

# Biosimilar Ranibizumab (Ranieyes) Safety and Efficacy in the Real World: BRESER Study

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## Abstract

**Purpose:** To evaluate the early real-world clinical outcomes regarding the safety and efficacy after administration of a ranibizumab biosimilar (Ranieyes). **Methods:** This multicenter retrospective uncontrolled observational study incorporated data from 7 centers in India. All patients were treated with at least 1 intravitreal injection of 0.5 mg of ranibizumab biosimilar between July 2022 and July 2023 for various indications. **Results:** A total of 474 ranibizumab biosimilar injections were given in 268 eyes of 254 patients. Indications were diabetic macular edema (DME) (n = 112), macular neovascularization (MNV) (n = 92), retinal vein occlusion (RVO) (n = 54), cystoid macular edema (n = 4), and proliferative diabetic retinopathy with vitreous hemorrhage (n = 6). The mean logMAR BCVA ( $\pm$ SD) improved significantly from baseline to the last follow-up as follows: DME cases, from  $0.77 \pm 0.37$  (Snellen equivalent, 6/36) to  $0.43 \pm 0.25$  (6/15) ( $z = -8.0$ ;  $r = -0.8$ ); MNV cases, from  $0.95 \pm 0.53$  (6/60) to  $0.59 \pm 0.42$  (6/24) ( $z = -7.1$ ;  $r = -0.8$ ); RVO cases, from  $0.83 \pm 0.40$  (6/45) to  $0.44 \pm 0.32$  (6/15) ( $z = -5.5$ ;  $r = -0.8$ ) (all  $P < .001$ ). All groups also had a significant improvement in the central subfield thickness (all  $P < .001$ ). No site reported drug-related adverse events (eg, inflammation, vasculitis, systemic adverse effects). **Conclusions:** The preliminary real-world data from this limited early series suggest that Ranieyes has clinical efficacy and is safe as a ranibizumab biosimilar across the approved indications.

## Keywords

Ranieyes, ranibizumab, biosimilars, anti-VEGF, retina, ophthalmology

## Introduction

Intravitreal (IVT) biologic agents inhibiting vascular endothelial growth factor (VEGF) have become the primary treatment modality for the management of retinal vascular diseases.<sup>1</sup> However, the financial burden of frequent IVT injections required to maintain disease inactivity is a key factor in patient noncompliance in India,<sup>2</sup> which might be true in other regions as well.<sup>3</sup> Biosimilars are meant to address this issue and increase access to IVT anti-VEGF agents without compromising their well-established safety or efficacy profiles.<sup>3</sup>

A biosimilar is defined as a molecule that is highly similar in safety, purity, and potency to another biologic that has already been approved for clinical use, known as the originator biologic or reference product, and that has no clinically meaningful differences from the originator product.<sup>1</sup> Biosimilars typically cost 20% to 30% less than the originator product.<sup>4</sup>

There is a misperception that biosimilars are similar to generic drugs and that the safety and efficacy of in these products may be compromised, inducing a nocebo effect.<sup>5</sup> In the recently published Bio-USER Survey, the majority of ophthalmologists in the United States and Europe expressed concern about the safety and efficacy of biosimilars.<sup>6</sup> This may be based on the immunogenic reaction caused by the first ranibizumab biosimilar in India in 2015 (Razumab, Intas Pharmaceuticals Ltd). However, based on our understanding, the inflammation associated with this product was caused by the high endotoxin limit set by the regulatory authorities in 2015. After further restriction of the endotoxin limit by the US Food and Drug Administration (FDA), companies have changed the manufacturing process to meet the updated limits.<sup>7</sup> This alteration may have resulted in a reduction in safety concerns, with no alarming signs of inflammation in the past 5 years.

Based on the results of a biosimilar perception survey in India in collaboration with the International Retina Biosimilar Study Group (Inter-BIOS Group) and the Vitreoretinal Society of India, the majority of clinicians said they prefer real-world data over biosimilar trial data.<sup>8</sup> In this paper, we share our preliminary real-world experience with Ranieyes (Lupin Ltd), which is the third biosimilar ranibizumab approved by the Drug Controller General of India (DCGI).<sup>9</sup> The phase 3 trial data have been published.<sup>10</sup> To our knowledge, real-world clinical data on Ranieyes use have not been published. Thus, we analyzed the early clinical outcomes of the safety and efficacy of Ranieyes administration. This study is part of an initiative by the Inter-BIOS Group.

