considered “compliant” if the weight of the artificial tear bottle at end of the run-in phase was 80% or more of the target level expected for the number of days the participant had been in the run-in phase.

Compliant participants at the end of run-in phase proceeded to the randomization phase. Before randomization, blood pressure measurement, best corrected E-ETDRS visual acuity, ocular examination, including intraocular pressure assessment, slit lamp and fundus examination in each eye, OCT scan and fundus photography of the study eye were performed to confirm that the participant still met the eligibility criteria. Eligible eyes were assigned randomly (1:1) to topical eye drops of nepafenac 0.1% (Alcon Research Inc., Fort Worth, TX) or placebo (consisting of the nepafenac vehicle). Randomization, completed on the study website, was stratified by site. Masking of investigators, other site personnel, and participants to treatment group assignment was achieved by using identical opaque study bottles for both groups. Protocol visits occurred at 4, 8 and 12 months after randomization with the primary outcome at the 12-month visit. At each protocol visit, information about adverse events was solicited, visual acuity was measured, an ocular examination performed, and an OCT of the study eye was obtained. Fundus photographs also were obtained at the 12-month visit. Visual acuity was measured following a standardized refraction using the E-ETDRS method by a masked study certified technician. Optical coherence tomography images were obtained by study-certified OCT technicians masked to treatment groups. Baseline and 12-month OCT images were graded by a central reading center (Duke Reading Center, Duke University, Durham, NC) as were retinal fundus photographs (Fundus Photograph Reading Center, University of Wisconsin-Madison, Madison, WI).

Participants were instructed to apply the study drug (masked nepafenac or placebo) to the study eye as one drop, 3 times per day with subsequent light closure of the eyelid for about 30 seconds. Participants who wore contact lens were asked to remove the lens prior to application of study drops. Prior to dispensing the study drug to the participant, the weight of each bottle was obtained using a calibrated scale. Participants were instructed to bring all bottles that were dispensed at the previous visit when they returned for the next visit.

Treatment for DME during the study was not allowed unless the central subfield retinal thickness increased to at least the gender-specific and OCT machine-specific threshold value (defined as the mean + 2 standard deviations of a normal cohort. [Zeiss, Personal Communication December 15, 2010]<sup>14</sup>) and there was at least a 10% increase in central subfield thickness from baseline. If the eye did not meet these criteria and the investigator believed it was in the study participant's best interest to receive treatment for DME, a discussion with the Protocol Chair was required. Before initiation of DME treatment, OCT scans and fundus photographs were obtained. Treatment with study drug was continued regardless of any DME treatment received.

## Statistical Analysis

The primary efficacy analysis was a treatment group comparison of change in OCT volume from baseline to 12 months, adjusted for the baseline measurement (from randomization). Sample size was computed to be 120 eyes (60 per group) in order to have 90% power with type I error of 5% to detect a difference, assuming the true difference was  $0.40 \text{ mm}^3$  with a standard deviation of 0.60, allowing for 10% loss to follow up. The standard deviation of mean retinal volume change was based on unpublished DRCR.net data, in which the standard deviation for change in retinal volume from baseline to 1 year in 16 eyes with untreated non-center DME was  $0.37 \text{ mm}^3$  (95% confidence interval (CI): 0.28 to 0.56).

The primary analysis followed the intention-to-treat principle. Missing 12-month OCT and visual acuity measurements were imputed using the last observation carried forward. In eyes that received DME treatment during the study, the last OCT and visual acuity measurements prior to DME treatment were imputed for the 12-month visit value. Additional OCT measurements analyzed included the number of thickened subfields and retinal thickness change in the subfield with the maximum thickness at baseline. If randomization OCT values were not available or non-gradable, the enrollment visit OCT values were used as baseline (occurred in one eye in the nepafenac group). Optical coherence tomography values from spectral-domain machines were converted to time-domain equivalent values,<sup>15</sup> since a formula for converting thickness values from one spectral-domain to another spectral-domain value is not currently available. The change in OCT retinal volume and thickness was calculated using the original machine values (i.e. without converting to time-domain equivalent values), since the same OCT machine was used within individuals at baseline and follow-up visits.

Analysis of covariance adjusting for baseline value of the dependent variable was used to compare the change from baseline of the specific parameter between the two treatment groups. Confounding was assessed by including variables imbalanced between treatment groups that were potentially associated with the outcome as covariates in a model. Comparison of the two treatment groups for categorical outcomes was conducted using Fisher's exact test. All reported *P* values were two-sided. SAS software, version 9.3 (SAS, Cary, NC), was used for all analyses.

Safety outcomes included corneal complications (including corneal edema, superficial keratitis, corneal erosion, corneal thinning, corneal ulceration and corneal melting), intraocular pressure changes, cataract formation and cataract surgery, ocular inflammation and/or infection, and local reactions or symptoms such as redness, burning, itching or watering.

## Results

From June 2011 to November 2012, 169 participants were enrolled into the run-in phase of the study at 43 DRCR.net sites (Figure 2). Of these, 125 (74%) successfully completed the run-in phase and entered the randomized trial, with 61 assigned to the nepafenac group and 64 assigned to the placebo group. Median age was 60 years with 41% women and 66% White. Mean visual acuity letter score was 83 (approximate Snellen equivalent, 20/25).

Mean time-domain equivalent retinal volume was 7.8 mm<sup>3</sup> and mean time-domain equivalent central retinal subfield thickness was 223 μm. Participant and study eye characteristics according to treatment group are shown in Table 1.

### Study Completion

The 12-month study visit was completed by 57 participants (93%) in the nepafenac group and 60 participants (94%) in the placebo group (Figure 2). There were no deaths among the 8 participants who did not complete the study.

