

# Efficacy and Safety of Ranibizumab 0.5 mg for the Treatment of Macular Edema Resulting from Uncommon Causes

## Twelve-Month Findings from PROMETHEUS

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**Purpose:** To evaluate the efficacy and safety of ranibizumab 0.5 mg in adult patients with macular edema (ME) resulting from any cause other than diabetes, retinal vein occlusion, or neovascular age-related macular degeneration.

**Design:** A phase 3, 12-month, double-masked, randomized, sham-controlled, multicenter study.

**Participants:** One hundred seventy-eight eligible patients aged  $\geq 18$  years.

**Methods:** Patients were randomized 2:1 to receive either ranibizumab 0.5 mg ( $n = 118$ ) or sham ( $n = 60$ ) at baseline and month 1. From month 2, patients in both arms received open-label individualized ranibizumab treatment based on disease activity. A preplanned subgroup analysis was conducted on the primary end point on 5 predefined baseline ME etiologies (inflammatory/post-uveitis, pseudophakic or aphakic, central serous chorioretinopathy, idiopathic, and miscellaneous).

**Main Outcome Measures:** Changes in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letters) from baseline to month 2 (primary end point) and month 12 and safety over 12 months.

**Results:** Overall, 156 patients (87.6%) completed the study. The baseline characteristics were well balanced between the treatment arms. Overall, ranibizumab showed superior efficacy versus sham from baseline to month 2 (least squares mean BCVA,  $+5.7$  letters vs.  $+2.9$  letters; 1-sided  $P = 0.0111$ ), that is, a treatment effect (TE) of  $+2.8$  letters. The mean BCVA gain from baseline to month 12 was 9.6 letters with ranibizumab. The TE at month 2 was variable in the 5 predefined etiology subgroups, ranging from  $>5$ -letter gain to 0.5-letter loss. The safety findings were consistent with the well-established safety profile of ranibizumab.

**Conclusions:** The primary end point was met and ranibizumab showed superiority in BCVA gain over sham in treating ME due to uncommon causes, with a TE of  $+2.8$  letters versus sham at month 2. At month 12, the mean BCVA gain was high (9.6 letters) in the ranibizumab arm; however, the TE was observed to be variable across the different etiology subgroups, reaching a  $>1$ -line TE in BCVA in patients with ME resulting from inflammatory conditions/post-uveitis or after cataract surgery. Overall, ranibizumab was well tolerated with no new safety findings up to month 12. *Ophthalmology* 2018;125:850-862 © 2018 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/>).



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Macular edema (ME) is characterized by vascular leakage and accumulation of fluid resulting from pathologic changes in the retinal vasculature and may result in irreversible structural damage and permanent loss of vision.<sup>1</sup> The underlying pathophysiology of ME is multifactorial, complex, and poorly understood.<sup>1-3</sup> Thus, ME remains one of the major therapeutic challenges in ophthalmology. In many cases, ME involves abnormally increased vascular endothelial growth factor (VEGF) levels in the retina that cause disruption of the blood-retinal barrier, followed by increased accumulation of fluid within the intraretinal layers of the macula.<sup>1</sup>

The most common causes for ME in the working-age population are diabetic retinopathy and retinal vein occlusion (RVO).<sup>2,3</sup> These ocular conditions can lead to severe and irreversible vision loss if left untreated.<sup>1-6</sup> Less frequent retinal vascular disorders, inflammatory disorders, choroidal vascular diseases, inherited retinal dystrophies, intraocular tumors, and optic nerve abnormalities also cause ME and their prevalence varies worldwide.<sup>2,3</sup> Currently, there is no health authority-approved therapy for treating ME caused by conditions other than diabetic retinopathy, RVO, or neovascular age-related macular degeneration (nAMD). Different available treatment options for ME

resulting from less common causes include topical nonsteroidal anti-inflammatory drugs, topical corticosteroids, verteporfin photodynamic therapy (vPDT), laser photocoagulation, and intravitreal corticosteroids along with the off-label use of anti-VEGF agents.<sup>3,7–12</sup> Considering the well-established efficacy and safety of ranibizumab for the treatment of visual impairment resulting from diabetic ME (DME) and ME after RVO,<sup>13–24</sup> ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech, Inc, South San Francisco, CA) as an anti-VEGF agent could be beneficial also for the treatment of ME secondary to uncommon ocular conditions.

Previously published reports assessed the potential of anti-VEGF agents like bevacizumab and ranibizumab in the treatment of ME resulting from uncommon causes like uveitis, pseudophakia or aphakia, central serous chorioretinopathy (CSC), radiation retinopathy, and others.<sup>9,25–36</sup> The treatment effect observed with anti-VEGF agents was variable<sup>7,25–29,32,36</sup>; hence, there was need for a long-term randomized clinical trial to establish the efficacy and safety of anti-VEGF in these uncommon conditions.

The PROMETHEUS study (a complete listing of the members of the study group is available in [Appendix 1](#), available at [www.aaojournal.org](http://www.aaojournal.org)) was designed to evaluate the efficacy and safety of an individualized ranibizumab 0.5-mg dosing regimen, based on disease activity, in adult patients with visual impairment resulting from ME associated with uncommon causes other than DME, nAMD, and RVO.

## Methods

### Study Design

The PROMETHEUS study was a 12-month, phase 3, randomized, double-masked, sham-controlled multicenter study conducted across 19 countries ([Appendix 2](#), available at [www.aaojournal.org](http://www.aaojournal.org)). The study was initiated in October 2013 and was completed in September 2015. The study protocol was reviewed and approved by an independent ethics committee or institutional review board for each center and the study was conducted in accordance with the tenets of the Declaration of Helsinki. Patients provided written informed consent at screening and a re-consent after the implementation of the first protocol amendment. The study is registered with [Clinicaltrials.gov](http://Clinicaltrials.gov) (identifier, NCT01846299).

### Patients

The study population consisted of patients 18 years of age or older with visual impairment due to active ME secondary to causes other than diabetic retinopathy, nAMD, or RVO. The inclusion criteria were diagnosis of active chronic ME (>3 months) confirmed by the presence of 1 of the following 3 criteria: (1) posterior pole changes compatible with active ME observed by fundus ophthalmoscopy, biomicroscopy, and fundus photography; (2) leakage from ME documented by fluorescein angiography (FA); and (3) intraretinal fluid or cysts seen by OCT and best-corrected visual acuity (BCVA) between 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more and 83 ETDRS letters or fewer.

Patients were excluded if they demonstrated ME associated with diabetic retinopathy, nAMD, or RVO; retinal angiomatous proliferation lesions in patients 50 years of age or older; any type of

systemic advanced, severe, or unstable disease or its treatment that could interfere with primary or secondary outcome evaluations, or both; uncontrolled systemic inflammation or infection related directly to the underlying causal disease of ME; active diabetic retinopathy and active ocular or periocular infectious disease or active severe intraocular inflammation (intraocular pressure  $\geq 25$  mmHg); history of laser photocoagulation with involvement of the macular area, vPDT, and vitreoretinal surgery and intravitreal implants at any time; and use of anti-VEGF agents and intravitreal steroids within 6 months of the baseline visit (inclusion and exclusion criteria are listed in detail in [Appendix 3](#), available at [www.aaojournal.org](http://www.aaojournal.org)).

