



# Macular Atrophy in Neovascular Age-Related Macular Degeneration

## *A Randomized Clinical Trial Comparing Ranibizumab and Aflibercept (RIVAL Study)*

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**Purpose:** To investigate differences in the development of macular atrophy (MA) over 24 months between treat-and-extend (T&E) ranibizumab and aflibercept in patients with neovascular age-related macular degeneration (nAMD).

**Design:** A phase 4 randomized, partially masked, multicenter study.

**Participants:** Individuals 50 years of age or older diagnosed with active, treatment-naïve subfoveal choroidal neovascularization secondary to nAMD with baseline best-corrected visual acuity (BCVA) of 23 logarithm of minimum angle of resolution letters or more.

**Methods:** Patients were randomized 1:1 to receive either intravitreal injections of ranibizumab 0.5 mg or aflibercept 2.0 mg and were treated according to the same reading center-guided T&E regimen after 3 initial monthly injections.

**Main Outcome Measures:** The primary outcome was mean change in square root area of MA from baseline to month 24. Key secondary outcomes included number of injections and mean change in BCVA from baseline to months 12 and 24.

**Results:** Two hundred seventy-eight patients were included in the analysis (ranibizumab 0.5 mg, n = 141; aflibercept 2.0 mg, n = 137). Mean change in square root area of MA from baseline to month 24 was +0.36 mm (95% confidence interval [CI], 0.27–0.45 mm) for ranibizumab and +0.28 mm (95% CI, 0.19–0.37 mm) for aflibercept (treatment difference, +0.08 mm [95% CI, –0.05 to 0.21 mm];  $P = 0.24$ ). The proportion of patients with MA increased from 7% (10/141) to 37% (43/117) for ranibizumab and from 6% (8/137) to 32% (35/108) for aflibercept from baseline to month 24. The average number of injections received per year was similar between both groups: 9.6 (95% CI, 9.2–10.0) for ranibizumab and 9.5 (95% CI, 9.1–9.9) for aflibercept. The mean change in BCVA from baseline to month 24 was +6.6 letters (95% CI, 4.7–8.5 letters) for the ranibizumab group and +4.6 letters (95% CI, 2.7–6.6 letters) for the aflibercept group ( $P = 0.15$ ). Rates of adverse events (AEs) were similar between both groups.

**Conclusions:** No significant differences in the rate of development or growth of MA over 24 months were observed between ranibizumab and aflibercept in nAMD patients treated using an identical T&E regimen. *Ophthalmology* 2019;■:1–13 © 2019 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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Anti-vascular endothelial growth factor (VEGF) inhibitors such as ranibizumab and aflibercept are the mainstay of therapy for patients with neovascular age-related macular degeneration (nAMD).<sup>1</sup> However, there is some concern that long-term use of anti-VEGF agents may have an undesirable effect on the macula, possibly related to the role that VEGF plays in maintaining the integrity of the retinal pigment epithelium.<sup>2</sup>

Data on the development of macular atrophy (MA) in patients receiving anti-VEGF therapy for nAMD are conflicting. A number of studies have suggested a relationship between anti-VEGF therapy and MA development, particularly with more frequent treatment regimens.<sup>3–11</sup> In contrast, other studies have found no statistically significant association between the development of MA and treatment with anti-VEGF agents,<sup>12,13</sup>

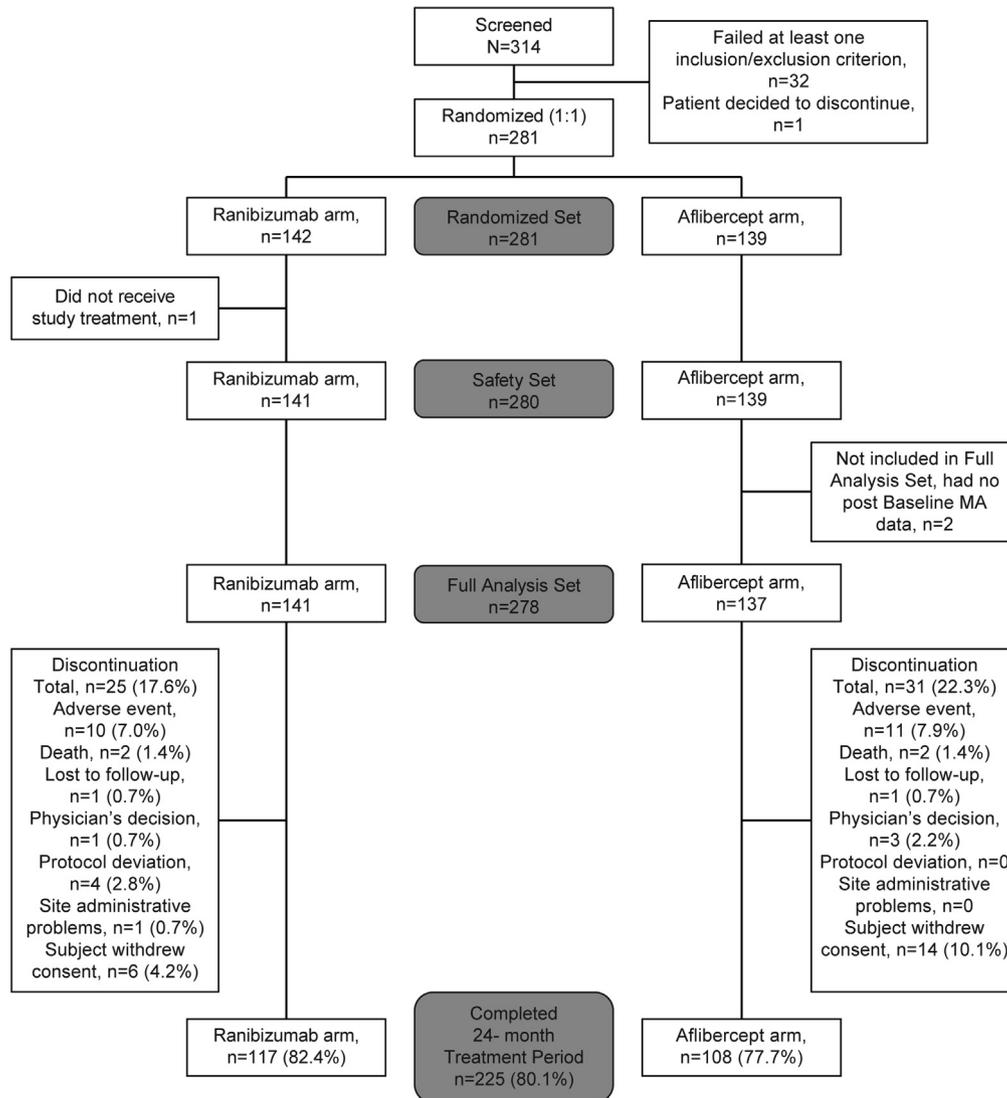


Figure 2. Flowchart showing patient disposition. MA = macular atrophy.

suggesting that MA may develop in these eyes as part of the natural history of the underlying disease, rather than its treatment. In addition, the current evidence for involvement of anti-VEGF therapy in the development of MA mainly is from studies of patients taking ranibizumab or bevacizumab, with very limited information on those taking aflibercept.

The Development of Macular Atrophy in Patients with Neovascular Age-Related Macular Degeneration: A Comparison of Ranibizumab and Aflibercept (RIVAL) study is a prospective, randomized, head-to-head study to assess the difference in the mean change in square root area of MA from baseline to month 24 between ranibizumab and aflibercept when these agents are administered via an identical treat-and-extend (T&E) regimen. A 12-month interim analysis of the RIVAL study results has been presented elsewhere.<sup>14</sup> The results of the full 24-month analysis are described here.

## Methods

The methods for the RIVAL study, which have been provided in detail previously,<sup>14</sup> are summarized here briefly. The RIVAL study was a 24-month, phase 4, randomized, partially masked, multicenter study in patients with nAMD conducted at 24 sites across Australia between April 2014 and November 2017. The study protocol was reviewed and approved by an independent ethics committee for each study site (detailed list of institutions provided in Appendix 1, available at [www.aaojournal.org](http://www.aaojournal.org)). The RIVAL study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients. The study is registered at [clinicaltrials.gov](http://clinicaltrials.gov) (identifier, NCT02130024).