### Adherence with Study Drug

For participants who completed at least one protocol visit (58 [95%] in nepafenac and 61 [95%] in placebo), 57% and 62% of participants in the nepafenac and placebo groups, respectively, returned all bottles for compliance assessment during the study. Among the participants who did not return all bottles, the mean number of missing bottles was 3.0±2.6 and 3.8±4.0 bottles in the nepafenac and placebo groups, respectively, through the 12-month visit out of a mean total of approximately 19±3 bottles dispensed to each participant. Among participants with no missing bottles (33 in nepafenac, and 38 in placebo group), no participant had a cumulative final weight of the bottles that was less than 80% of the expected weight given the participant's duration in the study.

### OCT Outcomes

The 12-month changes in retinal volume from baseline (adjusted for baseline value) was -0.03 mm<sup>3</sup> (95% CI: -0.21 to 0.14) and 0.02 mm<sup>3</sup> (95% CI: -0.19 to 0.16) in the nepafenac and placebo groups respectively. The 12-month treatment group difference was -0.02 mm<sup>3</sup>, 95% CI: -0.27 to 0.23, *P* = 0.89 (Table 2, Figure 3), and 0.004 mm<sup>3</sup> [95% CI: -0.25 to 0.26] after adjusting for baseline lens status; results were similar when adjusting for duration of diabetes and HbA<sub>1c</sub> level. In the subgroup of eyes that returned all bottles dispensed (*n* = 33 for nepafenac and 38 for placebo), the 12-month mean change in retinal volume adjusted for baseline was -0.23 mm<sup>3</sup> (95% CI: -0.43 to 0.03 mm<sup>3</sup>) in nepafenac group and -0.05 mm<sup>3</sup> (95% CI: -0.24 to 0.14 mm<sup>3</sup>) in placebo group, with difference of -0.18 (95% CI: -0.46 to 0.10 mm<sup>3</sup>; *P* = 0.20). Treatment group differences among the other OCT outcomes (Table 2) could not be identified. Seven eyes (11%, 95% CI: 5% to 22%) in the nepafenac group and 9 eyes (14%, 95% CI: 7% to 25%) in the placebo group developed central-involved DME on OCT, defined as central subfield thickness at or more than the gender and OCT machine-specific average thickness from a normal cohort + 2 standard deviations with at least 10% increase from baseline (*P* = 0.79). In the nepafenac treated eyes, 6 of 40 (15%) phakic and 1 of 21 (5%) of the pseudophakic eyes developed central-involved DME versus 7 of 53 (13%) phakic and 2 of 11 (18%) pseudophakic eyes in the placebo group (*P* = 0.25 for interaction).

### DME Treatment

Prior to the 12-month visit, 5 eyes (8%) in the nepafenac group and 3 (5%) in the placebo group received DME treatment (*P* = 0.48). Of eyes that received DME treatment, 3 in the nepafenac group, and 1 in placebo group did not meet the protocol criteria for DME treatment, but received treatment after discussions with the Protocol Chair. All other eyes

that received DME treatment met the protocol-defined criteria for treatment. At the 12-month visit following the outcome assessments, an additional 5 eyes in each of the nepafenac and placebo groups, received DME treatment.

### Visual Acuity

At the 12-month visit, the mean E-ETDRS letter scores were  $82 \pm 7$  ( $\sim 20/25$  Snellen equivalent) and  $83 \pm 8$  ( $\sim 20/25$  Snellen equivalent) in the nepafenac and placebo groups, respectively. The 12-month change in E-ETDRS letter scores from baseline, adjusted for baseline values were 0.09 and -0.15 in the nepafenac and placebo groups, respectively, for a treatment group difference of 0.2 letters (95% CI: -1.8 to 2.3 letter difference,  $P = 0.82$ ). Three eyes (5%) in nepafenac and 2 eyes (3%) in placebo group lost 10 letters from baseline (Table 3).

### Safety Outcomes

All reported ocular adverse events in the study eyes are listed in Table 4. One case of corneal melt occurred in the non-study eye of a participant who used the study drug (nepafenac) in that eye. The affected non-study eye had a pre-existing history of severe dry eye. Following treatment with a tarsorrhaphy and topical antibiotics, the melt resolved with a residual corneal scar. Other corneal complications reported included superficial keratitis in one eye in each of the treatment groups.

The mean IOP at 12 months was similar between the two treatment groups ( $16 \pm 3$  and  $15 \pm 3$  mmHg in nepafenac and placebo groups, respectively). No eyes in either group had an increase in intraocular pressure of 10 mmHg or more nor an IOP of 30 mmHg or more. There were no differences in systemic adverse events between the two treatment groups that could not be attributed to chance.

### Discussion

This placebo-controlled randomized trial of 125 eyes with non-center involved DME found no evidence of a beneficial effect of 12 months of topical nepafenac 0.1% on retinal thickening based on OCT or visual acuity outcomes. This is in contrast to recent reports indicating a beneficial effect of nepafenac 0.1% on macular edema in patients with diabetes, but presumably from a different mechanism, specifically macular edema in the setting of cataract surgery.<sup>16, 17</sup> The results of this DRCR.net study also are not consistent with a recent report by Singh et al in which nepafenac compared with placebo showed a beneficial effect in preventing the development of macular edema in eyes of persons with diabetes who were undergoing cataract surgery.<sup>18</sup> However, it is unknown whether the beneficial effect seen in that study was attributable to post-surgical macular edema or on DME. The effect of NSAIDs on DME remains controversial among the ophthalmic community,<sup>10</sup> but the data from this DRCR.net study suggest that any beneficial effect of nepafenac on macular edema in patients with diabetes may be limited to a beneficial effect on macular edema associated with recent cataract surgery rather than DME.