### Randomization and Treatment

Eligible patients were randomized in a 2:1 ratio to either of 2 treatment arms (ranibizumab 0.5 mg or sham) at baseline using interactive response technology. Although patients received open-label therapy from month 2 onward, the examiners who assessed the efficacy outcomes were masked and not allowed to perform any other tasks that would unmask them to the treatment received by the patients through the entire study period of 12 months.

Patients in the ranibizumab arm received ranibizumab 0.5 mg at baseline followed by an individualized pro re nata (PRN) treatment regimen based on evidence of disease activity (judged clinically or based on morphologic features or imaging) as judged and assessed by the investigator at each individual follow-up visit ([Fig S1](#), available at [www.aaojournal.org](http://www.aaojournal.org)). All the patients were monitored for disease activity by the masked investigator (details of masking are available in [Appendix 4](#), available at [www.aaojournal.org](http://www.aaojournal.org)) at each monthly visit.

Patients in the sham arm received a sham injection at baseline and another sham injection PRN at month 1. From month 2, sham patients could be switched to open-label treatment with PRN ranibizumab 0.5 mg based on the evidence of disease activity (with no mandatory ranibizumab injection at month 2 in case of no disease activity). Thus, as of month 2, patients in both treatment arms could receive open-label PRN ranibizumab.

### Rescue Medication

Patients could receive rescue treatment, as per routine clinical practice, only at month 1, and patients could be treated with laser photocoagulation or periocular treatments (e.g., sub-Tenon's, retrobulbar, or subconjunctival corticosteroid) at the discretion of the masked investigator if the patient had a visual acuity (VA) loss of more than 5 letters from baseline to month 1 because of disease activity. Further details are provided in [Appendix 5](#) (available at [www.aaojournal.org](http://www.aaojournal.org)).

### Objectives

The primary objective was to demonstrate that individualized ranibizumab 0.5 mg had superior efficacy compared with sham treatment in adult patients with visual impairment due to ME with respect to the change in BCVA from baseline to month 2. Pre-planned subgroup analyses were conducted on the primary end point for the following predefined baseline ME etiologies: inflammatory or post-uveitis, pseudophakic or aphakic, CSC, idiopathic retinopathy or retinohoroidopathy, and miscellaneous (causes that did not fit into the other ME etiology subgroups and were insufficiently frequent to form a separate subgroup). The secondary objectives were to evaluate (1) mean change in BCVA from baseline to month 12, (2) mean change in central subfield thickness (CSFT) and central subfield volume (CSFV) from baseline to month 12 and from baseline to months 2 and 12 by baseline ME cause subgroups, (3) overall treatment exposure of

ranibizumab up to month 11 and by baseline ME etiology subgroups, and (4) the overall safety of ranibizumab treatment and by baseline ME etiology subgroups up to month 12. The exploratory objectives were to evaluate (1) mean change in BCVA from baseline to months 2 and 12 by baseline ME etiology, (2) mean change in CSFT and CSFV from baseline to months 2 and 12 by baseline ME etiology, (3) the proportion of patients with absence of ME by baseline ME cause at months 2 and 12, and (4) the proportion of patients with absence of intraretinal fluid, cysts, and subretinal fluid by baseline ME etiology at months 2 and 12.

## Efficacy and Safety Assessments

The study eye was assessed at all visits and assessments were performed before administering the study treatment, if applicable.

**Best-Corrected Visual Acuity.** BCVA was assessed at all study visits by a certified VA examiner using ETDRS charts at an initial distance of 4 m, reduced to 1 m, if necessary.

**OCT.** OCT was performed by certified site personnel at every study visit using either time-domain OCT equipment (1 site used the Zeiss Stratus) or spectral-domain OCT equipment (e.g., Cirrus, Spectralis, Topcon, Nidek, Optovue, and Opko). To ensure a standardized evaluation of the quantitative (e.g., CSFT and CSFV) and qualitative (e.g., ME, cysts, and intraretinal and subretinal fluid) anatomic parameters and their change over time as end points, the raw images were forwarded to a central reading center (CRC; Bern Photographic Reading Center, Bern, Switzerland). Thickness at all visits was measured between Bruch's membrane and the inner limiting membrane, and the same device was used for a given patient throughout the study. The CSFT was defined as the average retinal thickness of the circular area with a 1-mm diameter around the foveal center, and the CSFV (macular volume) was defined as the average volume of the 3-mm field centered around the fovea. The (change in) retinal thickness was similar across different equipment. Intraretinal fluid was defined and diagnosed by the CRC as noncystoid fluid (i.e., did not include cysts) on OCT. Intraretinal cysts were defined as hyporeflective defined spaces of 25  $\mu$ m or more in any dimension within the retina on OCT.

**Fluorescein Angiography and Color Fundus Photography.** FA and 7-field color fundus photography were performed at screening and months 2, 6, and 12. The investigators evaluated the FA and color fundus images for presence or absence of active leakage per standard clinical practice and forwarded these images to the CRC for standardized evaluation.

**Treatment Exposure.** Data were collected on the overall number of ranibizumab treatments up to month 11.

**Safety Assessments.** Safety assessments included collection of type, frequency, and severity of adverse events (AEs) and serious AEs (SAEs) up to month 12.

## Statistical Analysis

Assuming a standard deviation (SD) of 15 ETDRS letters for the change in BCVA at month 2 compared with baseline, based on a randomization ratio of 2:1, a sample size of 112 and 56 patients in the ranibizumab and sham arms, respectively, was considered. With this sample size, the resulting power for analysis of covariance was 89.7% to detect a mean treatment difference of 8 ETDRS letters at a 1-sided  $\alpha$  level of 0.025. Conservative sample size calculations were performed using the 2-sample *t* test.

The primary and secondary efficacy outcomes were analyzed in the full analysis set using observed data and the randomized treatment. The full analysis set included all randomized patients to whom treatment regimen was assigned. Hypothesis tests were evaluated at a 1-sided significance level of 2.5% and 2-sided

asymptotic 95% confidence intervals (CIs) were reported. The primary efficacy outcome, defined as the change in BCVA from baseline to month 2, was analyzed using a mixed-effects repeated measure model. For the subgroup analyses, a forest plot was provided. In addition, the *P* value for the treatment subgroup interaction for each subgroup was displayed. The *P* value was obtained using the same model used for the primary analysis and also including terms for the subgroup and the treatment subgroup interaction.