Patients 50 years of age or older with baseline best-corrected visual acuity (BCVA) of 23 logarithm of minimum angle of resolution (logMAR) letters or more (approximate Snellen equivalent, 20/400 + 3) diagnosed with choroidal neovascularization affecting the foveal center, secondary to nAMD in a treatment-naïve eye,

Table 1. Baseline Demographic Characteristics

	Ranibizumab 0.5 mg (n = 142)	Aflibercept 2.0 mg (n = 139)
Age (yrs)*		
Mean (SD)	76.6 (8.5)	78.7 (7.5)
Median	78	79
Gender, no. (%)		
Male	70 (49.3)	63 (45.3)
Female	72 (50.7)	76 (54.7)
Family history (AMD), no. (%)		
Yes	30 (21.1)	26 (18.7)
No	112 (78.9)	113 (81.3)
History of ATE, no. (%)		
Yes	15 (10.6)	25 (18.0)
No	127 (89.4)	114 (82.0)
Ethnicity, no. (%)		
White	132 (93.0)	130 (93.5)
Black	0 (0.0)	1 (0.7)
Asian	8 (5.6)	7 (5.0)
Other	2 (1.4)	1 (0.7)
Smoking history		
Never smoked, no. (%)	67 (47.2)	67 (48.2)
Current smoker, no. (%)	12 (8.5)	10 (7.2)
Smoked in the past, no. (%)	63 (44.4)	62 (44.6)
Number of pack years, mean (SD)	34.4 (48.1)	26.0 (37.6)

AMD = age-related macular degeneration; ATE = arterial thromboembolic event; SD = standard deviation.

Randomized set.

\*Age calculated at date of informed consent.

without restriction of lesion size or type, were included in the study. Patients with 1 or more patches of MA that were more than 250  $\mu\text{m}$  in the greatest linear dimension in either eye (measured with multimodal imaging) were ineligible.<sup>15</sup> Detailed inclusion and exclusion criteria have been described previously.<sup>14</sup>

Patients were randomized 1:1 using a dynamic allocation method in an interactive web-based response system (Medidata Rave; Medidata Solutions, Inc, New York, NY) to receive either ranibizumab 0.5 mg or aflibercept 2.0 mg according to a T&E regimen for 24 months, as shown in Figure S1 (available at [www.aajournal.org](http://www.aajournal.org)).

Patients were stratified at randomization by current treatment or no current treatment for nAMD of the nonstudy fellow eye to account for any potential contralateral effect of the medication on the study eye. Randomization occurred within 3 strata: 2 treatment-naïve eyes, 1 eye (first or fellow nonstudy eye) being treated with ranibizumab and 1 eye (first or fellow nonstudy eye) being treated with an anti-VEGF other than ranibizumab.

Patients in each group initially underwent 3 monthly loading doses (baseline, week 4, and week 8). Subsequent treatment intervals were determined according to the following disease activity criteria: (1) loss of visual acuity (VA) of 5 letters or more than the best VA recorded since treatment started (where VA loss was the result of disease activity), (2) presence of new retinal hemorrhage (both determined by the investigator), and (3) presence of intraretinal fluid (IRF) or subretinal fluid (SRF) on spectral-domain OCT as determined by the masked central reading center (CRC). The CRC adjudicated the investigator's assessment of disease activity based on review of the images. The treatment interval was shortened by 2 weeks if 1 sign of activity was present and was shortened to 4 weeks if 2 or more signs of activity were present.<sup>14</sup> Patients, but not investigators, were masked to study treatment. Qualified personnel

masked to treatment allocation assessed BCVA scores at each study site.

The primary end point of the study was the mean change in square root area of MA from baseline to 24 months assessed by the masked CRC using multimodal imaging. Macular atrophy was defined as loss of the retinal pigment epithelium, ellipsoid zone, and external limiting membrane with concomitant subsiding of the outer retinal layers together with increased signal transmission below Bruch's membrane of 100  $\mu\text{m}$  or more in linear dimension on OCT. On fundus autofluorescence, an area of well-demarcated hypoautofluorescence of 100  $\mu\text{m}$  or more in longest linear dimension had to be present. Other causes of hypoautofluorescence such as blood or hard exudates had to be excluded using color fundus photography and OCT. Macular atrophy was defined as a sharply demarcated area of partial or complete depigmentation with visible underlying large choroidal vessels 100  $\mu\text{m}$  or more in longest linear dimension on color fundus photography. On fluorescein angiography, well-demarcated areas of window defects with sharply delineated hyperautofluorescence in the late phase of 100  $\mu\text{m}$  or more in longest linear dimension had to be present.

Key secondary efficacy end points included the number of injections from baseline to months 12 and 24 and the mean change in BCVA using 4-m logMAR charts from baseline to months 12 and 24. Other secondary efficacy end points included the proportion of patients showing new MA over 12- and 24-month periods (detailed list provided in Appendix 2, available at [www.aajournal.org](http://www.aajournal.org)).

Baseline measurements of MA were considered to be the last available nonmissing MA area value collected just before the start of treatment in the study eye, unless the baseline image was not gradable, in which case, the protocol allowed the CRC to use either the week 4 or week 8 image as the baseline image if a satisfactory image was available at one of those time points.

Safety end points assessed included ocular and nonocular adverse events (AEs) at all visits, retinal nerve fiber (RNF) analysis (performed using the mean thickness of the RNF layer on a circle scan of the optic nerve head using OCT at baseline and month 24) and ocular inflammation at baseline and 7 days after injection after the third mandated intravitreal injection.

Efficacy assessments included visual and anatomic evaluations. Macular atrophy was diagnosed by a multimodal approach using color fundus photography, fluorescein angiography, autofluorescence, and spectral-domain OCT. Macular atrophy diagnosis was confirmed if it was present on 2 of these modalities, one of which had to be either autofluorescence or OCT imaging.

Best-corrected VA assessment was performed with a protocol refraction by a trained refractionist masked to treatment allocation using a logMAR chart at all visits. Other assessment details are included in Appendix 3 (available at [www.aajournal.org](http://www.aajournal.org)).

The 24-month analysis was performed on the full analysis set, which comprised all randomized patients who had at least 1 postbaseline efficacy value for the primary end point. A random-effects mixed model was used for the analysis of the primary end point (with no imputation of missing data) to account for correlations between repeated measures for both treatment groups, with baseline area of MA as one of the covariates. The model included change in area of MA (square root transformed data) from baseline to months 12 and 24 as a response variable and included continuous baseline area of MA (as graded by the CRC), treatment, visit, and treatment by visit interaction as fixed effect. Square root transformation was used because this offsets the slower growth rates with smaller lesions.<sup>16</sup> The patient was modelled as a random effect. The least square means and corresponding 95% confidence intervals (CIs) were estimated for each treatment group at months 12 and 24. The treatment differences, 95% CIs, and *P* values also were estimated at months 12 and 24.

Table 2. Baseline\* Ocular Characteristics

	Ranibizumab 0.5 mg (n = 142)	Aflibercept 2.0 mg (n = 139)
Mean BCVA (logMAR letters)		
No.	142	139
Mean (SD)	65.0 (15.4)	65.2 (12.6)
Approximate Snellen equivalent	20/50	20/50
Median	68	67
CNV location on FA, no. (%)		
No.	141	139
Subfoveal	129 (92)	113 (81)
Juxtafoveal	9 (6)	20 (14)
Extrafoveal	3 (2)	5 (4)
N/A	—	1 (1)
CNV type on FA, no. (%)		
No.	141	139
Predominantly classic	21 (15)	27 (19)
Minimally classic/occult	119 (84)	111 (80)
Other	1 (1)	0 (0.0)
N/A	—	1 (1)
Area of lesion on FA (mm <sup>2</sup> )		
No.	141	138
Mean (SD)	6.0 (4.8)	6.0 (4.6)
Median	4.8	5.3
Area of active CNV on FA (mm <sup>2</sup> )		
Total no.	140	138
Mean (SD)	5.2 (4.1)	5.1 (3.9)
Median	4.2	4.4
Hemorrhage on CFP, no. (%)		
No.	140	138
Yes	62 (44)	52 (38)
No	78 (55)	86 (62)
N/A	1 (1)	—
CSFT (μm)		
No.	141	139
Mean (SD)	468 (151)	483 (168)
Median	423	451
IRF status, no. (%)		
No.	141	139
Absent	72 (51)	76 (55)
Present	69 (49)	63 (45)
SRF status, no. (%)		
No.	141	139
Absent	15 (11)	17 (12)
Present	126 (89)	122 (88)
SHRM status, no. (%)		
No.	141	139
Absent	23 (16)	38 (27)
Present	118 (84)	101 (73)
PED status, no. (%)		
No.	141	139
Absent	4 (3)	3 (2)
Present	137 (97)	136 (98)
PED type, no. (%)		
No.	141	139
Solid	17 (12)	17 (12)
Hollow	24 (17)	27 (19)
Mixed	96 (68)	92 (66)
N/A	4 (3)	3 (2)

Table 2. (Continued.)