Although this study was not powered to assess safety, nepafenac treatment appeared to be well-tolerated in the study eyes that were carefully screened for study enrollment and

monitored for risks, with no difference in the reported adverse effects in study eyes between the two treatment groups. The one case of corneal melt in this study occurred in a non-study eye treated with the study-supplied nepafenac, which was not intended for the non-study eye, and was applied by the participant to the non-study eye that had a pre-existing history of severe dry eye. Nevertheless, to our knowledge, this study is the first to compare the effect of a topical NSAID with that of a placebo drop when given for 12 months within a protocol in which study participants were monitored carefully for adverse effects.

Optical coherence tomography measured retinal volume was selected as the primary outcome for this phase 2 study because it provides a global assessment of the macula accounting for both potential increase and decrease in retinal thickening throughout the macula. Based on prior studies using fundus photographs,<sup>4, 5</sup> development of central DME among eyes with untreated non-central DME was projected to be 22% to 33%.<sup>5</sup> Our study found an OCT-based progression rate of non-central to central-involved DME of 14% (95% CI: 7% to 25%) in the placebo group, without a meaningful reduction in the progression rate in the nepafenac group. Prior to this study, limited data were available among similar cohorts to assess expected changes in retinal volume over time. Ultimately the amount of increase in retinal volume that occurred in the placebo group over 12 months was small. Thus, there was little opportunity to show a benefit of nepafenac treatment in terms of an effect on increasing retinal volume. However, the mean baseline retinal volume of 7.8 mm<sup>3</sup> is higher than the average retinal volume of 6.8 mm<sup>3</sup> in persons with diabetes but without diabetic retinopathy, indicating a reduction in retinal volume from nepafenac was potentially possible.<sup>19</sup>

As with any topical eye drop treatment study, medication adherence by the participant can affect the outcome. However, this is inherent with this type of treatment and we do not believe that additional methods to try to enhance adherence would have altered the results because the conclusions were not altered when limiting analyses to the participants who returned all the dispensed bottles and, according to bottle weight, received at least 80% of the targeted study drug dosing.

The results of this study directly apply only to eyes with non-center involved DME and may not be similar in other presentations of DME. In particular, the results of this study do not address whether topical nepafenac may be beneficial in reducing macular edema following cataract surgery among individuals with diabetes. In addition, the lack of benefit found with topical nepafenac does not preclude the possibility of benefit from other delivery methods of non-steroidal anti-inflammatory drugs, such as intravitreal injection.<sup>20</sup> Nevertheless, the results of this study in eyes with non-central DME and good visual acuity suggest that topical nepafenac 0.1% three times a day for 1 year does not have a meaningful effect on OCT-measured retinal thickness.

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## Appendix

### Diabetic Retinopathy Clinical Research Network Clinical Sites that participated on this protocol

Sites are listed in order by number of subjects enrolled into the study. The number of subjects enrolled is noted in parenthesis preceded by the site location and the site name. Personnel are listed as (I) for Study Investigator, (C) for Coordinator, (v) Visual Acuity Technician, and (P) for Photographer.

**Lakeland, FL Florida Retina Consultants (13):** Scott M. Friedman(I); Katrina L. Dawson(C); Damanda F. Fagan (C,V); Karen Sjoblom (C,V); Kimberly A. Williamson (C,V); Jessica Maldonado(C); Paige N. Walters(V); Steve Carlton(P); Allen McKinney(P)

**Boston, MA Joslin Diabetes Center (11):** George S. Sharuk(I); Paolo S. Silva(I); Christopher Michael Andreoli(I); Lloyd Paul Aiello(I); Sabera T. Shah(I); Jennifer K. Sun(I); Margaret E. Stockman (C,V); Troy Kieser (C,V); Hanna Kwak(C); Elizabeth S. Weimann(V); Leila Bestourous(V); Rita K. Kirby(V); John Head(P); Kate A. Palitsch(P); Robert W. Cavicchi(P)

**Baltimore, MD Elman Retina Group, P.A. (9):** Michael J. Elman(I); JoAnn Starr(C); Charlene K. Putzulo(C); Jennifer L. Belz(C); Dena Y. Salfer-Firestone(V); Pamela V. Singletary(V); Ashley Davis(V); Teresa Coffey(V); Daniel J. Ketner(P); Terri Cain(P); Peter Sotirakos(P)

**Paducah, KY Paducah Retinal Center (8):** Carl W. Baker(I); Tracey M. Caldwell(C); Lynnette F. Lambert (C,V); Tracey R. Martin(V); Mary J. Palmer(V); Tana R. Williams(P); Samantha Kettler(P)

**Plantation, FL Fort Lauderdale Eye Institute (8):** Stuart K. Burgess(I); Tirso M. Lara(I); Cindy V. Fernandez (C,V); Deborah Davis(V); Evelyn Quinchia(V); Karen Workman(P)

**Dubuque, IA Medical Associates Clinic, P.C. (6):** Michael H. Scott(I); Philomina M. Ozpirincci(C); Shannon R. Walsh(C); Matthew Arensdorff(V); Marcia J. Moyle(P); Brenda L. Tebon(P)

**Loma Linda, CA Loma Linda University Health Care, Department of Ophthalmology (6):** Joseph T. Fan(I); Mukesh Bhogilal Suthar(I); Michael E. Rauser(I); Kara E. Halsey (C,V); Brandi J Perez (C,V); Rene G. Obispo(P); Jesse Knabb(P); Diana Povero(P)