## Methods

This interventional retrospective uncontrolled multicenter study included data from 7 eye care centers in India. Institutional review board approval was obtained at each center, and the investigators adhered to the tenets of the Declaration of Helsinki. All patients provided informed consent to use their data for research purposes. The data were extracted anonymously. All patients were managed with at least 1 IVT injection of Ranieyes 0.5 mg between July 2022 and July 2023. To be included in the study, patients had to have a minimum of 4 weeks of follow-up.

The approved indications for Ranieyes administration included retinal vein occlusion (RVO) (branch RVO [BRVO], central RVO [CRVO], and hemi-RVO), diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), myopic macular neovascularization (MNV), and secondary MNV. The use of Ranieyes was off-label in patients with proliferative diabetic retinopathy (PDR), with cystoid macular edema (CME) related to retinitis pigmentosa (RP), and who had previous cataract surgery because the biosimilar has not yet received DCGI approval for these indications. Structural changes resulting from

pathologies other than the diseases mentioned above and eyes with vitreoretinal interface pathologies were excluded.

Each patient had visual acuity (VA) measurements with a Snellen chart (converted to logMAR notation for analysis), central subfield thickness (CST) measurement with spectral-domain optical coherence tomography (OCT), and intraocular pressure measurement. A complete ophthalmic examination, including a slitlamp and dilated fundus evaluation, was performed at baseline and at follow-up visits. Efficacy was assessed based on the best-corrected VA (BCVA) and CST. The baseline and the last follow-up data after Ranieyes injection were considered for analysis.

Descriptive statistics, including the mean  $\pm$  SD, median, and range, were calculated for continuous variables. The Wilcoxon signed rank test was used to analyze the differences between the preinjection and postinjection efficacy because of the nonparametric nature of the data assessed by the Shapiro-Wilk test. For small-group analyses, a paired *t* test was used. The safety analysis, including all the indications, was performed as a combined analysis. However, the efficacy assessment was performed based on disease because the combined data might not be the correct representation of efficacy as a result of the different characteristics of the diseases. Statistical significance was set at  $P < .05$ .

## Results

In this study, 474 Ranieyes injections were given in 268 eyes of 254 patients (14 bilateral). The mean follow-up after the first injection was  $7.7 \pm 5.4$  weeks. Table 1 shows the patients' demographics and the number of injections received.

The indications for the injections were DME in 112 cases, MNV in 92 cases (78 nAMD; 7 polypoidal choroidal vasculopathy; 7 secondary MNV), RVO in 54 cases (47 BRVO; 7 CRVO), CME in 4 cases (2 pseudophakic; 2 RP related), and PDR with vitreous hemorrhage in 6 cases.

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**Table 1.** Patient Demographics.

| Parameter                        | Value             |
|----------------------------------|-------------------|
| Total ranibizumab injections (n) | 474               |
| Total patients (n)               | 254               |
| Eyes (n)                         | 268               |
| Age (y)                          |                   |
| Mean $\pm$ SD                    | 58.20 $\pm$ 10.74 |
| Range                            | 24, 90            |
| Male sex, n (%)                  | 149 (58.7)        |
| Mean follow-up (wk) $\pm$ SD     |                   |
| Mean $\pm$ SD                    | 7.7 $\pm$ 5.4     |
| Range                            | 4, 28             |
| Treatment naïve, n (%)           | 186 (69.4)        |
| Pretreated, n (%)                | 82 (30.5)         |
| Injections, n (%)                |                   |
| 1                                | 135 (50.3)        |
| 2                                | 68 (25.3)         |
| 3                                | 58 (21.6)         |
| 4                                | 7 (2.6)           |

Approximately 50% of the patients received a single injection (Table 1). The pretreated eyes had previously received other IVT anti-VEGFs (bevacizumab, ranibizumab, or aflibercept) and/or steroids (IVT triamcinolone or an IVT dexamethasone implant). The median number of anti-VEGF injections in previously treated cases was 3 (range, 1-6).