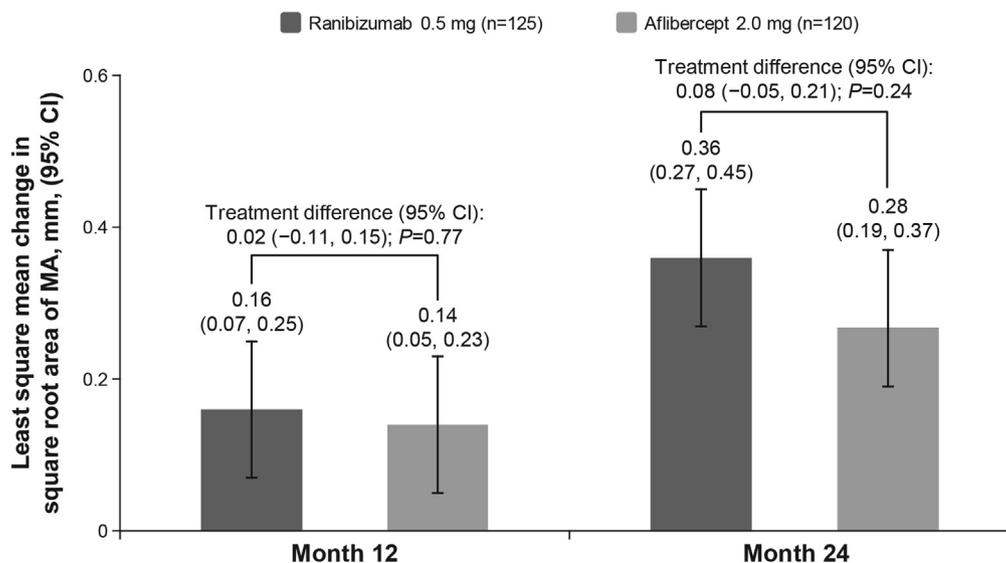
	Ranibizumab 0.5 mg (n = 142)	Aflibercept 2.0 mg (n = 139)
Subfoveal choroidal thickness (μm)		
No.	138	134
Mean (SD)	194 (78)	190 (82)
Median	191	172
Overall diagnosis of MA, no. (%)		
No.	141	139
Yes	10 (7)	9 (6)
No	131 (93)	130 (94)
Area of atrophy (mm <sup>2</sup> )		
No.	140	139
Mean (SD)	0.01 (0.05)	0.06 (0.35)
Median	0.000	0.000
Minimum	0.00	0.00
Maximum	0.44	3.69
Longest linear dimension (μm)		
No.	138	135
Mean (SD)	19.6 (82)	30.2 (193)
Median	0.0	0.0
Minimum	0	0
Maximum	518	1794
Atrophy location, no. (%)		
Central subfield		
No.	141	139
Yes	1 (1)	1 (1)
No	8 (6)	8 (6)
N/A	132 (93)	130 (93)
Inner subfield, no. (%)		
No.	141	139
Yes	7 (5)	9 (6)
No	2 (1)	0 (0)
N/A	132 (94)	130 (94)
Outer subfield, no. (%)		
No.	141	139
Yes	1 (1)	3 (2)
No	8 (6)	6 (4)
N/A	132 (93)	130 (94)

AF = autofluorescence; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CFP = color fundus photography; CSFT = central subfield foveal thickness; FA = fluorescein angiography; IRF = intraretinal fluid; logMAR = logarithm of minimum angle of resolution; MA = macular atrophy; N/A = not available; PED = pigment epithelial detachment; SRF = subretinal fluid; SHRM = subretinal hyperreflective material; SD = standard deviation.

Randomized set.  
\*Last available nonmissing value collected just before the start of treatment in the study eye.

A supporting analysis of the primary end point also was carried out on the per-protocol set using the same random-effects mixed model. The per-protocol set consisted of all patients in the full analysis set who followed the treatment regimen as randomized and completed the study without clinically significant protocol deviations. Sensitivity analyses were carried out by fitting the mixed model with missing data imputed using the last observation carried forward imputation method.

The proportion of patients with new MA at months 12 and 24 was analyzed using a logistic regression model, and the number of



**Figure 3.** Bar graph showing the mean change in square root area of macular atrophy (MA) from baseline, full analysis set. Least square means are the estimated change in area of MA from baseline; mixed-model analysis adjusting for baseline area of MA (primary analysis); mixed model: change from baseline (square root MA area [mm]) = baseline (square root MA area) + treatment + visit + treatment × visit + subject (random effect); treatment difference: ranibizumab – aflibercept; MA area is treated as 0 if MA is reported as absent (overall determination of MA presence). CI = confidence interval.

injections from baseline to months 12 and 24 was analyzed using a negative binomial regression model. The analysis of the change in BCVA from baseline was conducted using a similar random-effects mixed model as for the primary end point, with continuous baseline BCVA as one of the covariates. Further details of the statistical methods, including sample size calculations, are provided in [Appendix 4](#) (available at [www.aaojournal.org](http://www.aaojournal.org)).

## Results

### Patient Disposition

Overall, 314 patients were screened and 281 were randomized (ranibizumab, n = 142; aflibercept, n = 139). A total of 56 patients (19.9%) discontinued from the study. The proportion was similar between treatment groups: (ranibizumab, 25 [17.6%]; aflibercept, 31 [22.3%]); the most frequent reasons for discontinuation in the ranibizumab and aflibercept groups were AEs and the patient's decision to withdraw consent, respectively ([Fig 2](#)). Two hundred seventy-eight patients (98.9%) were included in the full analysis set (ranibizumab, n = 141 [99.3%]; aflibercept, n = 137 [98.6%]).

### Demographics and Baseline Characteristics

Demographics and baseline characteristics were comparable between the treatment groups ([Table 1](#)). Patients in the ranibizumab group had a mean age of 76.6 years (standard deviation [SD], 8.5 years), and 51% were women; those in the aflibercept group had a mean age of 78.7 years (SD, 7.5 years), and 55% were women. Most patients were treatment-naïve in both eyes (83.1% for ranibizumab and 87.1% for aflibercept). The mean total BCVA scores in the randomized set were 65.0 logMAR (SD, 15.4 logMAR; approximate Snellen equivalent, 20/50) and 65.2 logMAR (SD, 12.6 logMAR; approximate Snellen equivalent, 20/50) in the ranibizumab and aflibercept groups, respectively. Most patients showed minimally classic or occult choroidal

neovascularization type at baseline in both treatment groups ([Table 2](#)).