**Glenview, IL North Shore University Health System (5):** Manvi P. Maker(I); Veeral S. Sheth(I); Mira Shiloach(C); Courtney Kischuk (C,V); Qin Zhou (C,V); Nicole Pelkofer(P)

**Knoxville, TN Southeastern Retina Associates, P.C. (5):** Joseph M. Googe(I); Kristina Oliver(C); Jennifer Beerbower(V); Kathy L. Schulz(V); Ann Arnold(V); Cecile Hunt(V); Nicole Grindall(V); Jerry K. Whetstone(P); Chris Morris(P); Sarah M. Oelrich(P)

**Oklahoma City, OK Dean A. McGee Eye Institute (5):** Ronald M. Kingsley(I); Reshial D. Ellis (C,V); Sonny Icks (C,V); Brittany L Ross (C,V); Vanessa A. Bergman (C,V); Amanda M Butt(P); Russ Burris(P)

**Charlotte, NC Charlotte Eye, Ear, Nose and Throat Assoc., PA (4):** Justin C. Brown(I); Andrew N. Antoszyk(I); Ashley A. McClain (C,V); Jenna T. Herby (C,V); Merri F Walker (C,V); Sarah A. Ennis(V); Angella S. Karow(V); Swann J Bojaj(P); Michael D. McOwen(P); Lynn Watson(P); Loraine M. Clark(P); Donna R. Styles(P); Donna McClain(P); Susannah J Held(P); Uma M. Balasubramaniam(P); Lisa A. Jackson(P)

**Indianapolis, IN Raj K. Maturi, M.D., P.C. (3):** Raj K. Maturi(I); Laura A. Bleau (C,V); Ashley M. Harless(C); Charlotte Harris(P); Thomas Steele(P); Kerri A Wellman(P); Abby Maple(P)

**Seattle, WA University of Washington Medical Center (3):** James L.

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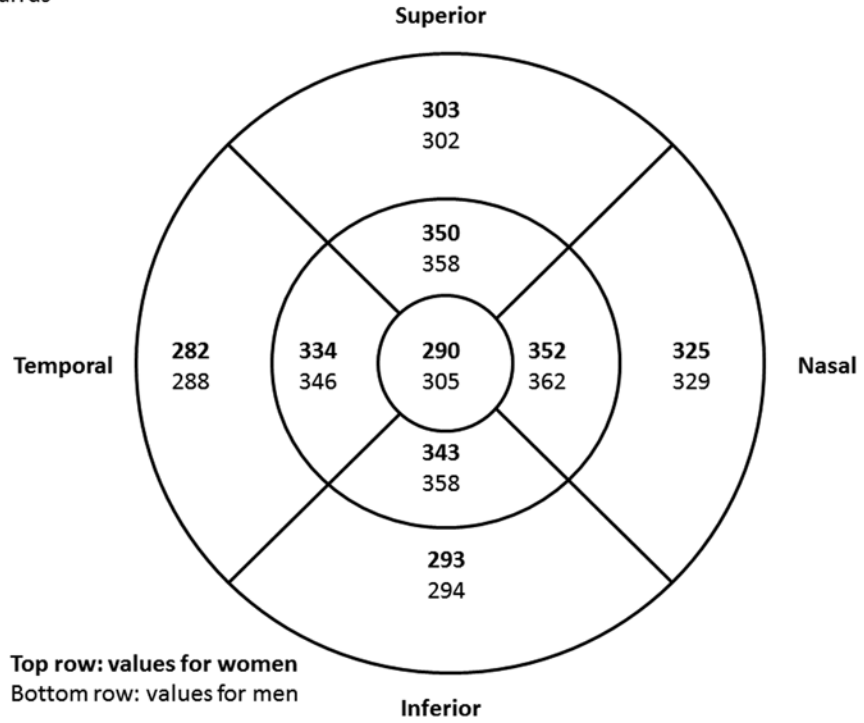
**Executive Committee:** Lloyd Paul Aiello (2002-present; Chair 2002 – 2005), Andrew N. Antoszyk (2009; 2014 - present), Carl W. Baker (2009-present), Roy W. Beck (2002-present), Neil M. Bressler (2006-present; Chair 2006 - 2008), Susan B. Bressler (2009-Present), Ronald P. Danis (2004-present), Matthew D. Davis (2002-present), Michael J. Elman (2006-present; Chair 2009 and 2012), Frederick L. Ferris III (2002-present), Adam R. Glassman (2005-present), Jeffrey G. Gross (2012-present), Glenn J. Jaffe (2012-present), Lee M. Jampol (2012-present; Chair 2013-present), Raj K. Maturi (2009-2011, 2013-Present), Eleanor Schron (2009-present), Jennifer K. Sun (2009-present), John A. Wells (2012-present). Prior Members: Abdhish Bhavsar (2007-2008, 2010-2012), Alexander J. Brucker (2009-2011), Kakarla V. Chalam (2009-2011), Donald F. Everett (2002-2009), Joan Fish (2008 - 2009), Scott Friedman (2007 –2013), Joseph Googe, Jr. (2009-2011), Diana M. Holcomb (2011-2012), Andreas Lauer (2007-2008), Dennis M. Marcus (2011-2012), Ashley McClain (2013); Brandi J. Perez (2013), Ingrid U. Scott (2009-2010), JoAnn Starr (2009-2011).

