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Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration

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Objective: To evaluate the 24-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly or as needed (pro re nata [PRN]) in patients with neovascular age-related macular degeneration (wet AMD).

Design: Twenty-four-month, multicenter, randomized, double-masked, active treatment-controlled phase 3 trial.

Participants: Patients (n = 1098) ≥50 years of age with treatment-naïve subfoveal wet AMD.

Methods: Patients were randomized to receive intravitreal injections of ranibizumab 0.5 mg or 2.0 mg monthly or PRN after 3 monthly loading doses.

Main Outcome Measures: The primary efficacy end point was the mean change in best-corrected visual acuity (BCVA) from baseline at month 12. Key secondary end points included mean change in BCVA from baseline at month 24, proportion of patients who gained ≥15 letters in BCVA, mean number of ranibizumab injections, and mean change in central foveal thickness from baseline over time by spectral-domain optical coherence tomography. Ocular and systemic safety events also were evaluated through month 24.

Results: At month 24, the mean change from baseline in BCVA was (letters) +9.1 (0.5 mg monthly), +7.9 (0.5 mg PRN), +8.0 (2.0 mg monthly), and +7.6 (2.0 mg PRN). The change in mean BCVA from month 12 to 24 was (letters) −1.0, −0.3, −1.2, and −1.0, respectively. The proportion of patients who gained ≥15 letters from baseline in BCVA at month 24 was 34.5%, 33.1%, 37.6%, and 34.8%, respectively. The mean number of ranibizumab injections through month 24 was 21.4, 13.3, 21.6, and 11.2, respectively; 5.6 and 4.3 mean injections were required in year 2 in the 0.5 mg and 2.0 mg PRN groups, respectively. The average treatment interval in the 0.5 mg PRN group was 9.9 weeks after 3 monthly loading doses, and 93% of these patients did not require monthly dosing. Ocular and systemic safety profiles over 2 years were similar among all 4 treatment groups and were consistent with previous ranibizumab trials in AMD.

Conclusions: At month 24, mean BCVA improvements were clinically meaningful and similar among all 4 ranibizumab treatment groups. The 0.5 mg PRN group achieved a mean gain of 7.9 letters at month 24 with an average of 13.3 injections (5.6 injections in year 2). No new safety events were identified over 24 months. *Ophthalmology 2014;121:2181-2192 © 2014 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/3.0/).*

*Supplemental material is available at www.aaojournal.org.

Strategies to improve treatment effectiveness for neovascular age-related macular degeneration (wet AMD) aim to enhance visual function and reduce treatment burden, characterized by frequent intravitreal injections and patient encounters. Improved strategies are impactful because wet AMD affects approximately 1.75 million individuals in the United States and remains a leading cause of blindness among adults older than 50 years of age in many regions of the world.[1,2] Although the underlying disease pathogenesis has not been elucidated fully, vascular endothelial growth factor (VEGF) has been shown to play a key role in the development of choroidal neovascularization (CNV), which can lead to severe vision loss if left untreated.[2,3] Anti-VEGF agents have become the standard-of-care treatment option for the management of wet AMD.[4–12] Evidence from prospective, randomized clinical trials of intravitreal anti-VEGF therapy for the treatment of wet AMD demonstrate that visual outcomes are, on average, significantly improved from baseline after treatment, and the rates of serious ocular and systemic adverse events (AEs) are low and generally well tolerated.[4–13]

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The pivotal studies, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)[4,5] and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the treatment of Neovascular AMD (MARINA),[6] were the first phase 3 clinical trials to demonstrate that administration of 0.3 mg and 0.5 mg ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA)—a humanized, monoclonal anti-VEGF antigen binding fragment specifically designed for intraocular use that neutralizes all active isoforms of VEGF-A[14]—not only prevented vision loss associated with wet AMD, but also improved mean visual acuity (VA) over 2 years. Most of the functional and anatomic outcomes favored the 0.5 mg dose; in ANCHOR, the mean change from baseline in best-corrected VA (BCVA) at month 24 was +10.7 letters for ranibizumab 0.5 mg (n = 139) compared with +8.1 letters for ranibizumab 0.3 mg (n = 140) and −9.8 letters for verteporfin photodynamic therapy (n = 143). In MARINA, the mean change from baseline in BCVA at month 24 was +6.6 letters for ranibizumab 0.5 mg (n = 240) compared with +5.4 letters for ranibizumab 0.3 mg (n = 238) and −14.9 letters for sham injection (n = 238). An open-label, dose-ranging study demonstrated that ranibizumab doses up to 2.0 mg are well tolerated,[15] and the 2.0 mg dose has been shown to improve visual and anatomic outcomes significantly in wet AMD patients who were recalcitrant to ranibizumab 0.5 mg therapy.[16]

Although patients in the ANCHOR and MARINA trials received monthly ranibizumab injections, many retina specialists in clinical practice individualize treatment regimens in an effort to reduce patient burden.[17] Variable dosing regimens, such as treat-and-extend and pro re nata (PRN; as needed) administration, are used frequently and may reduce treatment burden.[17,18] Nonmonthly treatment approaches with VEGF inhibitors have been investigated in several clinical trials.[7–12,19–21] Visual outcomes were most favorable when optical coherence tomography (OCT) was used—in addition to VA decline criteria—to initiate PRN treatment for recurrent macular fluid.[22,23] For example, in the 2-year Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis (PRONTO) study, 40 patients received 3 monthly loading doses of ranibizumab 0.5 mg and were monitored monthly and re-treated based on time-domain OCT and VA criteria.[22,23] At month 24, patients treated with ranibizumab 0.5 mg PRN achieved comparable VA gains (+11.1 letters), as did the fixed monthly ranibizumab 0.5 mg dosing arms in ANCHOR (+10.7 letters) and MARINA (+6.6 letters), but with fewer injections over 2 years (on average, 9.9 injections in the PRONTO study versus the 24 scheduled injections in both ANCHOR and MARINA).[22,23] Pro re nata therapy was adopted by many retina specialists after the results of the PRONTO study. In the past few years, OCT technology has advanced, with practices now routinely using higher-resolution spectral-domain OCT (SD-OCT), which is more sensitive than time-domain OCT for the detection of fluid.[24]