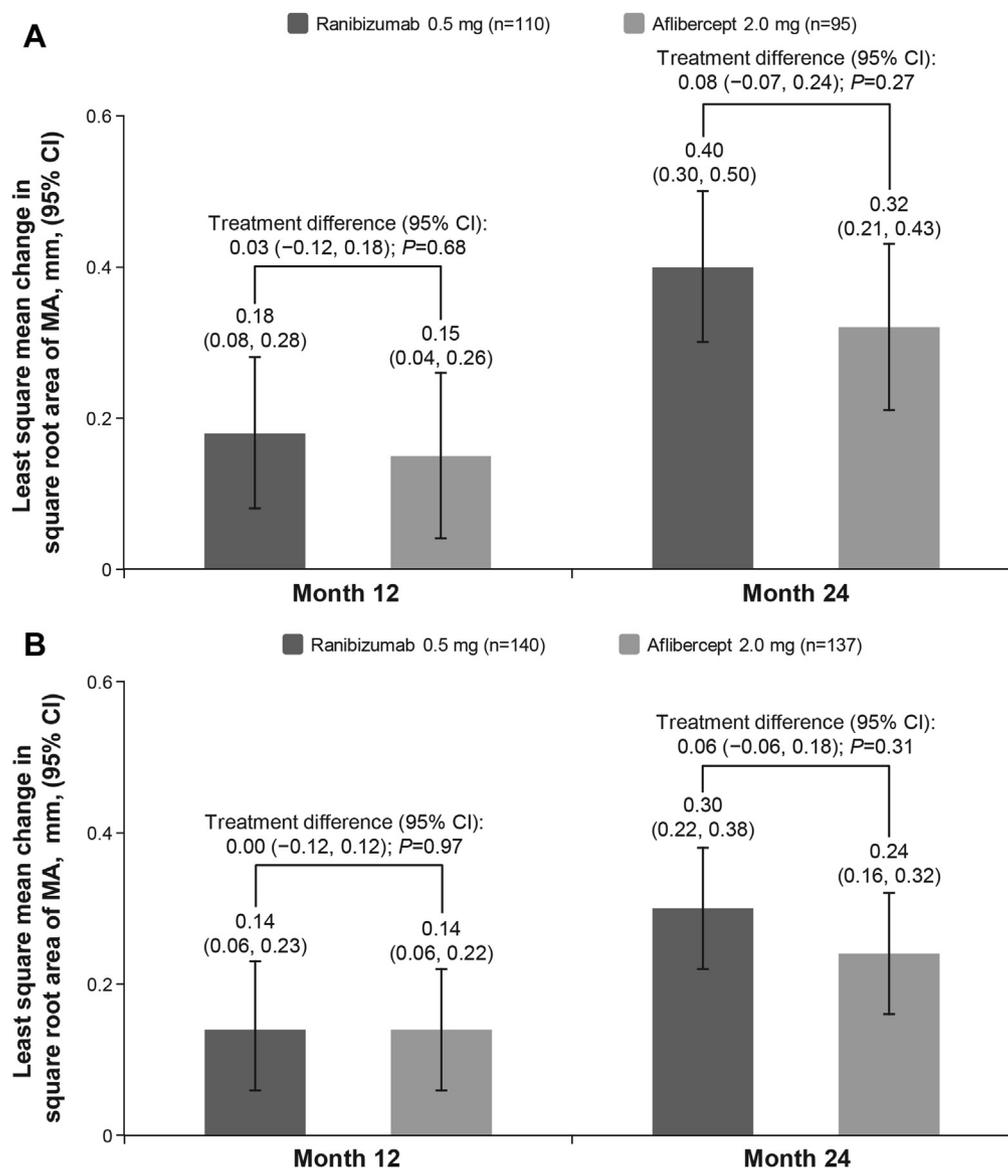
### Efficacy Analyses

**Macular Atrophy.** The mean square root area of MA increased from 0.02 mm (SD, 0.10 mm; n = 140) at baseline to 0.19 mm (SD, 0.45 mm; n = 126) at 12 months and 0.40 mm (SD, 0.73 mm; n = 114) at 24 months in the group receiving ranibizumab, whereas it increased from 0.05 mm (SD, 0.23 mm; n = 137) at baseline to 0.20 mm (SD, 0.44; n = 120) at 12 months and 0.35 mm (SD, 0.65 mm; n = 106) at 24 months in the group receiving aflibercept.

The primary mixed-model analysis estimated the mean change in square root area of MA from baseline at month 12 to be +0.16 mm (95% CI, 0.07–0.25 mm) for ranibizumab and +0.14 mm (95% CI, 0.05–0.23 mm) for aflibercept, a treatment difference of +0.02 mm (95% CI, -0.11 to 0.15 mm;  $P = 0.77$ ) and +0.36 mm (95% CI, 0.27–0.45 mm) for ranibizumab and +0.28 mm (95% CI, 0.19–0.37 mm) for aflibercept at month 24, a treatment difference of +0.08 mm (95% CI, -0.05 to 0.21 mm;  $P = 0.24$ ; [Fig 3](#)).

Results from the per-protocol analysis were consistent with those of the primary analysis. The mean change in square root area of MA from baseline at month 12 was +0.18 mm (95% CI, 0.08–0.28 mm) for ranibizumab and +0.15 mm (95% CI, 0.04–0.26 mm) for aflibercept; a treatment difference of 0.03 mm (95% CI, -0.12 to 0.18 mm;  $P = 0.68$ ), and +0.40 mm (95% CI, 0.30–0.50 mm) for ranibizumab and +0.32 mm (95% CI, 0.21–0.43 mm) for aflibercept at month 24; a treatment difference of 0.08 mm (95% CI, -0.07 to 0.24 mm;  $P = 0.27$ ), as shown in [Figure 4A](#).

The results of a sensitivity analysis for the square root transformed area of MA using data imputation following the last observation carried forward method for eyes that dropped out was consistent with those of the primary analysis. The mean change in square root area of MA from baseline at month 12 was +0.14 mm (95% CI, 0.06–0.23 mm) for ranibizumab and +0.14 mm (95% CI, 0.06–0.22 mm) for aflibercept; a treatment difference of 0.00 mm (95% CI, -0.12 to 0.12 mm;  $P = 0.97$ ); and +0.30 mm (95% CI, 0.22–0.38 mm) for ranibizumab and +0.24 mm (95% CI,



**Figure 4.** A, Bar graph showing the mean change in square root area of macular atrophy (MA) from baseline (per-protocol analysis). Mixed model: change from baseline (square root MA area [mm]) = baseline (square root MA area) + treatment + visit + treatment × visit + subject (random effect); least square means are the estimated changes in area of MA from baseline. CI = confidence interval; n = number of patients. B, Bar graph showing the mean change in square root area of macular atrophy from baseline (sensitivity analysis), full analysis set. Mixed model: change from baseline (square root MA area [mm]) = baseline (square root MA area) + treatment + visit + treatment × visit + subject (random effect); least square means are the estimated changes in area of MA from baseline. CI = confidence interval.

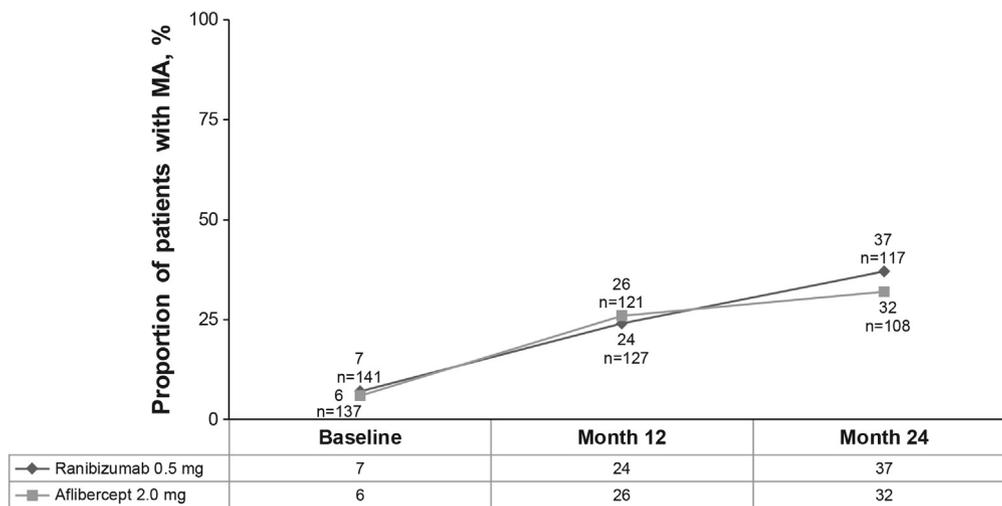
0.16–0.32 mm) for aflibercept at month 24; a treatment difference of 0.06 mm (95% CI, –0.06 to 0.18 mm;  $P = 0.31$ ), as shown in Figure 4B.

The proportion of patients with MA increased from 7% (10/141) at baseline to 24% (31/127) and 37% (43/117) at months 12 and 24 for ranibizumab and from 6% (8/137) to 26% (31/121) and 32% (35/108) for aflibercept (Fig 5). A logistic regression analysis estimated that patients in the ranibizumab group had a 19% higher chance (odds ratio [OR], 1.19; 95% CI, 0.67–2.09) of new MA developing than the aflibercept group. However, this difference was not statistically significant ( $P = 0.55$ ; Fig 6).