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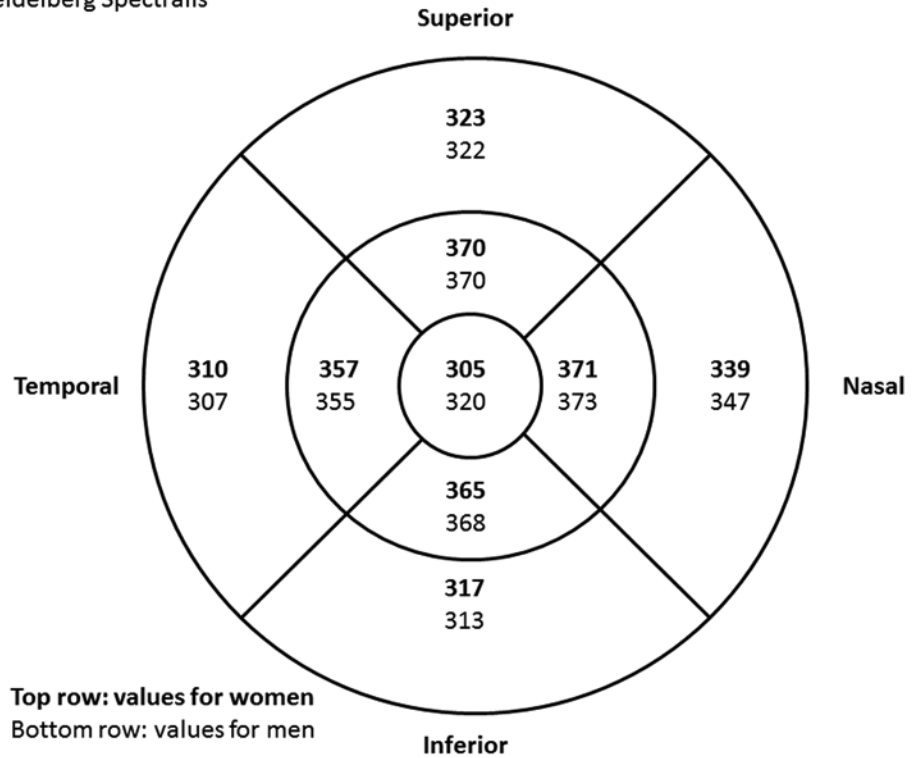
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A. Zeiss Cirrus