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 (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration (HARBOR) evaluated over 2 years the potential beneficial effects of both a higher dose and PRN dosing of ranibizumab after 3 monthly loading doses compared with 0.5 mg ranibizumab monthly on functional and anatomic outcomes in patients with treatment-naïve subfoveal wet AMD.[7] At 12 months (the primary end point), the ranibizumab 2.0 mg monthly dose was not superior to the 0.5 mg monthly dose and did not offer any incremental improvements in efficacy outcomes (model-adjusted mean difference, −1.1 letters; 95.1% confidence interval, −3.4 to 1.3; $P = 0.8145$).[7] Additionally, the ranibizumab 0.5 mg PRN and 2.0 mg PRN groups failed to meet the prespecified 4-letter noninferiority margin compared with the 0.5 mg monthly group (noninferiority comparison between 0.5 mg PRN and 0.5 mg monthly: model-adjusted mean difference, −2.0 letters [97.5% confidence interval, −4.5 to 0.6]; noninferiority comparison between 2.0 mg PRN and 0.5 mg monthly: model-adjusted mean difference, −1.6 letters [98.4% confidence interval, −4.4 to 1.1]).[7]

Despite not meeting prespecified superiority and noninferiority comparisons, the HARBOR year 1 results demonstrated that PRN dosing with ranibizumab using VA and SD-OCT–guided re-treatment criteria decreased treatment burden and provided similar VA gains as monthly dosing for the treatment of wet AMD. The mean change in BCVA from baseline at month 12 was +8.2 and +8.6 letters in the ranibizumab 0.5 mg and 2.0 mg PRN groups, respectively, compared with +10.1 and +9.2 letters in ranibizumab 0.5 mg and 2.0 mg monthly groups, respectively. Over the first year, the ranibizumab 0.5 mg and 2.0 mg PRN groups required approximately 4 fewer injections, on average, than the 0.5 mg and 2.0 mg monthly groups (7.7 and 6.9 injections vs. 11.3 and 11.2 injections, respectively).[7] No new safety events were identified in year 1 of the HARBOR study. In particular, there was no difference in the safety profile regardless of dose group (0.5 vs. 2.0 mg) or treatment regimen (monthly vs. PRN).[7] The HARBOR study has been completed, and the 2-year efficacy and safety results are reported herein.

Methods

The methods for the HARBOR study have been published previously[7] and are summarized below.

Study Design and Eligibility

The HARBOR study was a 24-month, phase 3, randomized, multicenter, double-masked, active treatment-controlled study (ClinicalTrials.gov identifier NCT00891735) with 100 investigator sites across the United States. The HARBOR study was conducted in accordance with Good Clinical Practice (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6), applicable United States Food and Drug Administration regulations, and the Health Insurance Portability and Accountability Act. Institutional review boards approved the study protocol before the start of the study, and all participants provided written informed consent for study participation.

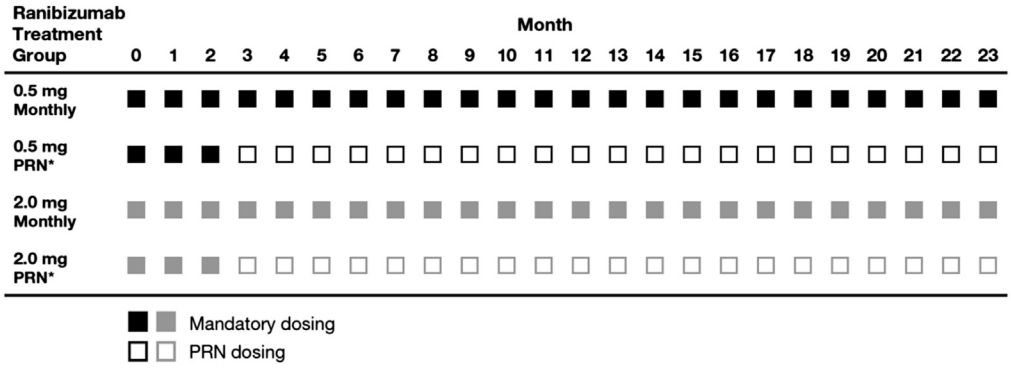

Figure 1. HARBOR treatment schedule. *Starting at month 3, pro re nata (PRN; as needed) groups were evaluated for re-treatment monthly and treated if there was a ≥5-letter decrease from the previous visit or any evidence of disease activity on spectral-domain optical coherence tomography. All groups continued on the same treatment schedule through month 24.

Patients were eligible to participate in the HARBOR trial if they were ≥50 years of age and met the following key inclusion criteria for the study eye: (1) BCVA of 20/40 to 20/320 (Snellen equivalent), using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at a distance of 4 m; (2) active subfoveal lesions with classic CNV, with some classic CNV component, or with purely occult CNV; (3) total area of lesion <12 disc areas (DAs) or 30.48 mm^2; and (4) total CNV area constituting 50% or more of total lesion area based on fluorescein angiography. For the inclusion of purely occult or occult with some classic CNV component, activity of the lesion had to be demonstrated by one of several criteria, including a ≥10% increase in CNV lesion size at interval visits, a documented visual loss of >1 line of Snellen vision, or the presence of hemorrhage at presentation. Key exclusion criteria for the study eye were a history of vitrectomy surgery; prior treatment with photodynamic therapy with verteporfin, external beam radiation therapy, or transpupillary thermotherapy; previous intravitreal drug delivery; previous subfoveal laser photocoagulation; uncontrolled blood pressure; atrial fibrillation not managed by the patient's primary care physician or cardiologist within 3 months of the screening visit; or a history of stroke within 3 months of the screening visit.

Randomization and Treatment Schedule

One eye was chosen as the study eye for each patient. Eligible patients received a computer-generated subject number on day 0 that randomly assigned patients in a 1:1:1:1 ratio to 1 of 4 ranibizumab treatment groups: 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, or 2.0 mg PRN. Randomization was stratified by VA at day 0 (≤54 letters [approximate Snellen equivalent, 20/80 or worse] vs. ≥55 letters [approximate Snellen equivalent, 20/80 or better]); CNV classification at baseline (predominantly classic, minimally classic, or purely occult); and study center. All study site personnel, the designated physician(s), central reading center personnel, patients, and the sponsor and its agents were masked to treatment drug dose assignment (0.5 vs. 2.0 mg) until study completion. However, the sponsor and study personnel were unmasked to the treatment assignment after analysis of the year 1 data. Fundus photographs and fluorescein angiograms were obtained at baseline and at months 3, 6, 12, 18, and 24; images were not graded at month 18. Spectral-domain OCT was performed at each study visit and images were graded at baseline, day 7, and months 1 through 4, 6, 9, 12, 18, and 24. Fluorescein angiography and SD-OCT images were read manually by a single central reading center to provide an objective, masked assessment of these evaluations.