Frequencies and percentages, with corresponding Clopper–Pearson exact 2-sided 95% CIs, were provided for selected binary efficacy variables. Least squares (LS) means and 95% CIs were used to support the conclusions of statistical inferences. Descriptive statistics included number of observations, mean, SD, standard error (as required), median and ranges for continuous variables, and frequencies and percentages for categorical values; where appropriate, estimates of treatment group differences, CIs, and *P* values were presented. The primary safety analysis was a comparison between treatment arms, conducted for the period after the first treatment, while sham treatment was administered (day 1 to month 2). All other safety analyses (from day 1 to month 12) were descriptive—there were no comparisons between the treatment arms—and were performed using the safety set that included all patients who received 1 or more administrations of the study treatment and underwent 1 or more safety assessments after baseline. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

## Results

### Patient Disposition and Baseline Characteristics

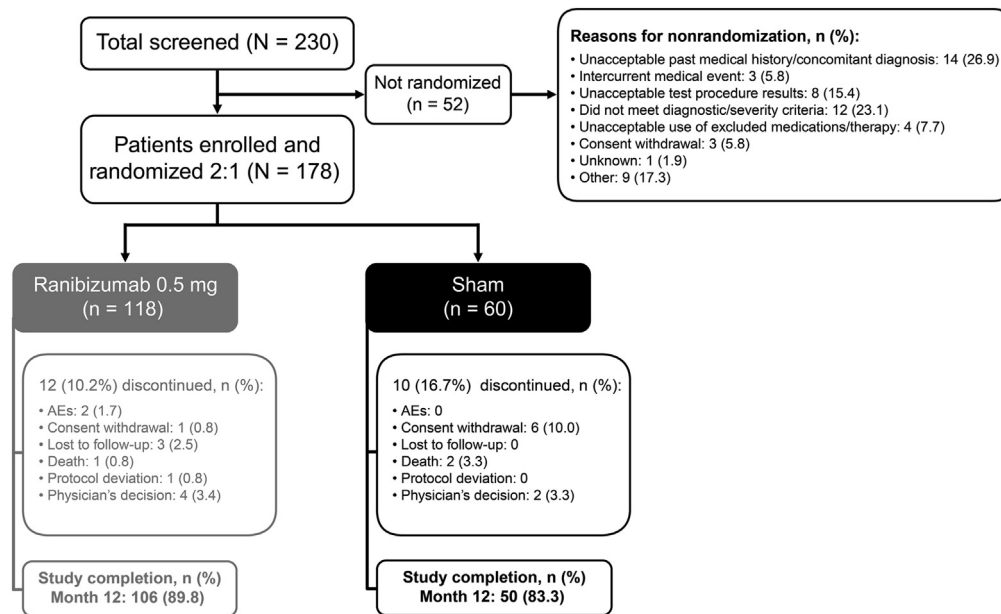
Of the 178 patients randomized to receive either ranibizumab (*n* = 118) or sham (*n* = 60), 156 patients (87.6%) completed the study (ranibizumab, *n* = 106 [89.8%]; sham, *n* = 50 [83.3%]). The most common reasons for discontinuation were consent withdrawal (*n* = 7) and physician's decision (*n* = 6; Fig 1).

The study treatment was received by all patients in the full analysis set (*n* = 177). Of the 177 patients in the safety set, 119 patients and 58 patients were included in the ranibizumab and sham arms, respectively. In the sham arm, 56 patients (97.0%) received at least 1 ranibizumab injection at or after month 2, or at both points. For safety analyses, patients who were assigned initially to sham followed by open-label ranibizumab from month 2 onward were designated as 'sham with ranibizumab' patients (*n* = 56) and those who did not were designated as 'sham without ranibizumab' patients (*n* = 2).

Baseline patient demographics and ocular characteristics generally were well balanced across both treatment arms. The mean age of the patients was 62.9 years (SD, 14.50), the proportion of men was 61.8%, and most patients (87.6%) were white (Table 1). The baseline mean BCVA and CFST were 65.0 letters (SD, 12.47) and 465.5  $\mu$ m (SD, 141.95), respectively (Table 1).

## Efficacy

**Best-Corrected Visual Acuity.** Ranibizumab was superior in efficacy compared with sham from baseline to month 2 (LS mean, +5.7 letters [95% CI, 4.1–7.3] vs. +2.9 letters [95% CI, 1.2–4.7]; 1-sided *P* = 0.0111); hence, the primary end point was met with a treatment effect of +2.8 letters (Fig S2, available at [www.aaojournal.org](http://www.aaojournal.org)).



**Figure 1.** Diagram showing patient disposition (randomized set\*). \*Consisted of all patients who were randomized. AE = adverse event.

Overall, the mean change in BCVA from baseline to month 2 was 5.7 letters (95% CI, 3.96–7.35) with ranibizumab and 3.0 letters (95% CI, 1.20–4.80) with sham. The mean gain in BCVA from baseline to month 12 was 9.6 letters (95% CI, 7.47–11.72) and 8.7 letters (95% CI, 5.43–11.97) in patients originally randomized to ranibizumab and sham, respectively (Fig 2).

Across the predefined baseline ME etiology subgroups, the treatment effect (LS mean) ranged from –0.5 letters (95% CI, –6.10 to 5.11) to +5.9 letters (95% CI, 0.91–10.81; Fig 3). A treatment effect of 5.86 letters and 5.45 letters was seen in pseudophakic or aphakic subgroup and the inflammatory or post-uveitis subgroup, respectively, whereas that observed in the miscellaneous group was 3.26 letters. Insignificant treatment effect was seen in the CSC (0.54 letters) and idiopathic (–0.49 letters) subgroups.

Because of the variability in treatment effects observed across different subgroups, analyses for other efficacy variables are shown by ME etiology only. Across baseline ME etiology, the mean change in BCVA from baseline to month 2 ranged from +3.0 letters to +8.5 letters in the ranibizumab arm and +1.0 letter to +4.7 letters in the sham arm. All patients received open-label ranibizumab treatment from month 2 onward, indicated by disease activity. At month 12, the mean change in BCVA by baseline ME etiology ranged from +5.6 letters to +14.5 letters in the ranibizumab arm, whereas this was +5.7 letters to +10.5 letters in patients originally assigned to the sham arm (Table 2).

In the ME miscellaneous group, the mean BCVA change at month 2 ranged from –2.0 letters (Coats' disease) to 25.0 letters (pattern dystrophies of the retinal pigment epithelium), whereas at month 12, the mean BCVA ranged from –5.0 letters (radiation retinopathy) to 28.0 letters (pattern dystrophies of the retinal pigment epithelium; Table S1, available at [www.aaojournal.org](http://www.aaojournal.org)).

**Anatomic Outcomes.** Overall, from baseline to month 2, there was a higher reduction with ranibizumab compared with sham in CRC-assessed CSFT (LS mean, –81.8  $\mu$ m [95% CI, –107.5

to –56.1] vs. –30.8  $\mu$ m [95% CI, –58.0 to –3.6]; 1-sided  $P = 0.0037$ ; Fig S3, available at [www.aaojournal.org](http://www.aaojournal.org)). At month 12, the reductions in CRC-assessed CSFT were similar in both treatment arms (Fig 4).