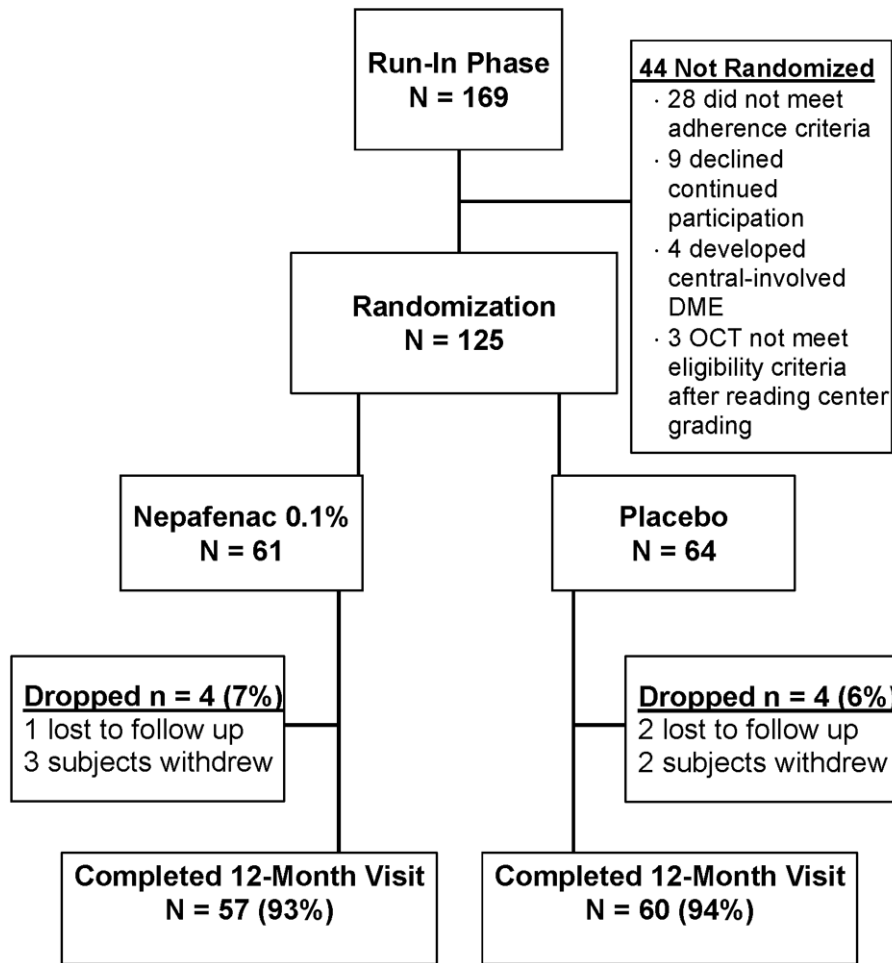


B. Heidelberg Spectralis



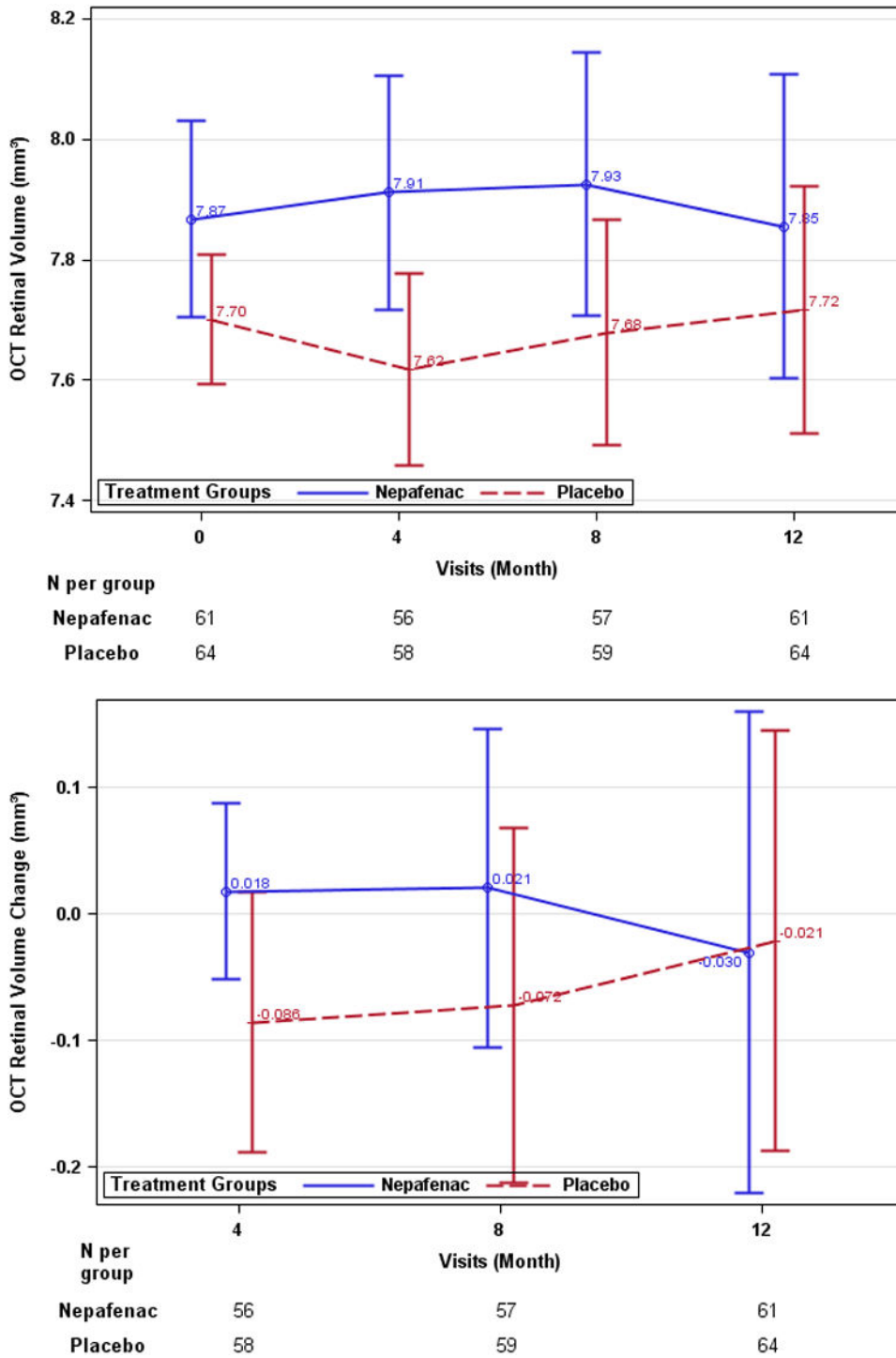
**Figure 1.** OCT threshold values to define eligibility in Zeiss Cirrus (Zeiss, Personal Communication, December 15, 2010) (A) and Heidelberg Spectralis<sup>14</sup> (B) machines. Values in top row (bold

font) are women-specific, and values in bottom row (regular font) are men-specific. Threshold is defined as the mean OCT thickness value from normal cohort+ 2 standard deviations (SD). For eligibility, study eye must have had central subfield thickness below the threshold, and meeting one of the following: 1) At least 2 non-central subfields with thickness values above threshold; or 2) At least 1 non-central subfield with thickness value more than 15  $\mu\text{m}$  above threshold.



**Figure 2.**  
Summary of Study Recruitment.





**Figure 3.** Optical Coherence Tomography retinal volume data (last observation carried forward). A: mean time-domain-equivalent retinal volume (mm<sup>3</sup>). B: mean retinal volume change from baseline (mm<sup>3</sup>). Error bars represent 95% confidence limit.

**Table 1**  
**Baseline Characteristics of Participants in the Randomized Trial**

	<b>Nepafenac</b>	<b>Placebo</b>
	<b>N = 61</b>	<b>N = 64</b>
<b>Age, years</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	60 (52, 68)	59 (51, 66)
65, N (%)	21 (34%)	20 (31%)
<b>Gender, N (%)</b>		
Women	23 (38%)	28 (44%)
<b>Race/Ethnicity, N (%)</b>		
White	44 (72%)	38 (59%)
African American	7 (11%)	13 (20%)
Hispanic or Latino	5 (8%)	12 (19%)
American Indian/Alaskan Native	0 (0%)	1 (2%)
Native Hawaiian/Other Pacific Islander	2 (3%)	0 (0%)
Asian	2 (3%)	0 (0%)
More than one race	1 (2%)	0 (0%)
<b>Type of Diabetes, N (%)</b>		
Type I	5 (8%)	5 (8%)
Type II	53 (87%)	56 (88%)
Uncertain	3 (5%)	3 (5%)
<b>Duration of Diabetes, years</b>		
Mean±SD	19±11	17±11
10 years, N (%)	51 (84%)	44 (69%)
<b>HbA1c, % *</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	8.1 (7.1, 8.7)	7.9 (7.2, 10.0)
<8%	28 (47%)	32 (54%)
8%	32 (53%)	27 (46%)
<b>Contact Lens Wear, % (N)</b>		
	2 (3%)	3 (5%)
<b>E-ETDRS VA Letter Score,</b>		
Mean±SD	82±6	83±7
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	82 (78, 86)	84 (78, 89)
<b>Snellen Equivalent VA</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	20/25 (20/32, 20/20)	20/20 (20/32, 20/16)
<b>History of DME treatment, N (%)</b>		
	30 (49%)	28 (44%)
<b>History of Panretinal Photocoagulation, N (%)</b>		
	13 (21%)	11 (17%)
<b>Level of Diabetic Retinopathy from Reading Center grading, N (%)</b>		
Microaneurysms only	0 (0%)	1 (2%)