**Number of Injections.** The mean number of intravitreal injections from baseline to month 12 was similar for the ranibizumab

(9.7 injections [SD, 2.8 injections]) and aflibercept (9.7 injections [SD, 2.5 injections]) groups. The mean number of injections administered between months 12 and 24 was similar between both groups, with 8.9 injections (SD, 3.2 injections) in the ranibizumab group and 8.3 injections (SD, 3.6 injections) in the aflibercept group. Over the entire 24-month study period, the mean number of injections was 17.7 injections (SD, 6.4 injections) in the ranibizumab group and 17.0 injections (SD, 6.3 injections) in the aflibercept group (Fig 7).

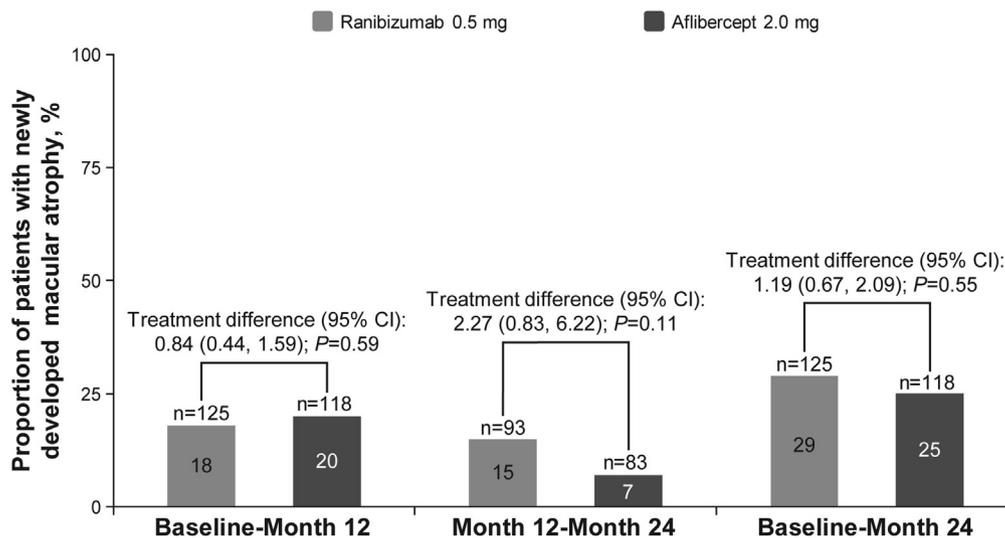
A negative binomial regression model applied to the 24-month study period estimated that the average number of injections received per year was similar between the groups: 9.6 injections (95% CI, 9.2–10.0 injections) for ranibizumab and 9.5 injections (95% CI, 9.1–9.9 injections) for aflibercept, with an injection rate ratio for ranibizumab to aflibercept of 1.01 (95% CI, 0.95–1.08;  $P = 0.75$ ).



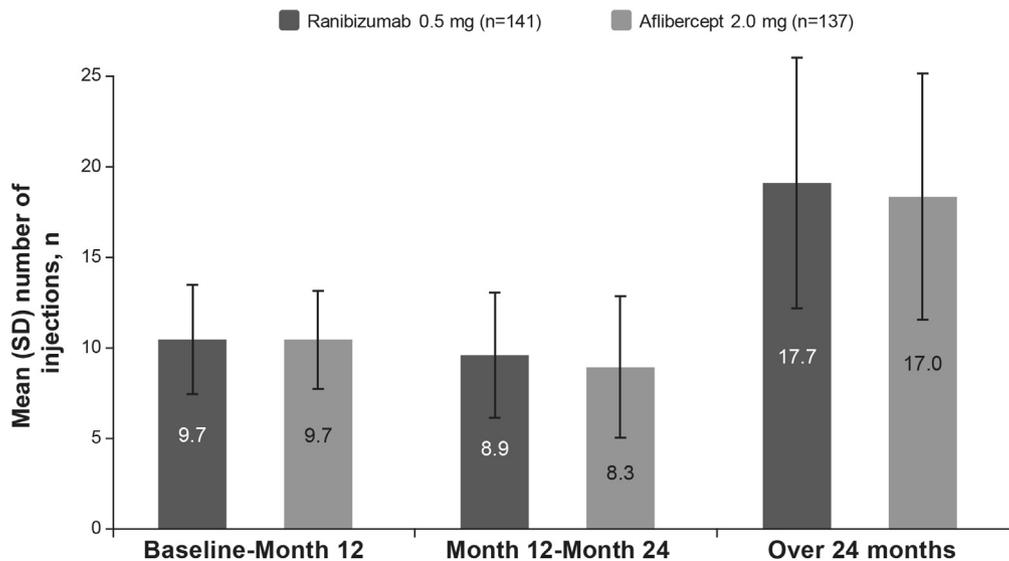
**Figure 5.** Graph showing the proportion of patients with macular atrophy (MA) at months 12 and 24, full analysis set. A diagnosis of MA was confirmed if it was present in 2 of the imaging methods, 1 of which had to be OCT or autofluorescence. Baseline measurements of MA were considered to be the last available nonmissing MA area value collected just before the start of treatment in the study eye, unless the baseline image was not gradable, in which case the protocol allowed the central reading center to use either the week 4 or week 8 image as the baseline image if a satisfactory image was available at one of those time points.

Similar proportions of patients in the ranibizumab and aflibercept groups achieved a maximum interval of 12 weeks (32% and 31%, respectively), 8 weeks (20% and 19%, respectively), or 6 weeks (20% and 23%, respectively) at least once during the study, as shown in Figure S8 (available at [www.aaojournal.org](http://www.aaojournal.org)). Eighty-six patients (64%) from the ranibizumab group and 79 patients (59%) from the aflibercept group returned to monthly injections at least once.

**Best-Corrected Visual Acuity.** Similar mean BCVA gains were observed between ranibizumab and aflibercept at Months 12 and 24. The mean BCVA at baseline was 65.3 letters (SD, 15.1 letters; approximate Snellen equivalent 20/50) and 65.1 letters (SD, 12.5 letters; approximate Snellen equivalent, 20/50) in the ranibizumab (n = 141) and aflibercept (n = 137) treatment groups, respectively. The mean change in BCVA was +6.9 letters (SD, 12.3 letters) for the ranibizumab group and +5.2 letters (SD, 12.8



**Figure 6.** Bar graph showing the proportion of patients with newly developed macular atrophy (MA) from baseline to month 24, full analysis set. Logistic regression analysis includes early withdrawal data. Baseline measurements of MA were considered to be the last available nonmissing MA area value collected just before the start of treatment in the study eye, unless the baseline image was not gradable, in which case the protocol allowed the central reading center to use either the week 4 or week 8 image as the baseline image if a satisfactory image was available at one of those time points. Baseline to month 12 = patients with no MA at baseline who demonstrated new MA (defined as diagnosis of MA change from “no” to “yes”) by month 12. Month 12 to month 24 = patients with no MA at month 12 who demonstrated new MA (defined as diagnosis of MA change from “no” to “yes”) by month 24. Baseline to month 24 = patients with no MA at baseline who demonstrated new MA (defined as diagnosis of MA change from “no” to “yes”) by month 24. The odds ratio for treatment difference is ranibizumab versus aflibercept comparing odds of newly developed MA (yes) at the specified study visit. The logistic regression model included treatment as factor. Model:  $\log(p / 1 - p) = \text{treatment}$ . Each visit was analyzed by a separate model. CI = confidence interval.