## Efficacy

**Visual Acuity.** Table 2 shows the BCVA (logMAR and Snellen equivalent) at baseline and the last follow-up. The BCVA improved significantly overall ( $z = -12.2$ ;  $r = -0.8$ ) and in the DME group ( $z = -8.0$ ;  $r = -0.8$ ; mean follow-up, 6.8  $\pm$  4.9 weeks [range 4-24]), MNV group ( $z = -7.1$ ;  $r = -0.8$ ; mean follow-up, 8.6  $\pm$  6.3 weeks [range, 4-28]), and RVO group ( $z = -5.5$ ;  $r = -0.8$ ; mean follow-up, 8.0  $\pm$  4.7 weeks [range, 4-16]) (all  $P < .001$ ).

Subanalysis of secondary MNV also showed a significant improvement, from 0.83  $\pm$  0.26 (Snellen equivalent, 6/45) at baseline to 0.45  $\pm$  0.23 (Snellen equivalent, 6/15) at the last follow-up ( $P = .04$ ; 95% CI, 0.012-0.588; mean follow-up, 7.3  $\pm$  8.5 weeks [range, 4-28]). In eyes with PDR and a vitreous hemorrhage, the overall mean logMAR BCVA was 0.71  $\pm$  0.54 (Snellen equivalent, 6/30) at baseline, which improved to 0.28  $\pm$  0.37 (Snellen equivalent, 6/12) at the last follow-up; however, the difference was not statistically significant ( $P = .13$ ; 95% CI, -0.164 to 1.031; mean follow-up, 5.6  $\pm$  1.8 weeks [range, 4-8]).

**Central Subfield Thickness.** Table 2 shows the CST at baseline and the last follow-up. Figure 1, A-C, shows representative cases of DME, nAMD with subretinal fluid, and BRVO with CME at baseline and 4 weeks after a single injection. The CST improved significantly overall ( $z = -13.3$ ;  $r = -0.8$ ) and in the DME group ( $z = -8.3$ ;  $r = -0.8$ ), MNV group ( $z = -7.8$ ;  $r = -0.8$ ), and RVO group ( $z = -6.4$ ;  $r = -0.9$ ) (all  $P < .001$ ).

**Table 2.** BCVA and CST at Baseline and Last Follow-up.

| Parameter/Indication           | Mean $\pm$ SD      |                   | P Value <sup>a</sup> |
|--------------------------------|--------------------|-------------------|----------------------|
|                                | Baseline           | Last Follow-up    |                      |
| <b>BCVA</b>                    |                    |                   |                      |
| Cumulative (N=268)             |                    |                   | <.001                |
| LogMAR                         | 0.84 $\pm$ 0.45    | 0.49 $\pm$ 0.34   |                      |
| Snellen equivalent             | 6/45               | 6/18              |                      |
| DME (n = 112)                  |                    |                   | <.001                |
| LogMAR                         | 0.77 $\pm$ 0.37    | 0.43 $\pm$ 0.25   |                      |
| Snellen equivalent             | 6/36               | 6/15              |                      |
| MNV(n = 92)                    |                    |                   | <.001                |
| LogMAR                         | 0.95 $\pm$ 0.53    | 0.59 $\pm$ 0.42   |                      |
| Snellen equivalent             | 6/60               | 6/24              |                      |
| RVO (n = 54)                   |                    |                   | <.001                |
| LogMAR                         | 0.83 $\pm$ 0.40    | 0.44 $\pm$ .032   |                      |
| Snellen equivalent             | 6/45               | 6/15              |                      |
| <b>CST (<math>\mu</math>m)</b> |                    |                   |                      |
| Cumulative (N=268)             | 425.55 $\pm$ 127.0 | 293.2 $\pm$ 100.6 | <.001                |
| DME (n = 112)                  | 432.7 $\pm$ 117.6  | 309.2 $\pm$ 105.9 | <.001                |
| MNV(n = 92)                    | 388.7 $\pm$ 118.7  | 285.1 $\pm$ 93.8  | <.001                |
| RVO (n = 54)                   | 490.0 $\pm$ 128.6  | 284.2 $\pm$ 100.9 | <.001                |

Abbreviations: BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; MNV, macular neovascularization; RVO, retinal vein occlusion.

<sup>a</sup>All clinically significant at  $P < .05$  (Wilcoxon signed rank test).

In eyes with PDR and a vitreous hemorrhage, the overall mean CST at baseline was 341.6  $\pm$  183.7  $\mu$ m, improving to 229.5  $\pm$  25.3  $\mu$ m at the last follow-up ( $P = .16$ ; 95% CI, -56.55 to 280.89). However, the difference was not significant.