By baseline ME cause subgroups, the mean CSFT change from baseline to month 2 ranged from –56.3 to –99.7  $\mu$ m in ranibizumab-treated patients, whereas the mean change in CSFT ranged from –17.9 to –51.4  $\mu$ m in patients in the sham group. At month 12 in the ranibizumab arm, the mean change in CSFT ranged from –79.4 to –181.7  $\mu$ m and from –51.5 to –165.2  $\mu$ m in patients assigned to sham arm (Table 3). Changes in CSFT (assessed in the central 1 mm area) and CSFV (assessed in the central 3 mm volume) showed very similar trends overall and by baseline ME etiology subgroups for the ranibizumab and sham arms.

At months 2 and 12, the proportion of patients in the ME etiology subgroups showing absence of macular edema (Fig S4, available at [www.aaojournal.org](http://www.aaojournal.org)), intraretinal fluid (Fig S5, available at [www.aaojournal.org](http://www.aaojournal.org)), cysts (Fig S6, available at [www.aaojournal.org](http://www.aaojournal.org)), and subretinal fluid (Fig S7, available at [www.aaojournal.org](http://www.aaojournal.org)) was greater with the ranibizumab compared with the sham arm.

## Treatment Exposure

**Ranibizumab Injections.** Up to month 11, patients received a mean of 6.7 ranibizumab injections (SD, 3.7) of a possible 12 injections in the ranibizumab arm versus 5.7 ranibizumab injections (SD, 3.1) of a possible 10 injections in the ‘sham with ranibizumab’ group. Depending on the baseline ME etiology, the mean number of ranibizumab injections in the ranibizumab arm up to month 11 ranged from 5.8 to 8.7; the mean number of ranibizumab injections in the ‘sham with ranibizumab’ group ranged from 4.2 to 7.0 (Table 4).

**Rescue Treatment.** No patients received any rescue treatment.



Table 1. Baseline Demographic, Ocular, and Disease Characteristics (Randomized Set\*)

Variables/Characteristics	Ranibizumab 0.5 mg (n = 118)	Sham (n = 60)	Total (N = 178)
Age, years			
n	118	60	178
Mean (SD)	63.5 (13.97)	61.8 (15.55)	62.9 (14.50)
Gender, n (%)			
Male	73 (61.9)	37 (61.7)	110 (61.8)
Predominant race, n (%)			
White	106 (89.8)	50 (83.3)	156 (87.6)
Black	1 (0.8)	1 (1.7)	2 (1.1)
Asian	11 (9.3)	7 (11.7)	18 (10.1)
Other	0	2 (3.3)	2 (1.1)
VA (letters)			
n	118	60	178
Mean (SD)	65.4 (12.73)	64.1 (12.00)	65.0 (12.47)
VA category (letters), n (%)			
≤60	33 (28.0)	24 (40.0)	57 (32.0)
>60	85 (72.0)	36 (60.0)	121 (68.0)
IOP, mmHg			
n	118	60	178
Mean (SD)	14.9 (2.90)	14.5 (2.81)	14.7 (2.87)
Baseline ME etiology, n (%)			
Inflammatory/after uveitis	14 (11.9)	7 (11.7)	21 (11.8)
Pseudophakic/aphakic	42 (35.6)	17 (28.3)	59 (33.1)
CSC	14 (11.9)	11 (18.3)	25 (14.0)
Idiopathic	37 (31.4)	14 (23.3)	51 (28.7)
Miscellaneous	11 (9.3)	11 (18.3)	22 (12.4)
Time since diagnosis of current ocular condition, mos			
n	118	60	178
Mean (SD)	3.76 (9.10)	2.36 (3.71)	3.29 (7.73)
Median	0.90	1.03	0.92
Time since diagnosis of underlying disease, mos			
n	118	60	178
Mean (SD)	15.90 (31.51)	10.10 (14.05)	13.94 (27.01)
Median	4.04	4.76	4.17
CSFT, μm			
n	116	60	176
Mean (SD)	466.3 (147.10)	464.0 (132.60)	465.5 (141.95)
CSFT category (μm), n (%)			
<300	13 (11.0)	6 (10.0)	19 (10.7)
300–500	64 (54.2)	29 (48.3)	93 (52.2)
>500–700	31 (26.3)	24 (40.0)	55 (30.9)
>700	8 (6.8)	1 (1.7)	9 (5.1)
Missing	2 (1.7)	0	2 (1.1)
CFSV (macular volume), μL <sup>†</sup>			
n	116	60	176
Mean (SD)	3.00 (0.64)	2.93 (0.59)	2.98 (0.62)
CSFV (macular volume) category (μL), n (%)			
<1.8	0	1 (1.7)	1 (0.6)
1.8–3.2	81 (68.6)	43 (71.7)	124 (69.7)
>3.2–4.6	34 (28.8)	15 (25.0)	49 (27.5)
>4.6	1 (0.8)	1 (1.7)	2 (1.1)
Missing	2 (1.7)	0	2 (1.1)

CRC = central reading center; CSC = central serous chorioretinopathy; CSFT = central subfield thickness; CSFV = central subfield volume; IOP = intraocular pressure; ME = macular edema; Mos = months; SD = standard deviation; VA = visual acuity.

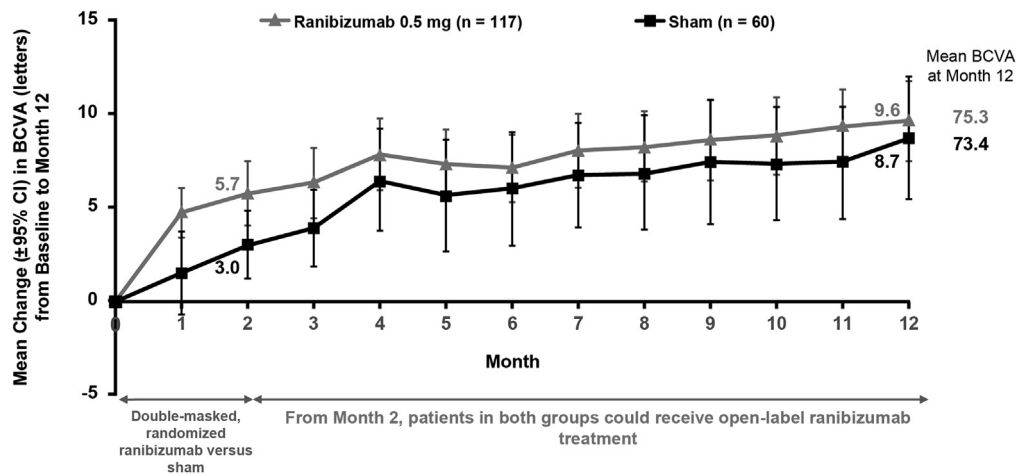
\*Consisted of all patients who were randomized.

<sup>†</sup>Recorded by CRC as inner subfield volume of the field with 3-mm diameter around the foveal center.

## Safety

**Serious Adverse Events.** Up to month 2, 1 patient in the ranibizumab arm experienced an ocular SAE in the study eye (endophthalmitis) that resolved within 33 days. The investigator considered

this SAE as not suspected to be related to the ranibizumab, but rather was related to ocular injection. Nonocular SAEs were reported in 6 patients up to month 2. Up to month 12, ocular SAEs were reported in 3 patients in the ranibizumab arm and none in the ‘sham with ranibizumab’ and ‘sham without ranibizumab’ groups (Table S2,



**Figure 2.** Graph showing the change in best-corrected visual acuity (BCVA) from baseline to month 12 (full analysis set\* [observed]). \*Consisted of all randomized patients to whom treatment regimen was assigned. CI = confidence interval.