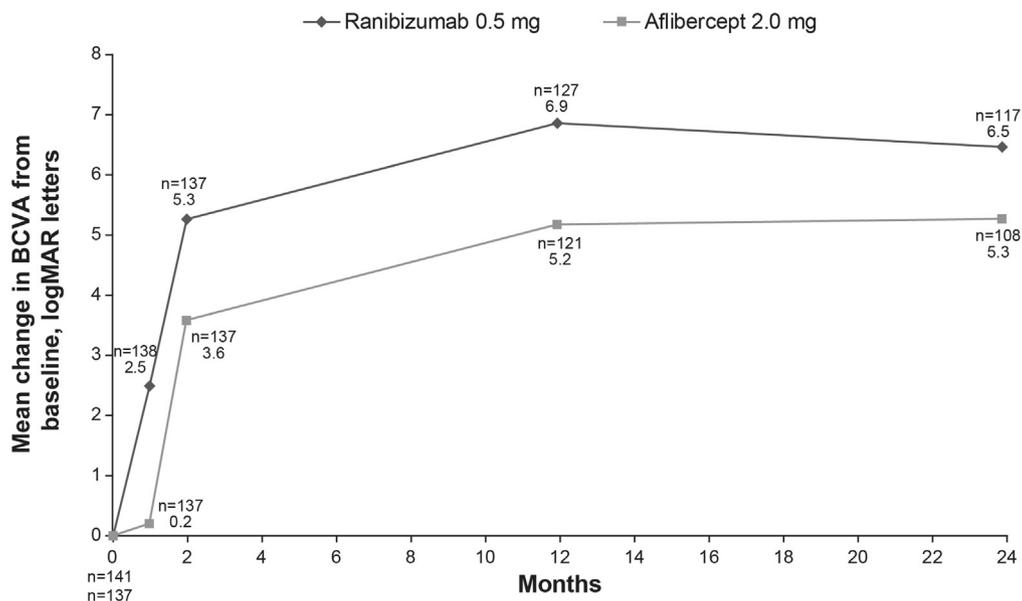
**Figure 7.** Bar graph showing the mean number of injections at months 12 and 24, full analysis set. At month 24,  $n = 127$  for the ranibizumab group and  $n = 121$  for the aflibercept group. The month 12 injection count was included in the second year of treatment. The period cutoff was based on nominal visit window. Injections per year are the total number of injections divided by the total exposure in years. Exposure is the follow-up duration in the specified period. SD = standard deviation.

letters) for the aflibercept group at month 12 and was +6.5 letters (SD, 14.4 letters) for the ranibizumab group and +5.3 letters (SD, 13.3 letters) for the aflibercept group at month 24 (Fig 9).

The mixed model (adjusting for baseline BCVA) estimated the mean change in BCVA from baseline to month 12 to be +7.2 letters (95% CI, 5.3–9.0 letters) for the ranibizumab group and +4.8 letters (95% CI, 3.0–6.7 letters) for the aflibercept group; the treatment difference was 2.3 letters (95% CI, –0.3 to 4.9 letters;  $P = 0.08$ ). At month 24, the mean change in BCVA was estimated to be +6.6 letters (95% CI, 4.7–8.5 letters) for the ranibizumab group and +4.6 letters (95% CI, 2.7–6.6 letters) for

the aflibercept group, with a treatment difference of 2.0 letters (95% CI, –0.7 to 4.6 letters;  $P = 0.15$ ), as shown in Table S3 (available at [www.aaojournal.org](http://www.aaojournal.org)). The results of the sensitivity analysis were consistent with those of the primary analysis, as described in Appendix 4 (available at [www.aaojournal.org](http://www.aaojournal.org)).

A gain of 15 letters or more from baseline in BCVA was achieved by 22% of patients (28/127) at month 12 in the ranibizumab group, compared with 21% of patients (25/121) in the aflibercept group. A gain of 15 letters or more from baseline in BCVA was achieved by 25% of patients (29/117) at month 24 in the ranibizumab group, compared with 19% of patients (20/108) in



**Figure 9.** Graph showing the mean change in best-corrected visual acuity (BCVA) at months 12 and 24, full analysis set. Observed data at the nominal visit window from the case report form, that is, fixed visits included baseline, week 4, week 8, month 12, and month 24. Baseline is the last available nonmissing value collected just before the start of treatment in the study eye. logMAR = logarithm of minimum angle of resolution.

Table 4. Most Frequent Ocular ( $\geq 2$  Patients in Any Group) Adverse Events, Regardless of Causal Relationship, by Preferred Term

Preferred Term*	Ranibizumab 0.5 mg (n = 141)	Aflibercept 2.0 mg (n = 139)
Ocular AEs, total	101 (71.6)	115 (82.7)
Eye pain	24 (17)	24 (17.3)
Vitreous floaters	18 (12.8)	17 (12.2)
Age-related macular degeneration	16 (11.3)	19 (13.7)
Dry eye	14 (9.9)	14 (10.1)
Cataract operation	12 (8.5)	16 (11.5)
Lacrimation increased	11 (7.8)	11 (7.9)
Cataract	8 (5.7)	22 (15.8)
Choroidal neovascularization	8 (5.7)	8 (5.8)
Eye irritation	8 (5.7)	9 (6.5)
Vision blurred	8 (5.7)	11 (7.9)
Visual acuity reduced	8 (5.7)	5 (3.6)
Vitreous detachment	8 (5.7)	20 (14.4)
Ocular hyperemia	7 (5.0)	11 (7.9)
Retinal hemorrhage	7 (5.0)	7 (5.0)
Conjunctival hemorrhage	6 (4.3)	4 (2.9)
Retinal pigment epithelial tear	6 (4.3)	4 (2.9)
Eye discharge	5 (3.5)	6 (4.3)
Corneal abrasion	4 (2.8)	4 (2.9)
Posterior capsule opacification	4 (2.8)	5 (3.6)
Asthenopia	3 (2.1)	2 (1.4)
Blepharitis	3 (2.1)	4 (2.9)
Conjunctivitis	3 (2.1)	3 (2.2)
Drug hypersensitivity	3 (2.1)	3 (2.2)
Eye pruritus	3 (2.1)	7 (5.0)
Eye swelling	3 (2.1)	2 (1.4)
Eyelid ptosis	3 (2.1)	0 (0.0)
Foreign body sensation	3 (2.1)	4 (2.9)
Intraocular lens implant	3 (2.1)	4 (2.9)
Intraocular pressure increase	3 (2.1)	3 (2.2)
Photopsia	3 (2.1)	3 (2.2)
Posterior lens capsulotomy	3 (2.1)	1 (0.7)
Punctate keratitis	3 (2.1)	1 (0.7)
Chalazion	2 (1.4)	7 (5.0)
Macular fibrosis	2 (1.4)	3 (2.2)
Metamorphopsia	2 (1.4)	7 (5.0)
Visual impairment	2 (1.4)	5 (3.6)
Detachment of retinal pigment epithelium	1 (0.7)	3 (2.2)
Diplopia	1 (0.7)	4 (2.9)
Glaucoma	1 (0.7)	3 (2.2)
Pain	N/A	3 (2.2)

AE = adverse event; N/A = not available.

Safety set. Data are no. (%). Percentages are based on the number of patients in each group. Events are arranged by decreasing order of incidence in the ranibizumab group. Treatment-emergent adverse events are included and are considered by the onset date on or after the date of first study treatment.

\*According to the Medical Dictionary for Regulatory Activities, version 17.

the aflibercept group, as seen in [Figure S10A](#) (available at [www.aaojournal.org](#)). A logistic regression model estimated the odds of a 15-letter or more gain from baseline at month 12 and month 24 to be 5% and 61% higher with ranibizumab versus aflibercept (month 12: OR, 1.05 [95% CI, 0.53–2.08;  $P = 0.89$ ]; month 24: OR, 1.61 [95% CI, 0.77–3.35;  $P = 0.21$ ]; [Fig S10A](#) [available at [www.aaojournal.org](#)]).

At month 12, 97% of patients (123/127) showed a 15-letter or fewer loss from baseline in BCVA in the ranibizumab group compared with 95.0% of patients (115/121) in the aflibercept group. At month 24, 94% of patients (110/117) showed a 15-letter or fewer loss from baseline in BCVA in the ranibizumab group compared with 94% of patients (102/108) in the aflibercept group, as shown in [Figure S10B](#) (available at [www.aaojournal.org](#)).

A logistic regression model estimated the odds of a 15-letter or fewer loss from baseline at month 12 to be 63% higher with ranibizumab versus aflibercept (OR, 1.63 [95% CI, 0.45–5.93];  $P = 0.46$ ). Patients in the ranibizumab group showed a similar chance (OR, 0.94 [95% CI, 0.30–2.90];  $P = 0.91$ ) as the aflibercept group to have a 15-letter or fewer loss from baseline in BCVA at month 24, as shown in [Figure S10B](#) (available at [www.aaojournal.org](#)).