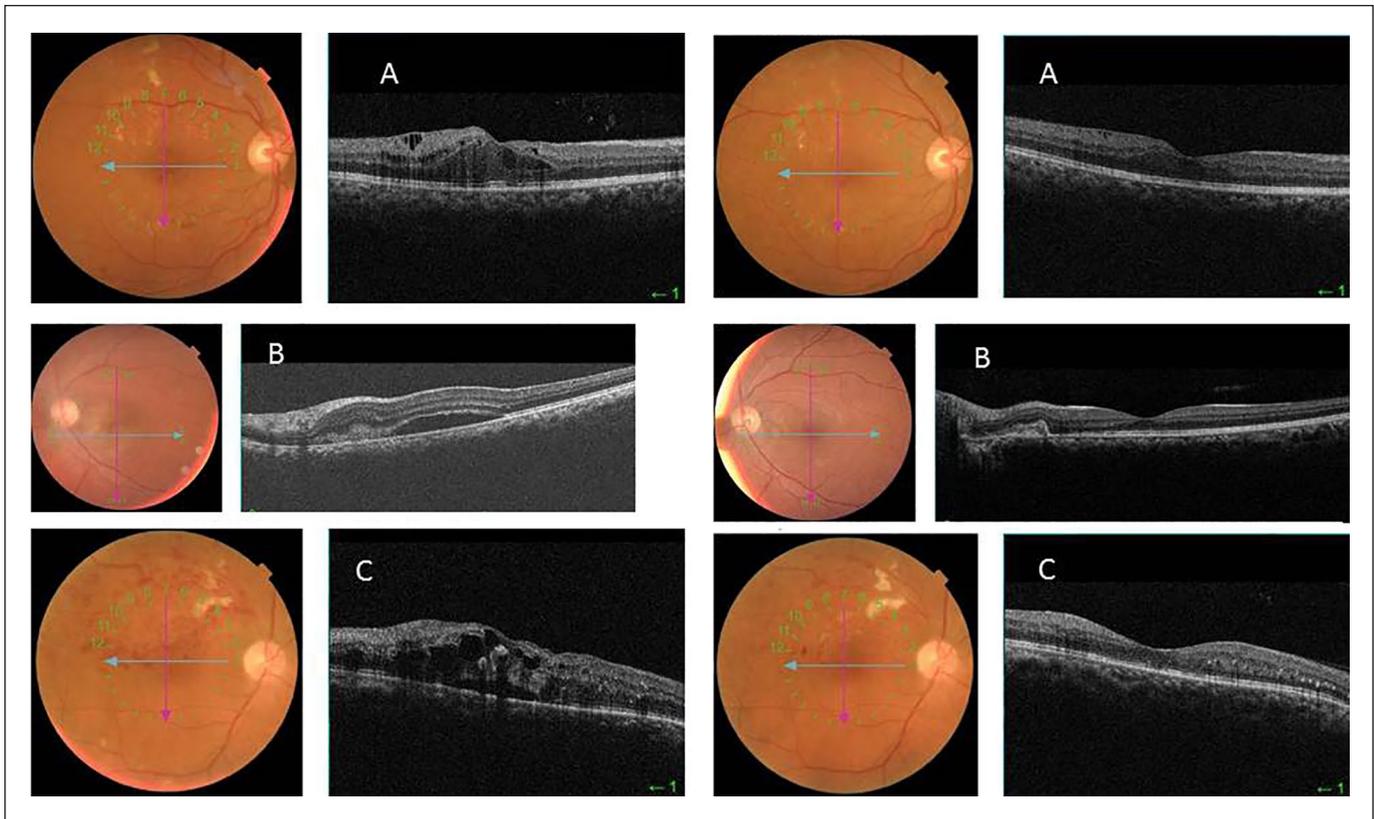
In eyes with CME, the overall mean CST at baseline was 325.5  $\pm$  50.9  $\mu$ m, improving to 251  $\pm$  65  $\mu$ m at the last follow-up ( $P = .12$ ; 95% CI, -26.61 to 175.61). However, the difference was not significant.

## Treatment-Naïve Patients vs Pretreated Patients

Both treatment-naïve patients and pretreated patients had a statistically significant improvement in VA and CST (Table 3).