	<b>Nepafenac</b>	<b>Placebo</b>
	<b>N = 61</b>	<b>N = 64</b>
Mild to moderate NPDR	28 (46%)	25 (39%)
Severe NPDR	16 (26%)	23 (36%)
PDR or Prior PRP	16 (26%)	15 (23%)
Cannot be graded	1 (2%)	0 (0%)
<b>Intraocular Pressure (mm Hg)</b>		
Mean±SD	16±3	16±4
<b>Lens Status, N (%)</b>		
Phakic	40 (66%)	53 (83%)
PC IOL	21 (34%)	11 (17%)
<b>OCT Machine, N (%)</b>		
Zeiss Cirrus	37 (61%)	41 (64%)
Heidelberg Spectralis	24 (39%)	23 (36%)
<b>OCT Central Subfield Thickness, <math>\mu\text{m}^{\dagger}</math></b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	228 (213, 242)	215 (205, 236)
Mean±SD	227±29	218±25
<b>OCT Retinal Volume, <math>\text{mm}^3</math> (Primary Outcome Variable)<sup>††</sup></b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	7.8 (7.4, 8.2)	7.7 (7.5, 8.0)
Mean±SD	7.9±0.6	7.7±0.4
<b>Number of thickened non-central subfields,</b>		
Mean ±SD	3±2	3±2

SD = standard deviation; DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; OCT = optical coherence tomography; PC IOL = posterior chamber intraocular lens

\* Not available for 1 and 5 participants in the nepafenac and placebo groups respectively.

<sup>†</sup> OCT CSF thickness conversion to Zeiss Stratus was applied as follows:  $-43.12 + 1.01 \times \text{Zeiss Cirrus}$ ;  $-72.76 + 1.03 \times \text{Spectralis}$ .

<sup>††</sup> OCT retinal volume conversion to Zeiss Stratus was applied as follows:  $-1.21 + 1.02 \times (((\text{CSF} \times (4/9) + \text{inner superior subfield thickness} \times (8/9) + \text{inner temporal subfield thickness} \times (8/9) + \text{inner inferior subfield thickness} \times (8/9) + \text{inner nasal subfield thickness} \times (8/9) + \text{outer superior subfield thickness} \times 3 + \text{outer temporal subfield thickness} \times 3 + \text{outer inferior subfield thickness} \times 3 + \text{outer nasal subfield thickness} \times 3) \times 3 \times 3 \times 3.14) / 16) / 1000$ ;  $-2.05 + 1.06 \times \text{Spectralis}$ . One volume value in nepafenac group used enrollment visit value because randomization visit reading center-graded value was “nongradable”

**Table 2**  
**OCT outcomes at 12-month visit (last observation carried forward)**

	<b>Nepafenac</b>	<b>Placebo</b>
	<b>N=61</b>	<b>N=64</b>
<b>Retinal Volume (Primary Outcome)<sup>§</sup></b>		
<b>At Baseline *</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	7.82 (7.36, 8.19)	7.74 (7.45, 8.03)
Mean ±SD	7.87±0.64	7.70±0.43
<b>At 12-month Visit, mm<sup>3</sup>*</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	7.72 (7.28, 8.33)	7.63 (7.18, 8.10)
Mean ±SD	7.85±0.99	7.72±0.82
<b>Change from Baseline, mm<sup>3</sup></b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	-0.10 (-0.27, 0.10)	-0.10 (-0.30, 0.12)
Mean ±SD	-0.03±0.74	-0.02±0.67
<b>Mean change from baseline adjusted for baseline value, estimate (95%CI), mm<sup>3</sup></b>	-0.03 (-0.21 to 0.14)	-0.02 (-0.19 to 0.16)
<b>Difference in mean change from baseline, adjusted for baseline value, estimate (95%CI)</b>	-0.02 (-0.27 to 0.23)	
<b>P value</b>	0.89	
<b>OCT Central Subfield<sup>¶</sup></b>		
<b>At Baseline, μm *</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	228 (213, 242)	215 (205, 236)
Mean ±SD	227±29	218±25
<b>At 12-month Visit, μm *</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	230 (210, 244)	219 (196, 243)
Mean ±SD	236±55	226±45
<b>Change from Baseline, μm **</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	0 (-10, 9)	-1 (-11, 8)
Mean ±SD	9±45	7±35
<b>Mean change from baseline adjusted for baseline value, estimate (95%CI), μm **</b>	9 (-1 to 19)	7 (-3 to 17)
<b>Difference in mean change from baseline, adjusted for baseline value, estimate (95%CI)</b>	2 (-13 to 16)	
<b>P value</b>	0.81	
1 log OCT step increase (worsen), N (%) **	4 (7%)	5 (8%)
1 log OCT step decrease (improve), N (%) **	0 (0%)	1 (2%)
Central-involved DME, N (%) ** †	7 (11%)	9 (14%)
Change in number of thickened subfields, Median (Min, Max) **	0 (-5, 4)	0 (-3, 4)
12-month change in thickness of the non-central subfield with maximum thickness at baseline, mean (95%CI), μm **	-1 (-10 to 8)	-3 (-15 to 8)

\* Values are converted to time-domain equivalent values

\*\* Change values are not converted to time-domain equivalent values since they occurred within the same machine within subjects

§ Original 12-month values are not available in 6 and 9 eyes of nepafenac and placebo groups respectively because 12-month visit was not completed or non-gradable OCT value and were imputed from the last available measurement; values at or before DME treatment were carried forward in 5 and 3 eyes of nepafenac and placebo groups respectively.