**Central Subfield Foveal Thickness.** The mean central subfield foveal thickness (CSFT) at baseline was 468  $\mu\text{m}$  (SD, 151  $\mu\text{m}$ ) and 484  $\mu\text{m}$  (SD, 168  $\mu\text{m}$ ) in the ranibizumab and aflibercept groups, respectively. The mean CSFT decreased to 314  $\mu\text{m}$  (SD, 85  $\mu\text{m}$ ;  $n = 127$ ) at month 12, with a mean change from baseline of  $-147 \mu\text{m}$  (SD, 128  $\mu\text{m}$ ), in the ranibizumab group and to 308  $\mu\text{m}$  (91  $\mu\text{m}$ ;  $n = 120$ ), with a mean change in baseline of  $-172 \mu\text{m}$  (SD, 150  $\mu\text{m}$ ), in the aflibercept group. The mean CSFT decreased further at month 24 to 306  $\mu\text{m}$  (SD, 81  $\mu\text{m}$ ;  $n = 117$ ), with a mean change from baseline of  $-151 \mu\text{m}$  (SD, 133  $\mu\text{m}$ ), in the ranibizumab group and to 299  $\mu\text{m}$  (SD, 78  $\mu\text{m}$ ;  $n = 108$ ), with a mean change from baseline of  $-182 \mu\text{m}$  (SD, 156  $\mu\text{m}$ ), in the aflibercept group.

The mixed-model analysis (adjusting for baseline CSFT) estimated the mean change in CSFT from baseline at month 12 to be  $-153 \mu\text{m}$  (95% CI,  $-167$  to  $-140 \mu\text{m}$ ) for the ranibizumab group and  $-163 \mu\text{m}$  (95% CI,  $-177$  to  $-150 \mu\text{m}$ ) for the aflibercept group, with a treatment difference of 10.1  $\mu\text{m}$  (95% CI,  $-8.8$  to 29  $\mu\text{m}$ ;  $P = 0.29$ ). At month 24, the mean change in CSFT was estimated to be  $-161 \mu\text{m}$  (95% CI,  $-174$  to  $-147 \mu\text{m}$ ) for the ranibizumab group and  $-173 \mu\text{m}$  (95% CI,  $-186$  to  $-159 \mu\text{m}$ ) for the aflibercept group, with a treatment difference of 11.9  $\mu\text{m}$  (95% CI,  $-7.4$  to 31  $\mu\text{m}$ ;  $P = 0.23$ ).

**Intraretinal Fluid and Subretinal Fluid.** Approximately 4% of patients in each group showed no IRF or SRF at baseline. This increased to 57% in the ranibizumab group and 61% in the aflibercept group at month 2. The proportion of patients with no SRF or IRF at months 12 and 24 appeared to be stable at 56% and 57% in the ranibizumab group and 64% and 61% in the aflibercept group, respectively, as shown in [Figure S11](#) (available at [www.aaojournal.org](#)).

**Plasma Vascular Endothelial Growth Factor Levels.** The mean concentration of plasma VEGF at baseline was 44 pg/ml (SD, 43 pg/ml) in the ranibizumab group ( $n = 139$ ) and 42 pg/ml (SD, 35 pg/ml) in the aflibercept group ( $n = 137$ ). The mean changes in plasma concentrations of VEGF from baseline at weeks 5 and 9 (7 days after the second and third intravitreal injections, respectively) were  $-0.5 \text{ pg/ml}$  and  $+0.5 \text{ pg/ml}$ , respectively, in the ranibizumab group and  $-26 \text{ pg/ml}$  and  $-25 \text{ pg/ml}$ , respectively, in the aflibercept group.

A random-effects mixed model adjusting for baseline plasma VEGF concentrations found a statistically significant difference between ranibizumab and aflibercept in the estimated change in plasma VEGF concentration from baseline at both week 5 and week 9 (both  $P < 0.001$ ), as shown in [Figure S12](#) (available at [www.aaojournal.org](#)). The least square means change at week 5 was  $+0.30 \text{ pg/ml}$  (95% CI,  $-3.8$  to 4.4  $\text{pg/ml}$ ) and  $-26.9 \text{ pg/ml}$  (95% CI,  $-31$  to  $-23 \text{ pg/ml}$ ) in the ranibizumab and aflibercept groups, respectively. At week 9, the change was  $+1.6 \text{ pg/ml}$  (95% CI,  $-2.5$  to 5.8  $\text{pg/ml}$ ) and  $-27.3 \text{ pg/ml}$  (95% CI,  $-31$  to  $-23 \text{ pg/ml}$ ) in the ranibizumab and aflibercept groups, respectively.

Table 5. Deaths and Serious Adverse Events

Preferred Term*	Ranibizumab 0.5 mg (n = 141)	Aflibercept 2.0 mg (n = 139)
Deaths, total <sup>†</sup>	3 (2.1)	6 (4.3)
Ocular SAEs, total	2 (1.4)	4 (2.9)
Ocular SAEs (≥1 patient in any group)		
Cataract traumatic	1 (0.7)	0 (0.0)
Retinal artery embolism	1 (0.7)	0 (0.0)
Retinal artery occlusion	1 (0.7)	0 (0.0)
Retinal detachment	0 (0.0)	2 (1.4)
Endophthalmitis	0 (0.0)	2 (1.4)
Nonocular SAEs, total	50 (35.5)	54 (38.8)
Nonocular SAEs (≥2% in any group)		
Atrial fibrillation	7 (5.0)	0 (0.0)
Basal cell carcinoma	7 (5.0)	2 (1.4)
Pneumonia	4 (2.8)	4 (2.9)
Squamous cell carcinoma	4 (2.8)	4 (2.9)
Aphasia	3 (2.1)	0 (0.0)
Chest pain	3 (2.1)	2 (1.4)
Fall	3 (2.1)	1 (0.7)
Femoral neck fracture	3 (2.1)	2 (1.4)
Renal failure acute	3 (2.1)	2 (1.4)
Syncope	3 (2.1)	2 (1.4)
Urinary tract infection	2 (1.4)	4 (2.9)
Cerebrovascular accident	1 (0.7)	3 (2.2)

SAE = serious adverse event.

Safety set. Data are no. (%). Percentages are based on the number of patients in each group. Events are arranged by decreasing order of incidence in the ranibizumab group. Treatment-emergent adverse events are included and are considered by the onset date on or after the date of first study treatment.

\*According to the Medical Dictionary for Regulatory Activities, version 17.

<sup>†</sup>Three in the ranibizumab group (cardiac failure, femoral neck fracture, and metastatic esophageal cancer, n = 1 each) and 6 in the aflibercept group (acute renal failure, adrenal gland cancer, angioimmunoblastic T-cell lymphoma, cardiac failure, malignant neoplasm progression with obstructive uropathy, metabolic acidosis, n = 1 each).

## Safety Analyses

Overall, 255 patients (91.1%) experienced at least 1 AE during the study (125 patients [88.7%] in the ranibizumab group and 130 patients [93.5%] in the aflibercept group). Eye pain was the most commonly reported ocular AE in both groups (Table 4). At least 1 nonocular serious AE during the study was reported by 50 patients (35.5%) in the ranibizumab group and 54 patients (38.8%) in the aflibercept group (Table 5). Nine patients (6%) in the ranibizumab group and 14 patients (10%) in the aflibercept group discontinued the study because of an AE, and 7 patients (5%) in the ranibizumab group and 14 patients (10%) in the aflibercept group discontinued the study because of a serious AE. A total of 9 deaths were reported; none was suspected by the investigator to be related to treatment (Table 5).

Arterial thromboembolic events were distributed similarly between the groups: 11 patients (8%) in the ranibizumab group and 7 patients (5%) in the aflibercept group, as shown in Table S6 (available at [www.aaojournal.org](http://www.aaojournal.org)). The proportion of patients who experienced a reduction in RNF thickness was similar between both groups at month 12 (3/122 [2.5%] in the ranibizumab group and 3/111 [2.7%] in the aflibercept group). These proportions were 3.6% in the ranibizumab group (4/110 patients) and 1% in the aflibercept group (1/97 patients) at month 24, as

shown in Table S7 (available at [www.aaojournal.org](http://www.aaojournal.org)). Approximately 5% of ranibizumab patients and 7% of aflibercept patients demonstrated grade 1+ anterior chamber cells by week 9, and approximately 6% of ranibizumab and 7% of aflibercept patients demonstrated grade 1 anterior chamber flare by week 9.