## Safety

Drug-related ocular or systemic adverse events (AEs), in particular signs of anterior and posterior segment inflammation, were seen at each follow-up visit. Based on the notes in the manual files and electronic record files, none of the 7 study sites reported signs of inflammation, vasculitis, loss of vision, or other systemic drug-related AEs. Given the retrospective nature of the study, non-drug AEs (procedure-related), such as conjunctival hemorrhage, pain, and foreign-body sensations, were not reported. However, when asked about these AEs, all contributors said they noticed these events but that they were not different from those after injection of other anti-VEGF agents.



**Figure 1.** (A) Representative case of diabetic macular edema (DME) (left) at baseline and (right) 4 weeks after a single Ranieyes injection, showing complete resolution of the DME. (B) Representative case of neovascular age-related macular degeneration with the subretinal fluid (SRF) (left) at baseline and (right) 4 weeks after a single Ranieyes injection, showing complete resolution of the SRF. (C) Representative case of branch retinal vein occlusion with cystoid macular edema (CME) (left) at baseline and (right) 4 weeks after a single Ranieyes injection, showing complete resolution of the CME.

**Table 3.** BCVA and CST in Treatment-Naïve Patients and Pretreated Patients.

| Group/Parameter              | Mean $\pm$ SD     |                   | P Value <sup>a</sup> |
|------------------------------|-------------------|-------------------|----------------------|
|                              | Baseline          | Last Follow-up    |                      |
| Treatment naïve<br>(n = 186) |                   |                   |                      |
| LogMAR BCVA                  | 0.95 $\pm$ 0.48   | 0.53 $\pm$ 0.37   | <.00001              |
| CST ( $\mu$ m)               | 430.6 $\pm$ 135.0 | 296.2 $\pm$ 109.6 | <.00001              |
| Pretreated (n = 82)          |                   |                   |                      |
| LogMAR BCVA                  | 0.60 $\pm$ 0.24   | 0.39 $\pm$ 0.25   | <.00001              |
| CST ( $\mu$ m)               | 414.3 $\pm$ 107.3 | 286.7 $\pm$ 75.0  | <.00001              |

Abbreviations: BCVA, best-corrected visual acuity; CST, central subfield thickness.

<sup>a</sup>All clinically significant at  $P < .05$  (Wilcoxon signed rank test).

## Conclusions

Safety has been the prime concern of physicians regarding the use of biosimilars, possibly because of the abbreviated approval path. Most physicians prefer to wait to assess the real-world experience before developing confidence in the use of these drugs.<sup>6</sup>

There have been a series of biosimilar ranibizumab approvals in the past year in multiple countries. The first drug was Byooviz

(ranibizumab-nuna) (Biogen), which received FDA approval in September 2021 and European Medical Agency (EMA) approval in August 2021. The second drug was Cimerli (ranibizumab-eqrn) (Coherus Biosciences), which received FDA approval in August 2022 and United Kingdom regulatory authority approval in early 2022 under the name Ongavia (Teva Pharmaceuticals). It has also received EMA approval under the name Ranivisio (Teva Pharmaceuticals). India was the first country to approve the use of biosimilar ranibizumab (Razumab, Intas Pharmaceuticals) in 2015.<sup>11</sup> Recently, the first aflibercept biosimilar (Yesafili, Biocon) received approval from the European Commission.<sup>12</sup>

In the past 2 years, India has approved 2 more ranibizumab biosimilars (Ranieyes, Lupin Ltd, and Ranizurel, Reliance Life Sciences). Japan approved its first ranibizumab biosimilar (ranibizumab BS1, Senju Pharmaceuticals) in 2021. We published real-world data on India's second ranibizumab biosimilar and found that it was safe and effective in a small series.<sup>13</sup> Furthermore, our group has published real-world data on ranibizumab BS1.<sup>14</sup>

Other than real-world data from India, there is a paucity of reports on these molecules. Therefore, we formed an international group, the International Retina Biosimilar Study Group (Inter-BIOS Group), to analyze real-world data related to biosimilar anti-VEGF agents used for retinal diseases across the globe. Early

real-world data in this study showed Ranieyes to be safe in both treatment-naïve patients and pretreated patients. In addition, the BCVA and CST improved significantly for all approved indications (DME, nAMD, and RVO). The BCVA and CMT did not improve significantly in the subgroup of CME and PDR with or without a vitreous hemorrhage. This is probably because there were only 4 cases of CME (2 pseudophakic; 2 RP related), which were predominantly not VEGF-driven diseases. The eyes with PDR did not have DME; therefore, the change in CST was probably not relevant. Our results agree with the real-world safety and efficacy of the first and most commonly used biosimilar in India (Razumab).<sup>15,16</sup>