All patients were scheduled to receive 3 consecutive monthly loading doses of intravitreal ranibizumab 0.5 mg or 2.0 mg at the beginning of the study (day 0). The monthly groups then continued with monthly dosing, whereas the PRN groups were evaluated monthly and re-treated if there was a ≥5-letter decrease in vision from the previous visit or any evidence of disease activity on SD-OCT (e.g., intraretinal fluid, subretinal fluid, or subretinal pigment epithelial fluid) using Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA). There was no crossover between the treatment groups over the course of the 2-year study (Fig 1).

Outcome Measures

The primary end point was the mean change in BCVA from baseline at month 12 (previously reported).[7] Key secondary end points in year 2 included the mean change in BCVA from baseline at month 24, the proportion of patients who gained ≥15 letters in BCVA, the mean number of ranibizumab injections, and the mean change in central foveal thickness (CFT) from baseline over time. Additional VA end points evaluated included the proportion of patients with a Snellen equivalent of 20/40 or better, the proportion of patients with a Snellen equivalent of 20/200 or worse, and the proportion of patients who lost <15 letters in BCVA from baseline.

Safety assessments included ocular and systemic safety events through month 24. Assessments of targeted events included study eye serious AEs (SAEs), Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events (ATEs), and SAEs potentially related to systemic VEGF inhibition.

Statistical Analysis

Analyses of efficacy end points were based on the intent-to-treat population, with patients grouped according to their treatment assignment at randomization and missing data imputed using the last observation carried forward method, unless otherwise noted. Efficacy analyses were stratified by baseline BCVA score (≤54 vs. ≥55 letters) and baseline CNV classification (predominantly classic, minimally classic, purely occult). The sample size of 1100 randomized patients ensured 80% power in the intent-to-treat population analysis for the 3 primary comparisons at month 12 (a superiority comparison between 2.0 mg monthly and 0.5 mg monthly and 2 noninferiority comparisons). The study was not powered to compare efficacy outcomes between the treatment groups at month 24. Thus, efficacy analyses over 2 years were based on descriptive statistics, and presented statistical comparisons of efficacy outcomes were performed post hoc. The incidence

Table 1. Patient Disposition during the 24-Month Treatment Period

Status	Ranibizumab Treatment Group, n (%)			
	0.5 mg Monthly (N = 275)	*0.5 mg PRN (N = 275)*	*2.0 mg Monthly (N = 274)*	*2.0 mg PRN (N = 273)*
Received study drug in study eye	274 (99.6)	275 (100.0)	274 (100.0)	272 (99.6)
In study at month 12	257 (93.5)	263 (95.6)	258 (94.2)	258 (94.5)
Completed study	230 (83.6)	237 (86.2)	239 (87.2)	237 (86.8)
Discontinued study	45 (16.4)	38 (13.8)	35 (12.8)	36 (13.2)
First year	17 (6.2)	12 (4.4)	16 (5.8)	15 (5.5)
Second year	28 (10.2)	26 (9.5)	19 (6.9)	21 (7.7)
Primary reason for study discontinuation in the second year				
Adverse event	2 (0.7)	2 (0.7)	1 (0.4)	4 (1.5)
Death	5 (1.8)	6 (2.2)	5 (1.8)	4 (1.5)
Lost to follow-up	8 (2.9)	4 (1.5)	4 (1.5)	4 (1.5)
Physician's decision to withdraw patient from study	0 (0)	1 (0.4)	1 (0.4)	2 (0.7)
Patient's decision to withdraw from study	12 (4.4)	12 (4.4)	7 (2.6)	7 (2.6)
Sponsor's decision to terminate study	1 (0.4)	0 (0)	0 (0)	0 (0)
Patient noncompliance	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Discontinued treatment in study eye	47 (17.1)	37 (13.5)	39 (14.2)	36 (13.2)
First year	21 (7.6)	16 (5.8)	18 (6.6)	18 (6.6)
Second year	26 (9.5)	21 (7.6)	21 (7.7)	18 (6.6)
Primary reason for treatment discontinuation in the second year				
Adverse event	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)
Death	5 (1.8)	6 (2.2)	5 (1.8)	5 (1.8)
Lost to follow-up	7 (2.5)	4 (1.5)	2 (0.7)	3 (1.1)
Physician's decision to discontinue treatment	0 (0)	1 (0.4)	2 (0.7)	2 (0.7)
Patient's decision to discontinue treatment	10 (3.6)	7 (2.5)	7 (2.6)	5 (1.8)
Sponsor's decision to terminate study	1 (0.4)	0 (0)	0 (0)	0 (0)
Patient noncompliance	0 (0)	1 (0.4)	2 (0.7)	0 (0)

PRN = pro re nata (as needed).

of ocular and systemic AEs, ocular SAEs, APTC ATEs, and SAEs potentially related to systemic VEGF inhibition were summarized for the cumulative 24-month study period with patients grouped according to the actual treatment received during the first year.

Results

Patient Disposition and Baseline Characteristics

Between July 2009 and August 2010, 1098 patients were enrolled at 100 study centers across the United States and were randomized in a 1:1:1:1 ratio to 1 of 4 ranibizumab treatment groups: 0.5 mg monthly (n = 276), 0.5 mg PRN (n = 275), 2.0 mg monthly (n = 274), and 2.0 mg PRN (n = 273). One patient in the 0.5 mg monthly group was randomized before screening failure (no baseline or postbaseline data were reported), and therefore 1097 patients were eligible for the study. In total, 86.0% of patients completed the HARBOR study through month 24. Discontinuation rates were similar between the 4 treatment groups; on average, 14.5% of patients discontinued from the study during the 24-month treatment period; the most common reason was the patient's decision to withdraw (Table 1).