¶ Original 12-month values are not available in 4 eyes of each of nepafenac and placebo groups because 12-month visit was not completed or non-gradable OCT value and were imputed from the last available measurement; values at or before DME treatment were carried forward in 5 and 3 eyes of nepafenac and placebo groups respectively.

† Define as CSF thickness at or more than the gender and OCT machine-specific average thickness from a normal cohort + 2 standard deviations, with at least 10% increase in thickness from baseline.

**Table 3**  
**Visual Acuity at 12-month visit (Last Observation Carried Forward)**

	<b>Nepafenac</b>	<b>Placebo</b>
<b>Visual Acuity<sup>¶</sup></b>	<b>N=61</b>	<b>N=64</b>
<b>At Baseline</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	82 (78, 86)	84 (78, 89)
Mean $\pm$ SD	82 $\pm$ 6	83 $\pm$ 7
<b>At 12-Month Visit</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	84 (78, 87)	85 (78, 88)
Mean $\pm$ SD	82 $\pm$ 7	83 $\pm$ 8
<b>Change from Baseline</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> Percentile)	0 (-3 to 3)	0 (-3, 3)
Mean $\pm$ SD	0.2 $\pm$ 5.7	-0.3 $\pm$ 6.2
<b>Mean change in letter score from baseline adjusted for baseline value, estimate (95%CI)</b>	0.09 (-1.4 to 1.6)	-0.15 (-1.6 to 1.3)
Difference in mean change from baseline, adjusted for baseline value, estimate (95%CI)	0.2 (-1.8 to 2.3)	
P value	0.82	
<b>Change from Baseline, n (%)</b>		
10 letters improve	4 (7%)	1 (2%)
5-9 letters improve	7 (11%)	5 (8%)
Same $\pm$ 4 letters	40 (66%)	46 (72%)
5-9 letters worse	7 (11%)	10 (16%)
14-10 letters worse	2 (3%)	1 (2%)
15 letters worse	1 (2%)	1 (2%)

<sup>¶</sup>Original 12-month values are not available in 4 eyes of each of nepafenac and placebo groups because 12-month visit was not completed and were imputed from the last available measurement; values at or before first DME treatment were carried forward in 5 and 3 eyes of nepafenac and placebo groups respectively.

**Table 4**  
**All reported adverse events in study eyes**

Ocular Adverse Events	Nepafenac N=61	Placebo N=64
	N %	N %
Blurred vision	4 (7%)	5 (8%)
Floaters	3 (5%)	4 (6%)
Eye itching	0 (0%)	3 (5%)
Proliferative diabetic retinopathy	0 (0%)	3 (5%)
Vision decreased	3 (5%)	3 (5%)
Burning eyes	2 (3%)	0 (0%)
Cataract	2 (3%)	2 (3%)
Conjunctivitis	0 (0%)	2 (3%)
Eye discharge	2 (3%)	0 (0%)
Eye pain	0 (0%)	2 (3%)
Visual acuity decreased	2 (3%)	1 (2%)
Watering eyes	0 (0%)	2 (3%)
Allergic conjunctivitis	0 (0%)	1 (2%)
Basal cell carcinoma	0 (0%)	1 (2%)
Blepharitis (eyelid irritation)	1 (2%)	1 (2%)
Cataract extraction	0 (0%)	1 (2%)
Chemical conjunctivitis	0 (0%)	1 (2%)
Corneal defect	1 (2%)	0 (0%)
Dot hemorrhages	0 (0%)	1 (2%)
Double vision	1 (2%)	0 (0%)
Eye ache	1 (2%)	1 (2%)
Eye irritation	1 (2%)	1 (2%)
Eye tearing	1 (2%)	0 (0%)
Eyelid disorder	1 (2%)	0 (0%)
Eyelid pain	1 (2%)	0 (0%)
Foreign body sensation in eyes	0 (0%)	1 (2%)
Glare	1 (2%)	1 (2%)
IVth nerve palsy	1 (2%)	0 (0%)
Iritis (anterior uveitis, iridocyclitis)	0 (0%)	1 (2%)
Itching	1 (2%)	0 (0%)
Mucus in eyes	0 (0%)	1 (2%)
Neovascularization	0 (0%)	1 (2%)
Nuclear sclerosis	0 (0%)	1 (2%)
Posterior vitreous detachment	0 (0%)	1 (2%)
Preretinal hemorrhage	1 (2%)	0 (0%)
Pseudoexfoliation of lens capsule	0 (0%)	1 (2%)

Ocular Adverse Events	Nepafenac N=61	Placebo N=64
	N %	N %
Ptosis	1 (2%)	1 (2%)
Sensitivity to light (photophobia)	0 (0%)	1 (2%)
Spots before eyes	0 (0%)	1 (2%)
Subconjunctival hemorrhage	0 (0%)	1 (2%)
Subconjunctival/conjunctival hemorrhage	0 (0%)	1 (2%)
Superficial punctate keratitis	1 (2%)	1 (2%)
Viral conjunctivitis	0 (0%)	1 (2%)
Visual field defect	1 (2%)	0 (0%)
Vitreous floater	1 (2%)	0 (0%)

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