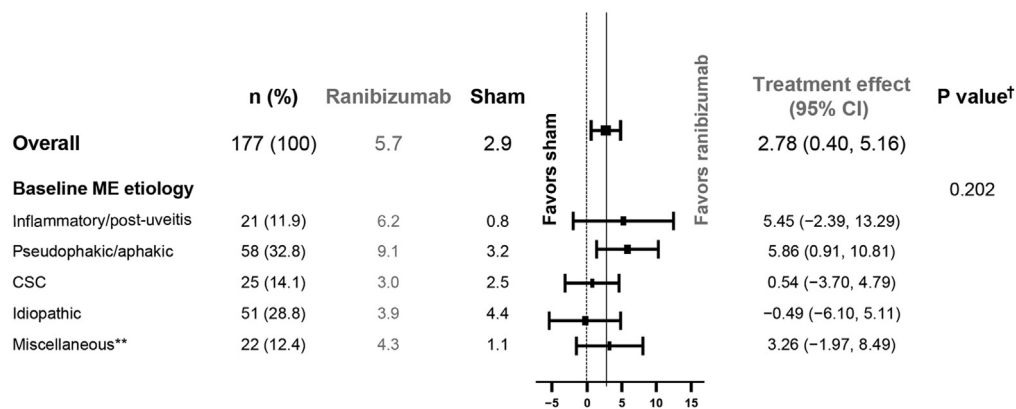
available at [www.aaojournal.org](http://www.aaojournal.org)). The percentage of SAEs reported in patients assigned to the ranibizumab arm and the ‘sham with ranibizumab’ group was similar; these SAEs primarily were the result of nonocular events. Up to month 12, nonocular SAEs were reported in 10.9% (13/119), 8.9% (5/56), and 50.0% (1/2) of patients in the ranibizumab arm and ‘sham with ranibizumab’ and ‘sham without ranibizumab’ groups, respectively (Table S2). None of the ocular or nonocular SAEs was suspected by the investigator to be related to ranibizumab. Up to month 12, there was 1 nonocular SAE (presyncope) in the ranibizumab arm suspected to be related to ocular injection. There were 3 deaths during the study (ranibizumab, n = 1; sham, n = 2). Up to month 2, 1 patient died of brain stem stroke and basilar artery thrombosis in the sham arm. From months 2 to 12, 1 patient died in the ‘sham with ranibizumab’ group of cardiorespiratory arrest and 1 patient died of cerebral hemorrhage in the ranibizumab arm. None of the deaths was considered to be related to ranibizumab and/or sham treatment.

**Adverse Events.** Ocular AEs were reported in 39 patients (ranibizumab, n = 33; sham, n = 6) and 89 patients (ranibizumab, n = 64; sham with ranibizumab, n = 25; sham without ranibizumab group, n = 0) up to months 2 and 12, respectively.

Conjunctival hemorrhage (10.2%), VA reduction (7.9%), and eye pain (6.8%) were the most frequently reported ocular AEs up to month 12 (Table 5). Up to months 2 and 12, nonocular AEs were reported in 34 patients (ranibizumab, n = 20; sham, n = 14) and 94 patients (ranibizumab, n = 65; ‘sham with ranibizumab,’ n = 28; ‘sham without ranibizumab,’ n = 1), respectively. The most frequently reported nonocular AEs up to month 12 were nasopharyngitis (7.9%), hypertension (4.5%), and influenza (5.1%; Table 5). Ocular and nonocular AEs suspected to be related to ocular drug and injection up to month 12 are shown in Tables S3 and S4, respectively (available at [www.aaojournal.org](http://www.aaojournal.org)).

## Discussion

PROMETHEUS was the first randomized phase 3 clinical trial that evaluated the efficacy and safety of ranibizumab in patients with ME resulting from uncommon causes, that is, causes other than diabetic retinopathy, nAMD, or RVO. Overall, ranibizumab demonstrated statistically significant superiority to sham at month 2 in improving BCVA; thus,



**Figure 3.** Graph showing change in best-corrected visual acuity from baseline to month 2 in each of the specified subgroups (full analysis set\* [observed]). \*Consisted of all randomized patients to whom treatment regimen was assigned. †P value is the interaction between the subgroup and treatment. \*\*Etiologies that did not fit into the other cause subgroups and were insufficiently frequent to form a separate subgroup. CI = confidence interval; CSC = central serous chorioretinopathy; ME = macular edema.

Table 2. Mean Best-Corrected Visual Acuity and Mean Change in Best-Corrected Visual Acuity from Baseline to Months 2 and 12 by Baseline Macular Edema Etiology (Full Analysis Set\* [Observed])