Patient demographics and baseline ocular characteristics for the study eye were reported previously[7] and were well-balanced among the 4 treatment groups. Patients predominantly were female (59%) and white (97%), and the mean age of all patients was 79 years. At baseline, mean VA was between 53.5 and 54.5 letters (approximate Snellen equivalent, 20/80) and mean CFT ranged from 333 to 348 μm among the 4 ranibizumab treatment groups. Overall, approximately 46% of patients had minimally classic CNV lesions, 16% had predominantly classic lesions, and 38% had purely occult CNV. Total CNV area and total lesion area ranged between 3.0 and 3.3 DAs and between 3.2 and 3.5 DAs, respectively.[7]

Visual Acuity End Points

As previously reported by Busbee et al,[7] the HARBOR study did not meet its 3 primary end point comparisons at year 1. However, all 4 ranibizumab treatment groups demonstrated clinically meaningful and similar improvements in BCVA from baseline, which were observed starting at day 7, continued through month 12, and were sustained through month 24. The mean changes in BCVA from baseline to month 24 were +9.1 letters (0.5 mg monthly), +7.9 letters (0.5 mg PRN), +8.0 letters (2.0 mg monthly), and +7.6 letters (2.0 mg PRN) (Fig 2, Table 2). From months 12 to 24, BCVA in the 0.5 mg PRN group remained relatively unchanged (difference of −0.3 letters), whereas the 0.5 mg monthly, 2.0 mg monthly, and 2.0 mg PRN groups lost approximately 1 letter on average (−1.0, −1.2, and −1.0, respectively; Fig 2).

The proportion of patients who gained ≥15 letters in BCVA from baseline (i.e., 3-line gainers using the ETDRS chart) at month 24 was 34.5%, 33.1%, 37.6%, and 34.5% in the 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, and 2.0 mg PRN groups, respectively (Table 2). These percentages were similar to or slightly higher than the percentage of those who gained 3 lines at month 12 (34.5%, 30.2%, 36.1%, and 33.0% for each ranibizumab

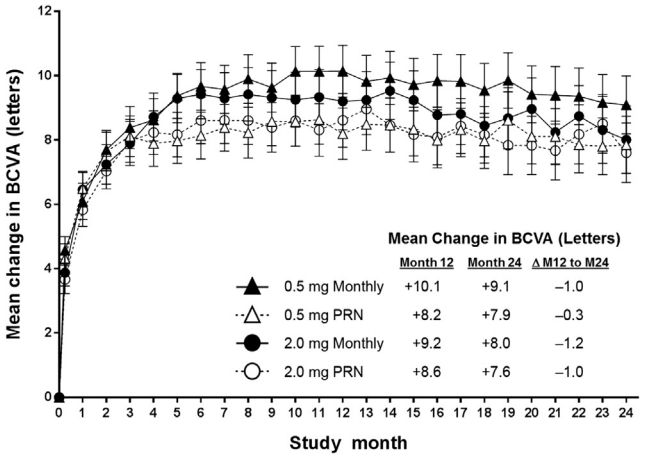

Figure 2. Graph showing the mean change in best-corrected visual acuity (BCVA) from baseline up to month 24. The last observation carried forward method was used to impute missing data. Vertical bars are ±1 standard error of the mean. M = month; PRN = pro re nata (as needed).

treatment group, respectively). The proportion of patients who lost <15 letters from baseline was explored post hoc and ranged from 93% to 98% at month 12 and 90% to 94% at month 24. The proportion of patients with a Snellen equivalent of 20/40 or better was similar between month 12 (range, 44%−52%) and month 24 (range, 45%−50%). The proportion of patients with a Snellen equivalent of 20/200 or worse was numerically slightly higher at month 24 (range, 10%−14%) compared with month 12 (range, 7%−12%; Table 2).

Treatment Frequency

The mean number of ranibizumab injections administered through month 24 in patients who completed the study or discontinued early is depicted in Figure 3. During year 1, the ranibizumab monthly dosed groups averaged 11.3 (0.5 mg) and 11.2 (2.0 mg) injections, whereas the ranibizumab PRN-dosed groups averaged 7.7 (0.5 mg) and 6.9 (2.0 mg) injections. During year 2, the ranibizumab monthly dosed groups averaged 10.1 (0.5 mg) and 10.4 (2.0 mg) injections, and the ranibizumab PRN-dosed groups averaged 5.6 (0.5 mg) and 4.3 (2.0 mg) injections. The total mean number of ranibizumab injections over 2 years was 21.4 and 21.6 in the ranibizumab 0.5 mg and 2.0 mg monthly groups, respectively, and was 13.3 and 11.2 in the 0.5 mg PRN and 2.0 mg PRN groups, respectively.

The treatment interval in the ranibizumab PRN groups and the injection frequency in a subset of patients receiving ranibizumab PRN were explored post hoc. For patients who completed the study (n = 237 for each PRN group), the median number of injections was 14.0 in the ranibizumab 0.5 mg PRN group (Fig 4A) and was 11.0 in the 2.0 mg PRN group (Fig 4B), with patients requiring 3 to 24 injections over 2 years. For patients in the 0.5 mg PRN group who received all 3 loading doses and completed the study (n = 232), the average treatment interval was 9.9 weeks after 3 monthly loading doses; among these patients, 7% received 24 ranibizumab injections (i.e., dosing once monthly), 44% received 14 to 23 injections (i.e., dosing every >37 days but ≤74 days), and 49% received 3 to 13 injections (i.e., dosing every >75 days; Fig 5A). Mean changes in BCVA from baseline at month 24 were +7.9, +6.7, and +9.7 letters for these 3 injection categories, respectively. For patients in the 2.0 mg PRN group

Table 2. Key Visual Acuity End Points at Months 12 and 24

	Ranibizumab Treatment Group			
	0.5 mg Monthly (N = 275)	*0.5 mg PRN (N = 275)*	*2.0 mg Monthly (N = 274)*	*2.0 mg PRN (N = 273)*
Mean change in BCVA from baseline, ETDRS letters (SD)				
At month 12	10.1 (13.3)	8.2 (13.3)	9.2 (14.6)	8.6 (13.8)
At month 24	9.1 (14.9)	7.9 (14.7)	8.0 (17.4)	7.6 (15.3)
Proportion of patients gaining ≥15 letters from baseline				
At month 12	95 (34.5)	83 (30.2)	99 (36.1)	90 (33.0)
At month 24	95 (34.5)	91 (33.1)	103 (37.6)	95 (34.8)
Proportion of patients losing <15 letters from baseline				
At month 12	269 (97.8)	260 (94.5)	256 (93.4)	259 (94.9)
At month 24	259 (94.2)	250 (90.9)	247 (90.1)	250 (91.6)
Proportion of patients with Snellen 20/40 or better				
Baseline	46 (16.7)	35 (12.7)	33 (12.0)	37 (13.6)
At month 12	144 (52.4)	127 (46.2)	137 (50.0)	119 (43.6)
At month 24	136 (49.5)	131 (47.6)	134 (48.9)	122 (44.7)
Proportion of patients with Snellen 20/200 or worse				
Baseline	40 (14.5)	31 (11.3)	41 (15.0)	39 (14.3)
At month 12	20 (7.3)	23 (8.4)	31 (11.3)	33 (12.1)
At month 24	28 (10.2)	28 (10.2)	35 (12.8)	39 (14.3)

BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = pro re nata (as needed); SD = standard deviation. Data are n (%) unless otherwise indicated.