Recently, the issue of immunogenicity in biologics and biosimilars has become challenging.<sup>17</sup> Because of safety concerns raised by immunogenicity, abicipar did not receive FDA approval and brolicizumab showed immunogenicity in real-world situations.<sup>18,19</sup> The recently approved drug pegcetacoplan (Syfovre, Apellis) has been associated with retinal vasculitis in a small number of cases; however, the etiology of the inflammation has not yet been determined.<sup>20</sup> The initial few batches of the first biosimilar of ranibizumab in India also showed immunogenicity.<sup>7</sup> However, the company altered the accepted endotoxin reference values and the drug is now being extensively used in India, with numerous published studies reporting its safety.<sup>15,16</sup>

Regulators have also been concerned about switching from a reference biologic to a biosimilar. To our knowledge, no switching trial has evaluated using biosimilars for retinal diseases other than our report of switching from the reference ranibizumab to the first biosimilar ranibizumab (Razumab). In this study, we did not observe any immunogenicity issues after the switch.<sup>21</sup> With the increasing number of biosimilar approvals, there is concern about the possible outcomes of switching from one biosimilar to another biosimilar; to our knowledge, no study has yet been published on this in terms of retinal diseases. However, based on the understanding of systemic diseases and existing switches between different anti-VEGF molecules, the risk does not seem to be high.<sup>22</sup>

In this study, there was no reported injection-related anterior or posterior segment inflammation. In addition, no systemic AEs were reported. The molecule appears to be safe and efficacious based on early real-world experience. The small sample is a major limitation of the study. Furthermore, injection procedure-related AEs were not flagged given the retrospective nature of the study. In addition to the above limitations, the variability in the OCT machines might have affected the assessment of disease activity. A long-term follow-up study with a larger sample is needed to identify more uncommon AEs.

### Ethical Approval

Institutional Review Board approval was obtained at each contributing center, and the investigators adhered to the tenets of the Declaration of Helsinki.

### Statement of Informed Consent

All patients provided informed consent to use their data for research purposes. The data were extracted anonymously.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of the article:

Dr. Sharma is a consultant to Allergan, Bayer, Intas, Lupin, and Novartis. Dr. Holz reported research grants and personal fees from Acucela, Allergan, Apellis, Bayer, Bioeq/Formycon, Geuder, Heidelberg Engineering, Iveric Bio, Novartis, Pixium Vision, Roche/Genentech, and Zeiss and personal fees from Aerie, Alexion, Grayburg Vision, LinBioscience, Oxurion, and Stealth BioTherapeutics.

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Dr. Eichenbaum is a consultant to Alimera, Allergan, Apellis, Bausch + Lomb, Dutch Ophthalmic, EyePoint, Genentech Inc, Gyroscope, Iveric Bio, KKR, Kodiak, Novartis, Recens Medical, Regeneron, RegenxBio, and Vial; has equity in and/or is a stockholder in Boston Image Reading Center, Clearside, Hemera, Network Eye, and US Retina; is the founder of Network Eye; is an investigator for Alkahest, Annexon, AsclepiX, Bayer, Chengdu, EyePoint, Gemini, Genentech Inc, Gyroscope, Ionis, Iveric Bio, Kodiak, Mylan, NGM, Novartis, Ocular Therapeutix, Ophthea, Recens Medical, Regeneron, RegenxBio, and Unity; and is a speaker for Allergan, Apellis, Bayer, Dutch Ophthalmic, EyePoint, Genentech Inc, and Novartis.

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Dr. Bandello is a consultant to Allergan, Bayer, Boehringer-Ingelheim, Fidia Sooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, and Zeiss.

Dr. Woo is a consultant to Panolos Bioscience and Samsung Bioepis; is a cofounder of Retimark; is on the advisory board of Novartis and Novelty Nobility; has received grants and personal fees from Alteogen, Curacle, Kookje, Novartis, Novelty Nobility, and Samsung Bioepis; and has received lecture fees from AbbVie, Alcon, Allergan, Alteogen, Bayer, Novartis, SCAI Therapeutics, and Taejoon.

Dr. Kuppermann is a clinical researcher for Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, and ThromboGenics and is a consultant to Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, and Theravance Biopharma.

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