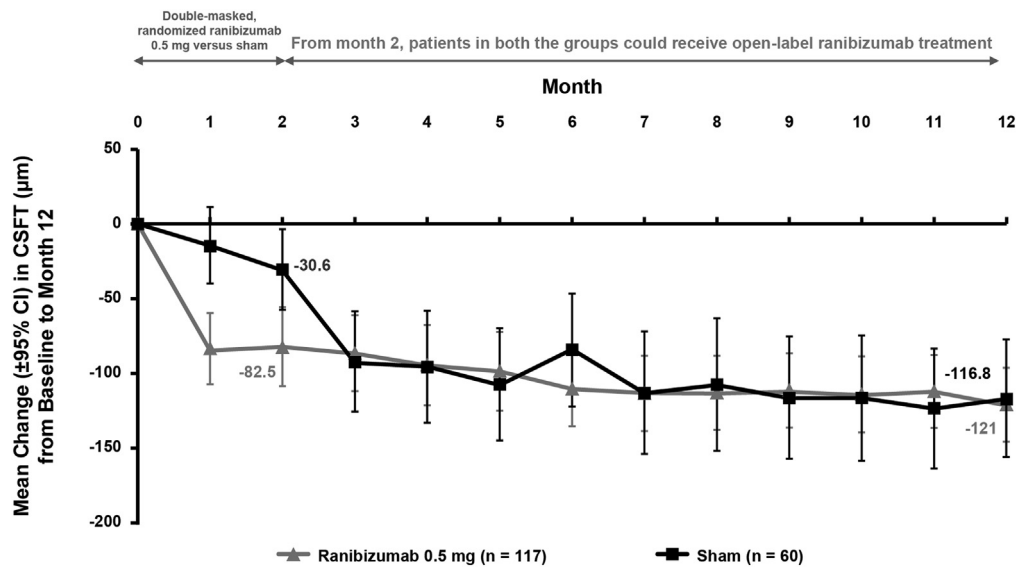
Macular Edema Etiology	Ranibizumab 0.5 mg	Sham
Inflammatory/after uveitis		
Month 2		
At baseline, n	13	7
Mean BCVA (95% CI) at baseline, letters	64.0 (54.91–73.09)	65.4 (60.20–70.66)
Mean BCVA (95% CI) at month 2, letters	70.2 (57.97–82.33)	66.4 (57.74–75.12)
Mean change (95% CI) from baseline, letters	6.2 (0.28–12.03)	1.0 (–5.43 to 7.43)
Month 12		
At baseline, n	12	6
Mean BCVA (95% CI) at baseline, letters	63.4 (53.53–73.30)	66.5 (60.88–72.12)
Mean BCVA (95% CI) at month 12, letters	69.3 (56.16–82.50)	76.5 (69.15–83.85)
Mean change (95% CI) from baseline, letters	5.9 (–0.94 to 12.78)	10.0 (1.82–18.18)
Pseudophakic/aphakic		
Month 2		
At baseline, n	40	16
Mean BCVA (95% CI) at baseline, letters	61.7 (58.36–65.04)	57.4 (51.79–63.08)
Mean BCVA (95% CI) at Month 2, letters	70.2 (67.19–73.21)	61.5 (55.77–67.23)
Mean change (95% CI) from baseline, letters	8.5 (5.48–11.52)	4.1 (–0.55 to 8.68)
Month 12		
At baseline, n	37	13
Mean BCVA (95% CI) at baseline, letters	62.1 (58.80–65.37)	57.6 (51.54–63.69)
Mean BCVA (95% CI) at Month 12, letters	76.6 (73.41–79.78)	68.2 (57.72–78.59)
Mean change (95% CI) from baseline, letters	14.5 (10.58–18.45)	10.5 (0.78–20.30)
CSC		
Month 2		
At baseline, n	14	11
Mean BCVA (95% CI) at baseline, letters	72.7 (66.68–78.75)	70.8 (63.34–78.29)
Mean BCVA (95% CI) at month 2, letters	75.7 (69.02–82.41)	73.3 (64.38–82.17)
Mean change (95% CI) from baseline, letters	3.0 (0.26–5.74)	2.5 (–0.96 to 5.87)
Month 12		
At baseline, n	14	10
Mean BCVA (95% CI) at baseline, letters	72.7 (66.68–78.75)	71.0 (62.62–79.38)
Mean BCVA (95% CI) at month 12, letters	78.4 (71.33–85.38)	77.6 (68.01–87.19)
Mean change (95% CI) from baseline, letters	5.6 (2.20–9.08)	6.6 (2.75–10.45)
Idiopathic retinopathy/retinochoroidopathy		
Month 2		
At baseline, n	36	14
Mean BCVA (95% CI) at baseline, letters	68.1 (64.04–72.24)	65.7 (15.17)
Mean BCVA (95% CI) at month 2, letters	71.9 (67.92–75.91)	70.4 (61.21–79.64)
Mean change (95% CI) from baseline, letters	3.8 (0.46–7.10)	4.7 (–0.05 to 9.48)
Month 12		
At baseline, n	32	11
Mean BCVA (95% CI) at baseline, letters	67.8 (63.16–72.40)	65.0 (53.83–76.17)
Mean BCVA (95% CI) at month 12, letters	75.5 (71.38–79.69)	75.5 (65.31–85.60)
Mean change (95% CI) from baseline, letters	7.8 (3.82–11.68)	10.5 (–0.01 to 20.92)
Miscellaneous		
Month 2		
At baseline, n	11	11
Mean BCVA (95% CI) at baseline, letters	65.7 (58.12–73.33)	64.4 (57.31–71.42)
Mean BCVA (95% CI) at month 2, letters	70.0 (61.60–78.40)	65.5 (58.65–72.26)
Mean change (95% CI) from baseline, letters	4.3 (–0.82 to 9.36)	1.1 (–0.65 to 2.83)
Month 12		
At baseline, n	11	10
Mean BCVA (95% CI) at baseline, letters	65.7 (58.12–73.33)	66.3 (60.04–72.56)
Mean BCVA (95% CI) at month 12, letters	73.2 (64.83–81.53)	72.0 (66.31–77.69)
Mean change (95% CI) from baseline, letters	7.5 (0.95–13.96)	5.7 (2.70–8.70)

BCVA = best-corrected visual acuity; CI = confidence interval; CSC = central serous chorioretinopathy.

\*Consisted of all randomized patients to whom treatment regimen was assigned.

the primary study end point was met. However, the overall treatment effect of +2.8 ETDRS letters at 2 months was considered to be of low clinical relevance. Nevertheless,

with ranibizumab treatment until month 11, patients originally assigned to ranibizumab or sham treatment gained 9.6 and 8.7 letters versus baseline, respectively, at month 12.



**Figure 4.** Graph showing change in central subfield thickness (CSFT) from baseline to month 12 (full analysis set\* [observed]). \*Consisted of all randomized patients to whom treatment regimen was assigned. CI = confidence interval.

The 2-month treatment effect was variable across different ME etiology subgroups from a gain of more than 5 letters to a loss of 0.5 letter on average. The limited treatment effect may have been caused in part by a longer time since diagnosis and a lower proportion of patients with lower baseline VA ( $\leq 60$  letters) in the ranibizumab arm (3.76 months and 28.0%, respectively) compared with the sham arm (2.36 months and 40.0%, respectively). The eligibility requirement of a diagnosis no less than 3 months before study entry was implemented in a protocol amendment, as was ME with a high likelihood of spontaneous resolution (e.g., CSC or pseudophakic ME) unless the persistent ME was introduced as an exclusion criterion in the amendment. By then, however, most patients were enrolled into the study; hence, the amendment had a minor impact on the enrolled patients. The higher potential of self-resolution in these ME conditions<sup>2,37</sup> and the higher potential to gain more with lower baseline BCVA may have contributed to a smaller treatment effect. Similarly to the observations from this study, variable treatment effects of anti-VEGF agents in patients with ME resulting from different uncommon causes have been described from previous smaller trials and case reports.<sup>2,3,7,25–29,32,36,37</sup>

In PROMETHEUS, a greater treatment effect at month 2 was achieved with ranibizumab in the inflammatory or post-uveitis subgroup (treatment effect of 5.45 letters; 14 patients received ranibizumab and 7 patients received sham treatment). The letter gain in the ranibizumab arm was maintained up to month 12 (5.9 letters). Sham-treated patients gained less than 1 letter on average up to month 2, but gained 10 letters at month 12 (after treatment with ranibizumab as of month 2 [ $n = 6$ ]). The pseudophakic or aphakic subgroup showed a clinically important treatment effect of 5.86 letters at month 2 (41 patients received ranibizumab and 17 patients received sham treatment). In the sham-treated patients, spontaneous VA recovery up to

month 2 was 3.2 letters (vs. 9.1 letters for ranibizumab-treated patients). At month 12, patients treated with ranibizumab from baseline had gained 14.5 letters, whereas patients originally treated with sham and eligible for ranibizumab treatment from month 2 gained 10.5 letters. The observed treatment effects in patients in the inflammatory or post-uveitis group and the pseudophakic or aphakic group in PROMETHEUS are consistent with the findings in similar subgroups reported previously with anti-VEGF agents.<sup>7,25–29,32,36</sup>