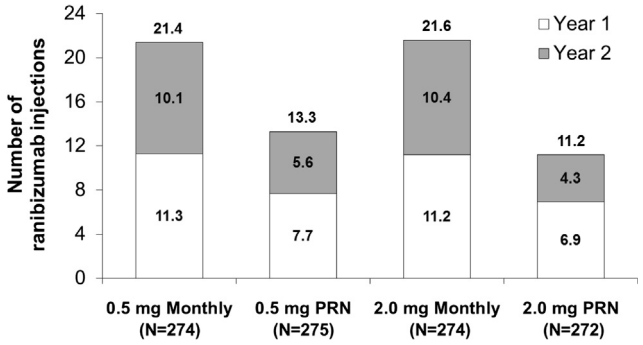

Figure 3. Bar graph showing the mean number of ranibizumab injections through month 24 in patients who completed the study or discontinued early. PRN = pro re nata (as needed).

who received all 3 loading doses and completed the study (n = 232), the average treatment interval was 12.5 weeks after 3 monthly loading doses; among these patients, 2% received 24 ranibizumab injections, 29% received 14 to 23 injections, and 69% received 3 to 13 injections (Fig 5B). Mean changes from baseline in BCVA at month 24 were +12.6, +8.5, and +7.8 letters for these 3 injection categories, respectively.

Anatomic End Points

Spectral-Domain Optical Coherence Tomography End Points. All groups showed a rapid reduction in CFT by SD-OCT at day 7 that continued through month 3 and was sustained from months 3 to 24 (Fig 6). At month 24, the mean change from baseline was −182.5 μm (0.5 mg monthly), −172.0 μm (0.5 mg PRN), −171.8 μm (2.0 mg monthly), and −181.0 μm (2.0 mg PRN). The difference in CFT between months 12 and 24 ranged from −9 to −11 μm.

Angiographic End Points. All 4 ranibizumab treatment groups showed regression of total lesion area and total CNV area from baseline over time on fluorescein angiography. The mean change from baseline in total CNV area at month 24 was −1.98 DAs (0.5 mg monthly), −1.60 DAs (0.5 mg PRN), −2.59 DAs (2.0 mg monthly), and −1.92 DAs (2.0 mg PRN). The mean change from baseline in total lesion area at month 24 was −1.57 DAs (0.5 mg monthly), −1.10 DAs (0.5 mg PRN), −2.12 DAs (2.0 mg monthly), and −1.36 DAs (2.0 mg PRN).

Safety Outcomes

Ocular Adverse Events. Ocular SAEs in the study eye through month 24 are summarized in Table 3. Ocular SAEs were mostly singular in nature, occurring in <4% of patients across all treatment groups. No new safety events were identified over 2 years. There were no SAEs of glaucoma and only 1 report (0.4%) of increased intraocular pressure in the ranibizumab 0.5 mg monthly group. Endophthalmitis was reported in 4 patients (1.5%) in the 0.5 mg monthly group and 1 patient (0.4%) in the 2.0 mg monthly group. No new reports of iridocyclitis or retinal tear were reported in year 2 of the trial.

Ocular AEs in the study eye (including those that were SAEs) over 2 years also were balanced among the treatment groups, with no dose response (0.5 vs. 2.0 mg) or dose exposure (monthly vs. PRN) trends observed. Increased intraocular pressure was reported

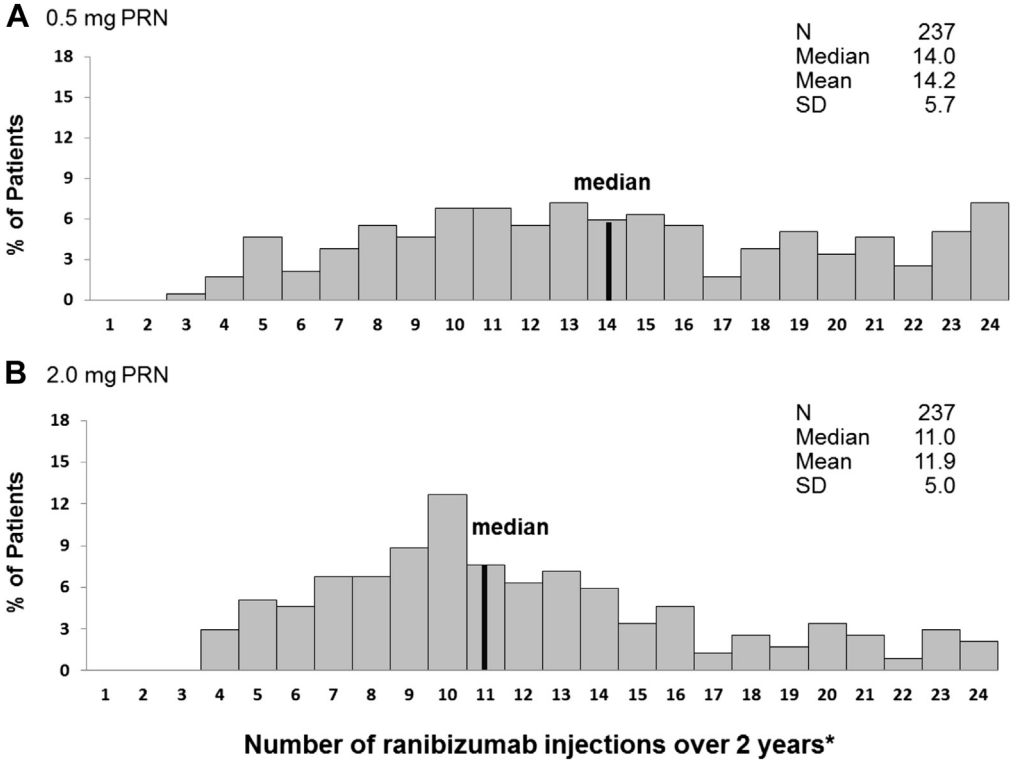

Figure 4. Bar graphs showing the distribution of the number of ranibizumab injections over 2 years in (**A**) the 0.5 mg pro re nata (PRN; as needed) group and (**B**) the 2.0 mg PRN group in patients who completed the study. SD = standard deviation.