## Discussion

The RIVAL study is a prospective randomized study to compare ranibizumab and aflibercept using a CRC-controlled T&E regimen. The square root area of MA increased from baseline to month 24 in both groups (ranibizumab, 0.36 mm; aflibercept, 0.28 mm), but there was no statistically significant difference between the 2 groups. The proportion of patients with new MA at 12 and 24 months was comparable between the 2 treatment groups. The change in square root area of MA at month 12 was similar to that found in earlier natural history studies, including the Age-Related Eye Disease Study 2.<sup>17,18</sup> Natural history studies of MA over a duration of 4 years and more have reported a growth rate in MA of 1.5 to 2.2 mm<sup>2</sup>/year, which may indicate faster growth than in our study.<sup>19</sup> The development of new MA results in our study were consistent with those described in the post hoc analysis of the Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (Pro Re Nata [PRN]) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration.<sup>20</sup> The Inhibition of VEGF in Age-Related Choroidal Neovascularization study also found no significant difference in the proportion of patients demonstrating MA with both continuous (monthly) and discontinuous regimens of 2 anti-VEGF agents (ranibizumab and bevacizumab).<sup>6</sup> Data on the development of MA in patients taking aflibercept are limited. Kuroda et al<sup>11</sup> reported that MA developed in 10% of eyes during 1 year of aflibercept treatment.

Some differences in injection rates were evident between the present study and others that used variable treatment regimens. The similar mean number of injections in the first year (approximately 10) between the ranibizumab and aflibercept groups is higher than that observed in many previous studies, although injection rates were similar for both the first and the second year to the T&E arm of the Treat-and-Extend Protocol in Patients with Wet Age-Related Macular Degeneration study.<sup>18,21–23</sup> The Fight Retinal Blindness! registry analysis of 2-year outcomes using T&E in a real-world setting reported a lower number of injections (14.2 injections) over 2 years than the RIVAL study.<sup>24,25</sup> One of the differences with other studies is that in the RIVAL study, the investigator assessments of fluid on OCT were adjudicated by a masked CRC that made the final treatment interval decision, unlike most other studies in which fluid assessments usually were made solely by investigators.

Approximately 60% of patients in our study needed to return to monthly injections at some point, twice on average, over 24 months in both groups. Approximately 30% of

patients in each group achieved a maximum treatment interval of 12 weeks at least once during the study, with maximum intervals of 6 and 8 weeks being the next most common (20% of patients in each group). Evidence also suggests that a T&E regimen can result in better outcomes than a pro re nata regimen.<sup>12,25</sup>

No differences were found in BCVA gains between the treatment groups, and the mean changes in BCVA in the RIVAL study were similar to those of previous studies.<sup>3,12,24,26</sup> The mean BCVA after 2 years was more than 70 letters in both groups, despite a high mean BCVA at baseline, which has been associated with lower mean visual improvements because of a ceiling effect whereby gains are limited by an upper threshold above which patients cannot improve. The good visual gains achieved despite the high baseline BCVA may be related to the high treatment frequency or to the restrictions on the presence and size of MA in either eye at baseline in our study.

The mean reduction in CSFT in the RIVAL study also was similar to that of earlier studies,<sup>3,12,26,27</sup> but the proportion of patients with a dry retina after 24 months in both groups was higher than that reported in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration study and the Inhibition of VEGF in Age-Related Choroidal Neovascularization study.<sup>3,6,26</sup> It is possible that further analysis of the current study's data could provide interesting insights into the association between a dry retina and good VA results. In fact, the 24-month results from the A Phase IV, Randomized, Controlled, Single Masked Study Investigating the Efficacy and Safety of Ranibizumab "Inject and Extend" Using an Intensive Retinal Fluid Retreatment Regimen Compared to a Relaxed Retinal Fluid Retreatment Regimen in Patients with Wet Age-Related Macular Degeneration study reported that patients treated with a ranibizumab T&E regimen that allows some SRF ( $\leq 200 \mu\text{m}$ ) achieved similar visual outcomes as a regimen that did not tolerate any SRF, with significantly fewer ranibizumab injections.<sup>28</sup> Although it is difficult to infer anything from the 2 nonsignificant trends, the tendency of aflibercept to dry the retina more and result in less atrophy seems inconsistent with the concern that more drying causes more atrophy.

The difference in change in plasma VEGF concentration between treatment groups was statistically significant ( $P < 0.001$ ) at weeks 5 and 9, that is, 7 days after the second and third injections. These results are aligned with previous studies that show that aflibercept therapy results in greater, more sustained reduction in systemic VEGF levels than ranibizumab, as may be expected based on the structural differences between the 2 molecules.<sup>29–31</sup> However, reduced systemic VEGF levels in the patients receiving aflibercept did not seem to be associated with an increased risk of arterial thromboembolic events.

Other safety results were similar between the ranibizumab and aflibercept groups, consistent with previous evidence comparing these agents.<sup>26</sup> Higher rates of ocular inflammation with aflibercept compared with ranibizumab have been reported in previous communications,<sup>32,33</sup> but in the current study, no difference in ocular inflammation or

RNF thickness was observed between the ranibizumab and aflibercept groups.

The randomized, prospective design of the RIVAL study is a strength, along with the identical treatment protocols used for both drugs. The study used a CRC, ensuring consistency in anatomic assessments. In addition, the masking of the BCVA assessors and the CRC to treatment allocation limits the bias in the results. Macular atrophy was assessed using multimodal imaging, which is a best practice recommendation,<sup>34</sup> and was analyzed using square root transformed data, which reduces the dependency of atrophy growth on the size of atrophy at baseline.<sup>16</sup>

In terms of study limitations, the RIVAL study had a discontinuation rate of 19.9% at 2 years, which is somewhat higher than some other studies (e.g., 16% in VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration and 14% in Inhibition of VEGF in Age-Related Choroidal Neovascularization).<sup>6,26,27</sup> In addition, longer follow-up might have provided greater insights. At 2 years, the study period might have been too short to observe effectively the development of new MA, which is known to be a very slow process.

Natural history studies indicate that progression of MA is relentless, although rates may differ at different stages of the lesions, both incident and enlargement of established MA.<sup>18</sup> The hypothesis that anti-VEGF therapies have a role in influencing rates of MA progression remains controversial.<sup>3–13</sup> The results from this study do not have any bearing on the potential role of these agents in MA progression. However, they do indicate that differing modes of action in retinal suppression of VEGF, where treatment exposure is virtually identical, does not seem to influence rates of progression over 2 years. The high proportion of patients who demonstrated MA over 2 years in both the ranibizumab and the aflibercept groups indicate that maintaining or at least stabilizing the VA gains that are achieved with anti-VEGF agents remains a challenge. Further studies are required to determine if this can be altered by the use of anti-atrophy agents such as neurotrophic factors. It remains to be seen how much longer longer-acting anti-VEGF agents will act. There is a potential for a greater amount of MA when drugs have longer half-lives. This should be studied when longer-acting agents are introduced.

In conclusion, the RIVAL study found no statistical difference between ranibizumab 0.5 mg and aflibercept 2.0 mg in the development of MA in nAMD patients treated over 24 months. Ranibizumab and aflibercept achieved similar visual acuities and retinal thickness improvements over 24 months using a T&E regimen for nAMD, with similar numbers of injections and comparable safety results.

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**Abbreviations and Acronyms:**

**AE** = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CRC** = central reading center; **CSFT** = central subfield foveal thickness; **IOP** = intraocular pressure; **IRF** = intraretinal fluid; **logMAR** = logarithm of minimum angle of resolution; **MA** = macular atrophy; **nAMD** = neovascular age-related macular degeneration; **OR** = odds ratio; **PED** = pigment epithelium detachment; **RNF** = retinal nerve fiber; **RIVAL** = Development of Macular Atrophy in Patients with Neovascular Age-Related Macular Degeneration: A Comparison of Ranibizumab and Aflibercept; **SD** = standard deviation; **SHRM** = subretinal hyperreflective material; **SRF** = subretinal fluid; **T&E** = treat-and-extend; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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