For the subgroup of patients with ME resulting from CSC, the treatment effect at month 2 was negligible (+0.54 letters; 14 patients received ranibizumab and 11 patients received sham treatment). Previous publications have shown that patients with CSC have a high spontaneous rate of resolution of ME<sup>38–41</sup> and consequently have a good visual prognosis. Currently, the preferred method of treatment in these patients is observation followed by off-label vPDT in cases without spontaneous resolution.<sup>39–41</sup> The role of VEGF in the pathogenesis of CSC is ambiguous, and previous findings have suggested that CSC could be entirely independent of VEGF.<sup>8,39–42</sup> In a small pilot study, patients with CSC when treated with unlicensed bevacizumab showed significantly less VA gain compared with those treated with off-label vPDT.<sup>34</sup> Although one previous study has reported higher VEGF levels in the aqueous humor of patients with CSC responding to bevacizumab treatment versus nonresponders,<sup>33</sup> the absence of any significant treatment effect with ranibizumab in patients with CSC in PROMETHEUS supports the assumption that CSC may not be driven by VEGF. In PROMETHEUS, CSC patients treated with ranibizumab recovered 3.0 letters of BCVA over 2 months, whereas sham-treated patients recovered 2.5 letters. However, it is important to point out that patients with choroidal neovascularization resulting from CSC have shown to benefit from anti-VEGF treatment.<sup>43</sup> Currently in



Table 3. Mean Central Subfield Thickness and Mean Change in Central Subfield Thickness from Baseline to Months 2 and 12 by Baseline Macular Edema Etiology (Full Analysis Set\* [observed])

Macular Edema Cause	Ranibizumab 0.5 mg	Sham
Inflammatory/post-uveitis		
Month 2		
At baseline, n	14	7
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	545.6 (527.89–663.40)	504.1 (387.00–621.28)
Mean CSFT (95% CI) at month 2, $\mu\text{m}$	450.5 (313.14–587.86)	452.7 (328.82–576.61)
Mean change (95% CI) from baseline, $\mu\text{m}$	–95.1 (–197.17 to 6.88)	–51.4 (–194.82 to 91.97)
Month 12		
At baseline, n	12	7
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	538.1 (397.94–678.23)	504.1 (387.00–621.28)
Mean CSFT (95% CI) at month 12, $\mu\text{m}$	444.0 (317.64–570.36)	390.7 (274.09–507.34)
Mean change (95% CI) from baseline, $\mu\text{m}$	–94.1 (–172.65 to –15.52)	–113.4 (–281.69 to 54.84)
Pseudophakic/aphakic		
Month 2		
At baseline, n	39	16
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	520.1 (479.12–560.98)	547.8 (484.68–610.94)
Mean CSFT (95% CI) at month 2, $\mu\text{m}$	420.4 (370.26–470.51)	511.1 (435.69–586.43)
Mean change (95% CI) from baseline, $\mu\text{m}$	–99.7 (–156.05 to –43.28)	–36.8 (–87.05 to 13.55)
Month 12		
At baseline, n	35	12
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	517.7 (472.52–562.97)	554.4 (468.71–640.12)
Mean CSFT (95% CI) at month 12, $\mu\text{m}$	336.0 (303.48–368.52)	389.3 (289.28–489.22)
Mean change (95% CI) from baseline, $\mu\text{m}$	–181.7 (–231.33 to –132.16)	–165.2 (–285.25 to –45.08)
CSC		
Month 2		
At baseline, n	13	11
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	362.0 (311.48–412.52)	400.4 (321.41–479.32)
Mean CSFT (95% CI) at month 2, $\mu\text{m}$	305.7 (260.52–350.87)	371.4 (293.75–448.98)
Mean change (95% CI) from baseline, $\mu\text{m}$	–56.3 (–110.43 to –2.18)	–29.0 (–99.69 to 41.69)
Month 12		
At baseline, n	13	10
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	362.0 (311.48–412.52)	401.3 (312.71–489.89)
Mean CSFT (95% CI) at month 12, $\mu\text{m}$	282.6 (245.36–319.87)	288.6 (243.21–333.99)
Mean change (95% CI) from baseline, $\mu\text{m}$	–79.4 (–119.72 to –39.05)	–112.7 (–205.10 to –20.30)
Idiopathic retinopathy/retinochoroidopathy		
Month 2		
At baseline, n	35	14
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	422.3 (381.33–463.24)	448.4 (377.69–519.16)
Mean CSFT (95% CI) at month 2, $\mu\text{m}$	347.7 (295.58–399.79)	423.9 (338.03–509.82)
Mean change (95% CI) from baseline, $\mu\text{m}$	–74.6 (–112.59 to –36.61)	–24.5 (–94.93 to 45.93)
Month 12		
At baseline, n	32	11
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	421.8 (378.24–465.32)	442.4 (361.37–523.35)
Mean CSFT (95% CI) at month 12, $\mu\text{m}$	335.3 (282.92–387.77)	313.0 (255.46–370.54)
Mean change (95% CI) from baseline, $\mu\text{m}$	–86.4 (–128.22 to –44.66)	–129.4 (–191.87 to –66.86)
Miscellaneous		
Month 2		
At baseline, n	11	11
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	424.8 (352.43–497.20)	396.6 (307.91–485.36)
Mean CSFT (95% CI) at month 2, $\mu\text{m}$	362.7 (273.32–452.13)	378.7 (287.23–470.22)
Mean change (95% CI) from baseline, $\mu\text{m}$	–62.1 (–122.21 to –1.97)	–17.9 (–51.17 to 15.35)
Month 12		
At baseline, n	11	10
Mean CSFT (95% CI) at baseline, $\mu\text{m}$	424.8 (352.43–497.20)	374.6 (291.66–457.54)
Mean CSFT (95% CI) at month 12, $\mu\text{m}$	318.1 (261.77–374.41)	323.1 (253.90–392.30)
Mean change (95% CI) from baseline, $\mu\text{m}$	–106.7 (–148.17 to –65.29)	–51.5 (–94.21 to –8.79)

CI = confidence interval; CSC = central serous chorioretinopathy; CSFT = central subfield thickness.

\*Consisted of all randomized patients to whom treatment regimen was assigned.

Table 4. Treatment Exposure up to Month 11 by Baseline Macular Edema Etiology Subgroup (Safety Set\*)

Macular Edema Etiology Subgroup	Ranibizumab 0.5 mg	Sham
Inflammatory/post-uveitis		
n	14	6
Total	99	35
Mean (SD)	7.1 (4.2)	5.8 (3.0)
Pseudophakic/aphakic		
n	41	16
Total	239	67
Mean (SD)	5.8 (3.9)	4.2 (2.8)
CSC		
n	15	10
Total	114	70
Mean (SD)	7.6 (2.9)	7.0 (3.5)
Idiopathic retinopathy/retinochoroidopathy		
n	37	14
Total	247	82
Mean (SD)	6.7 (3.5)	5.9 (3.0)
Miscellaneous		
n	12	10
Total	104	64
Mean (SD)	8.7 (3.5)	6.4 (2.7)

CSC = central serous chorioretinopathy; SD = standard deviation.