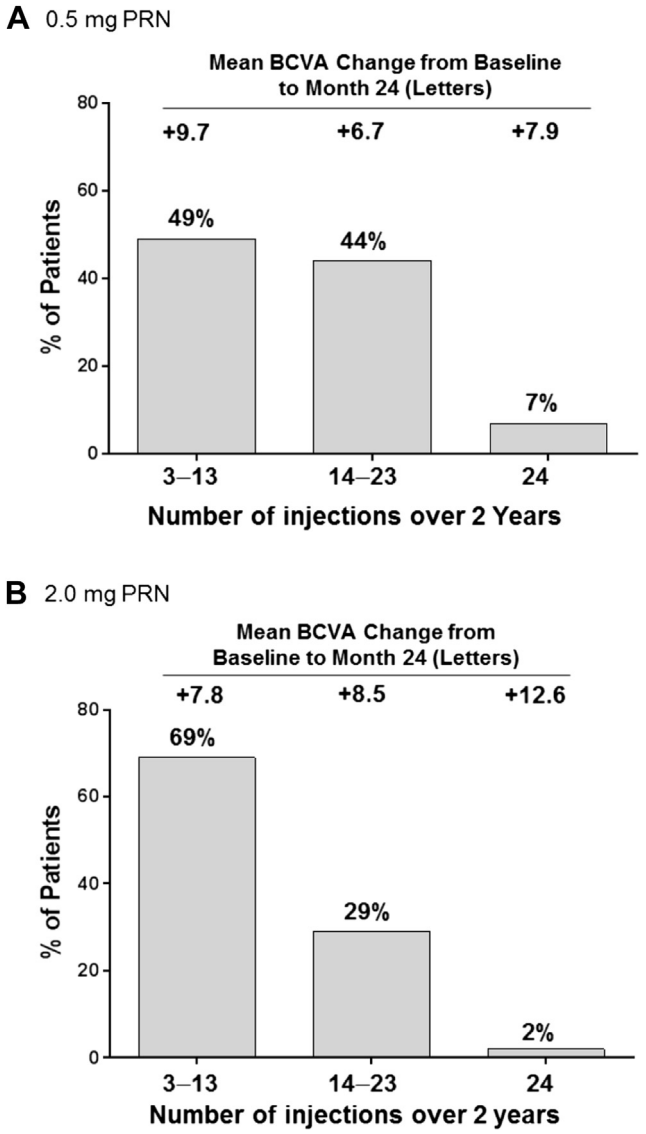

Figure 5. Bar graph showing the number of ranibizumab injections over 2 years in (**A**) the 0.5 mg pro re nata (PRN; as needed) group and (**B**) the 2.0 mg PRN group among patients who received all 3 loading doses and completed the study (n = 232). BCVA = best-corrected visual acuity.

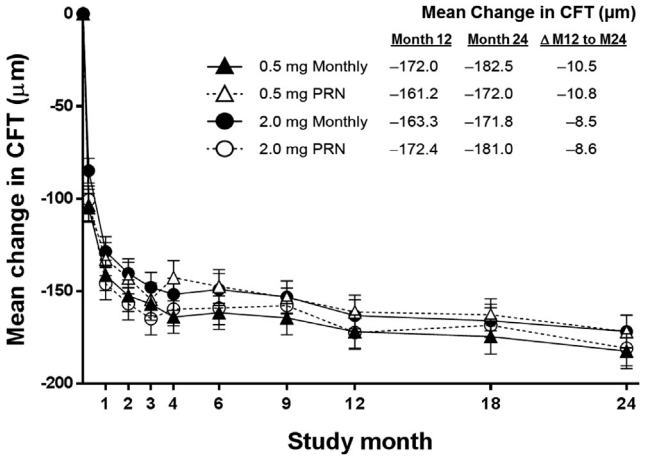

Figure 6. Graph showing the mean change in central foveal thickness (CFT) from baseline measured by spectral-domain optical coherence tomography over time up to month 24. The last observation carried forward method was used to impute missing data. Vertical bars are ±1 standard error of the mean. M = month; PRN = pro re nata (as needed).

in 16 patients (5.8%) in the 0.5 mg monthly group, 10 patients (3.6%) in the 0.5 mg PRN group, 13 patients (4.7%) in the 2.0 mg monthly group, and 10 patients (3.7%) in the 2.0 mg PRN group. Rates of glaucoma and iritis were low, with overall rates of 1.0% and 1.1%, respectively, among the 4 treatment groups.

Systemic Adverse Events. Systemic AEs, which were categorized by APTC ATEs and AEs of special interest (AESI) potentially related to systemic VEGF inhibition, were well balanced among treatment groups, with no obvious dose-response or dose-exposure trends observed (Table 4). Total APTC events were low, reported in 6.6% of patients in the 0.5 mg monthly group, 4.7% in the 0.5 mg PRN group, 5.8% in the 2.0 mg monthly group, and 5.9% in the 2.0 mg PRN group. The overall rate of death over 2 years was 4.7% (0.5 mg monthly), 3.6% (0.5 mg PRN), 3.6% (2.0 mg monthly), and 4.0% (2.0 mg PRN). The rates of nonfatal myocardial infarction and overall nonfatal cerebrovascular accidents were low (1.8%–2.9% and 0.4%–1.1%, respectively) and were similar among the treatment groups.