\*Consisted of all adult patients who received at least 1 application of study treatment and had at least 1 safety assessment after baseline.

the European Union, ranibizumab 0.5 mg is approved for the treatment of visual impairment resulting from choroidal neovascularization (regardless of the underlying etiology) in adult patients.<sup>43,44</sup>

Because of a lack of a differential diagnosis, it was not possible to assess the reason for lack of treatment effect of anti-VEGF in the subgroup with idiopathic disease (ocular

vascular disorder,  $n = 1$ ; idiopathic chorioretinopathy,  $n = 36$ ) at month 2, which represented 29% of the patients. The overall treatment effect at the primary end point showed no benefit for ranibizumab versus sham ( $-0.49$  letters; 37 patients received ranibizumab and 14 patients received sham treatment). At month 2, patients treated with ranibizumab had a gain of 3.9 letters, whereas sham-treated patients gained 4.4 letters. At month 12, the ranibizumab arm ( $n = 32$ ) gained 7.8 letters and the sham arm ( $n = 11$ ) gained 10.5 letters. Despite the small sample size in the subgroup, the result indicates a self-resolving nature of this disease and the unknown role of VEGF in its pathologic characteristics.

The miscellaneous subgroup in the PROMETHEUS study comprised patients whose disease resulted from various baseline etiologies (Coats' disease, Eales disease, macular telangiectasia types 1 and 2, Best disease, pattern dystrophies of the retinal pigment epithelium, trauma, radiation retinopathy, and retinitis pigmentosa) that could not be grouped under other specific ME subgroup. This subgroup showed a small treatment effect of 3.3 letters at month 2. At months 2 and 12, the highest BCVA gain was seen in the pattern dystrophies of the retinal pigment epithelium in 1 patient (25.0 letters and 28.0 letters, respectively). Small case studies have reported that anti-VEGF agents combined with laser photocoagulation may be an effective option for the treatment of adult-onset Coat's disease and recurrent vitreous hemorrhage resulting from Eales disease.<sup>45–47</sup>

The same magnitude of effect size that was observed in BCVA by baseline etiology subgroups was observed with CSFT and CSFV, with the highest reduction observed in the pseudophakic or aphakic subgroup at month 12 (CSFT,  $-181.7 \mu\text{m}$ ; CSFV,  $-0.64 \mu\text{L}$ ); at month 12, the least reduction was observed in the CSC subgroup (CSFT,  $-79.4 \mu\text{m}$ ; CSFV,  $-0.27 \mu\text{L}$ ). The CSFT changes

Table 5. Ocular (Study Eye) and Nonocular Adverse Events (at Least 5% in Any Arm) up to Month 12 Regardless of Study Drug Relationship (Safety Set\*)

Preferred Term, n (%)	Ranibizumab 0.5 mg (n = 119)	Sham with Ranibizumab 0.5 mg (n = 56)	Sham without Ranibizumab 0.5 mg (n = 2)	Total (N = 177)
Ocular AEs, total	64 (53.8)	25 (44.6)	0	89 (50.3)
Conjunctival hemorrhage	11 (9.2)	7 (12.5)	0	18 (10.2)
VA reduced	11 (9.2)	3 (5.4)	0	14 (7.9)
Eye pain	10 (8.4)	2 (3.6)	0	12 (6.8)
ME	7 (5.9)	2 (3.6)	0	9 (5.1)
Cystoid ME	6 (5.0)	0	0	6 (3.4)
Dry eye	6 (5.0)	1 (1.8)	0	7 (4.0)
IOP increased	6 (5.0)	3 (5.4)	0	9 (5.1)
Nonocular AEs, total	65 (54.6)	28 (50.0)	1 (50.0)	94 (53.1)
Nasopharyngitis	12 (10.1)	2 (3.6)	0	14 (7.9)
Hypertension	6 (5.0)	2 (3.6)	0	8 (4.5)
Influenza	6 (5.0)	3 (5.4)	0	9 (5.1)
Basilar artery thrombosis	0	0	1 (50.0)	1 (0.6)
Brain stem stroke	0	0	1 (50.0)	1 (0.6)

AE = adverse event; IOP = intraocular pressure; ME = macular edema; VA = visual acuity.

Preferred terms that occurred in  $\geq 5\%$  in any arm of the safety set are included in this summary. Preferred terms are sorted in descending order of frequency of the ranibizumab 0.5 mg arm. A patient with multiple occurrences of a preferred term is counted only once in the preferred term row. The number outside the parentheses represents the number of patients and the numbers inside the brackets represent the percentage.

\*Consisted of all adult patients who received at least 1 application of study treatment and had at least 1 safety assessment after baseline.

(assessed in the central 1 mm) and CSFV changes (assessed in the central 3 mm) showed very comparable profiles across causes and overall, indicating that the assessment of a larger field did not add any relevant information.

With respect to safety, ranibizumab was well tolerated in the study and there were no new safety findings up to month 12. Over 12 months, 3 deaths occurred that were not related to ranibizumab treatment. One case of endophthalmitis occurred that resolved spontaneously within 33 days and was not related to ranibizumab. The safety findings of ranibizumab in PROMETHEUS were in line with the established safety profile of ranibizumab reported previously in DME, nAMD, and RVO.<sup>13,14,16,18–24,48,49</sup>

The PROMETHEUS study had certain limitations. Before protocol amendment, the study allowed for enrollment of pathologic causes of ME that may have had a high likelihood of spontaneous resolution or for which the role of VEGF was unclear (e.g., CSC or nonrecurrent acute ME). Hence, the protocol was amended to exclude patients with ocular diseases known to resolve spontaneously, those in which the use of anti-VEGF agents was controversial, or both. In approximately 29% of the enrolled ME cases, the condition was deemed idiopathic; that is, in these patients, the pathologic mechanisms leading to ME remained unknown. Although relevant treatment effects were observed in 2 etiology subgroups, the respective number of patients was too small to draw clear conclusions on the treatment benefit of ranibizumab. Finally, to avoid potential undertreatment, the comparison versus sham had to be limited to month 2. This meant that any long-term treatment effects versus sham could not be analyzed. To conclude, although patients with ME resulting from inflammatory conditions or post-uveitis and patients with ME occurring after cataract surgery seem to benefit from ranibizumab treatment, ranibizumab treatment seems to have no benefit in ME resulting from CSC. For idiopathic ME, a more exploratory approach needs to be followed.

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## Footnotes and Financial Disclosures

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**Abbreviations and Acronyms:**

**AE** = adverse event; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CRC** = central reading center; **CSC** = central serous chorioretinopathy; **CSFT** = central subfield thickness; **CSFV** = central subfield volume; **DME** = diabetic macular edema; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **LS** = least squares; **ME** = macular edema; **nAMD** = neovascular age-related macular degeneration; **PRN** = pro re nata; **RVO** = retinal vein occlusion; **SAE** = serious adverse event; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **vPDT** = verteporfin photodynamic therapy.

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