Adverse events of special interest were balanced among the 4 treatment groups, ranging from 8.8% to 10.2%, with no evident dose-response or dose-exposure trends observed (Table 4). Rates of central nervous system–related bleeding events were similar among the 4 treatment groups: 2 patients (0.7%) in the 0.5 mg monthly group, 4 patients (1.5%) in the 0.5 mg PRN group, 2 patients (0.7%) in the 2.0 mg monthly group, and 3 patients (1.1%) in the 2.0 mg PRN group. Hypertension also was uncommon, reported in 0 patients (0%) in the 0.5 mg monthly group, 1 patient (0.4%) in the 0.5 mg PRN group, 1 patient (0.4%) in the 2.0 mg monthly group, and 3 patients (1.1%) in the 2.0 mg PRN group.

Discussion

The objectives for the first year of the HARBOR study were to assess the efficacy of the ranibizumab 2.0 mg monthly dose compared with the 0.5 mg monthly dose (superiority comparison), to evaluate the 0.5 mg PRN and 2.0 mg PRN dosing regimens compared with the 0.5 mg monthly dosing regimen (2 noninferiority comparisons using a 4-letter noninferiority margin), and to evaluate the safety of both ranibizumab doses administered monthly and PRN.[7] Although the prespecified superiority and noninferiority comparisons were not met at year 1 of the HARBOR trial, mean BCVA improvements were clinically meaningful and similar in all treatment groups over 12 months. Mean changes in BCVA from baseline at month 12 were +10.1 letters (0.5 mg monthly), +8.2 letters (0.5 mg PRN), +9.2 letters (2.0 mg monthly), and +8.6 letters (2.0 mg PRN).[7] These results are similar to the visual improvements achieved with fixed ranibizumab 0.5 mg monthly dosing at month 12 in the ANCHOR[4,5] and MARINA[6] trials

Table 3. Serious Ocular Adverse Events in the Study Eye through Month 24

Ocular SAEs in the Study Eye	Ranibizumab Treatment Group, n (%)			
	0.5 mg Monthly (N = 274)	*0.5 mg PRN (N = 275)*	*2.0 mg Monthly (N = 274)*	*2.0 mg PRN (N = 272)*
Any SAE*	7 (2.6)	7 (2.5)	10 (3.6)	4 (1.5)
Reduced visual acuity	1 (0.4)	4 (1.5)	5 (1.8)	2 (0.7)
Retinal hemorrhage	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)
Endophthalmitis	4 (1.5)	0 (0)	1 (0.4)	0 (0)
Corneal edema	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Iridocyclitis	0 (0)	0 (0)	1 (0.4)	0 (0)
Macular degeneration	1 (0.4)	0 (0)	0 (0)	0 (0)
Retinal artery occlusion	1 (0.4)	0 (0)	0 (0)	0 (0)
Retinal tear	0 (0)	0 (0)	1 (0.4)	0 (0)
Retinal vein occlusion	1 (0.4)	0 (0)	0 (0)	0 (0)
Vitreous floaters	0 (0)	0 (0)	1 (0.4)	0 (0)
Retinal detachment	0 (0)	0 (0)	2 (0.7)	0 (0)
Age-related macular degeneration	0 (0)	1 (0.4)	0 (0)	0 (0)
Herpes zoster ophthalmic	0 (0)	1 (0.4)	0 (0)	0 (0)
Medication error	0 (0)	0 (0)	0 (0)	1 (0.4)
Vitreous hemorrhage	0 (0)	0 (0)	0 (0)	1 (0.4)
Intraocular pressure increased	1 (0.4)	0 (0)	0 (0)	0 (0)

PRN = pro re nata (as needed); SAE = serious adverse event.
*Denotes total number of patients with ≥1 SAE. An adverse event was classified as an SAE if it caused or led to death, required prolonged hospitalization, resulted in persistent or significant disability, or was considered a significant medical event by the investigating physician.

(+11.3 and +7.2 letters, respectively). Through the first year of HARBOR, patients in the 0.5 mg and 2.0 mg PRN groups achieved improvements in BCVA similar to those in the 0.5 mg and 2.0 mg monthly groups, but the PRN groups required, on average, approximately 4 fewer injections compared with the monthly groups (7.7 and 6.9 injections vs. 11.3 and 11.2 injections, respectively).[7]

In year 2 of HARBOR, the VA gains achieved in year 1 largely were maintained in both the monthly and PRN treatment groups; similar visual gains were observed between PRN and monthly dosing, with fewer injections required in the PRN groups over 24 months (104 weeks). At year 2, the mean changes in BCVA from baseline were +9.1 (0.5 mg monthly), +7.9 (0.5 mg PRN), +8.0 (2.0 mg monthly), and +7.6 (2.0 mg PRN) letters; these VA improvements were achieved with a mean of 10.1, 5.6, 10.4, and 4.3 injections in year 2, respectively. Over 24 months, a total of 13.3 and 11.2 injections, on average, were administered in the 0.5 mg and 2.0 mg PRN groups, respectively, compared with a total of 21.4 and 21.6 injections, on average, in the 0.5 mg and 2.0 mg monthly groups, respectively. From month 12 to month 24, BCVA generally was maintained in the 0.5 mg PRN group (difference of −0.3 letters) and decreased, on average, by −1.0 letter in the 0.5 mg monthly and 2.0 mg PRN groups and by −1.2 letters in the 2.0 mg monthly group. These results demonstrate that PRN therapy can maintain the vision gains achieved in year 1 out to year 2 when patients are followed up using visual acuity and strict SD-OCT re-treatment criteria.

Patients receiving ranibizumab 0.5 mg and 2.0 mg PRN had individualized responses to treatment, as evidenced by a post hoc analysis of injection frequency in PRN-dosed patients who completed the study (n = 237 in each group). In the 0.5 mg PRN group, the total number of ranibizumab injections ranged from 3 to 24 per patient over 2 years (median, 14.0 injections; Fig 4A); for patients who received all 3 loading doses of 0.5 mg and completed the study (n = 232), the average treatment interval was 9.9 weeks following the 3 monthly loading doses, and 93% of these patients did not require monthly dosing (Fig 5A). In the 2.0 mg PRN group, the total number of ranibizumab injections ranged from 4 to 24 per patient over 2 years (median, 11.0 injections; Fig 4B); for patients who received all 3 loading doses of 2.0 mg and completed the study (n = 232), the average treatment interval was 12.5 weeks following the 3 monthly loading doses, and 98% of these patients did not require monthly dosing (Fig 5B).

Approximately 2 fewer injections were required, on average, in the 2.0 mg PRN group compared with the 0.5 mg PRN group over 2 years, suggesting a slight increase in the durability of the higher 2.0 mg dose compared with the 0.5 mg dose, although this did not translate to an increase in efficacy in this study. With an estimated intravitreal half-life of 9 days in humans,[25] the 2.0 mg dose, which is 4 times the marketed dose, adds 2 additional intravitreal half-life periods compared with the 0.5 mg dose. This increase would provide for approximately 18 days, on average, of additional residence time in the eye, which is consistent with the additional approximately 2.6 weeks of average durability observed in this study. The results of the post hoc analysis of injection frequency demonstrate that the PRN dosing regimen results in a broad range of the number of injections over 2 years (3−24 injections for the 0.5 mg PRN group), which supports individualized dosing and further suggests that patients may be overtreated or undertreated with a fixed dosing interval (e.g., injections monthly or every 2 months, respectively).

Table 4. Key Systemic Adverse Events through Month 24

Systemic Adverse Events	Ranibizumab Treatment Group, n (%)			
	0.5 mg Monthly (N = 274)	*0.5 mg PRN (N = 275)*	*2.0 mg Monthly (N = 274)*	*2.0 mg PRN (N = 272)*
APTC ATEs				
Any APTC events*	18 (6.6)	13 (4.7)	16 (5.8)	16 (5.9)
Deaths, overall	13 (4.7)	10 (3.6)	10 (3.6)	11 (4.0)
Vascular	9 (3.3)	7 (2.5)	6 (2.2)	4 (1.5)
Unknown cause	2 (0.7)	1 (0.4)	0 (0)	2 (0.7)
Nonfatal myocardial infarction	7 (2.6)	5 (1.8)	8 (2.9)	7 (2.6)
Nonfatal CVA, overall	2 (0.7)	1 (0.4)	2 (0.7)	3 (1.1)
Hemorrhagic CVA	1 (0.4)	0 (0)	0 (0)	0 (0)
Ischemic CVA	1 (0.4)	1 (0.4)	2 (0.7)	3 (1.1)
Serious AESI				
Any AESI†	27 (9.9)	28 (10.2)	27 (9.9)	24 (8.8)
ATE	14 (5.1)	13 (4.7)	14 (5.1)	11 (4.0)
Bleeding/hemorrhage (CNS)	2 (0.7)	4 (1.5)	2 (0.7)	3 (1.1)
Bleeding/hemorrhage (non-CNS)	5 (1.8)	7 (2.5)	7 (2.6)	7 (2.6)
Congestive heart failure	8 (2.9)	7 (2.5)	2 (0.7)	8 (2.9)
Fistulae	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Gastrointestinal perforation	0 (0)	0 (0)	1 (0.4)	0 (0)
Hypertension	0 (0)	1 (0.4)	1 (0.4)	3 (1.1)
Venous thrombotic events	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)
Wound healing complications	0 (0)	1 (0.4)	0 (0)	0 (0)

AESI = adverse event of special interest; APTC = Antiplatelet Trialists' Collaboration; ATEs = arterial thromboembolic events; CNS = central nervous system; CVA = cerebrovascular accident; PRN = pro re nata (as needed).
*Denotes total number of patients with ≥1 APTC events (including vascular deaths, deaths of unknown cause, nonfatal myocardial infarctions, and nonfatal CVAs).
†Denotes total number of patients with ≥1 serious AESI.
AESI classification: adverse events related to vascular endothelial growth factor inhibition as defined in Genentech, Inc. (South San Francisco, CA) bevacizumab (Avastin) oncology trials.

The VA outcomes and number of injections in the ranibizumab PRN groups in the HARBOR study compare favorably with findings reported in other wet AMD trials investigating nonmonthly dosing regimens with VEGF inhibitors (Fig 7). The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) was a large, randomized, noninferiority (noninferiority margin defined as 5 letters) study designed to evaluate the relative efficacy and safety of ranibizumab and bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) administered monthly or PRN for 2 years (104 weeks).[8,9] Patients assigned to the PRN groups were administered 1 loading dose of either VEGF inhibitor, followed by PRN dosing with monthly monitoring through 2 years. Time-domain OCT was used for approximately 77% of scans throughout the 2-year trial (SD-OCT was used for approximately 23% of scans during the second year).[9] For those CATT patients who initially were randomized to ranibizumab 0.5 mg PRN (n = 298) and remained on this treatment regimen for the 2-year period (n = 264), the mean BCVA change at year 2 was +6.7 letters, achieved with a mean of 12.6 injections (5.7 injections in year 2).[9] For those CATT patients who initially were randomized to bevacizumab 1.25 mg PRN (n = 300) and remained on this treatment regimen for the 2-year period (n = 251), the mean BCVA change at year 2 was +5.0 letters, achieved with mean of 14.1 injections (6.4 injections in year 2; Fig 7).[9]

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2) were methodologically identical studies that compared different dosing regimens of aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY) versus ranibizumab 0.5 mg for 2 years (96 weeks).[11] In year 1 of VIEW 1/2, ranibizumab and aflibercept were administered as 3 loading doses, followed by fixed dosing every 4 weeks (q4w) (ranibizumab 0.5 mg, aflibercept 0.5 mg, and aflibercept 2.0 mg) or every 8 weeks (q8w) (aflibercept 2.0 mg).[11] In year 2 of VIEW 1/2, patients continued their original dosing assignment and were switched to a capped PRN regimen in which they were assessed monthly with mandatory re-treatment at least every 12 weeks.[11] At year 2, the ranibizumab 0.5 mg q4w/PRN group (n = 595) gained a mean of +7.9 letters, achieved with a mean of 16.5 injections (4.7 in year 2; n = 513); the aflibercept 2.0 mg q4w/PRN group (n = 613) gained a mean of +7.6 letters, achieved with a mean of 16.0 injections (4.1 in year 2; n = 529); the aflibercept 0.5 mg q4w/PRN group (n = 597) gained a mean of +6.6 letters, achieved with a mean of 16.2 injections (4.6 in year 2; n = 499); and the aflibercept 2.0 mg q8w/PRN group (n = 607) gained a mean of +7.6 letters, achieved with a mean of 11.2 injections (4.2 in year 2; n = 511; Fig 7).[26]

Although there are obvious limitations to cross-trial comparisons, less-frequently-than-monthly dosing with ranibizumab 0.5 mg in the HARBOR, CATT, and VIEW

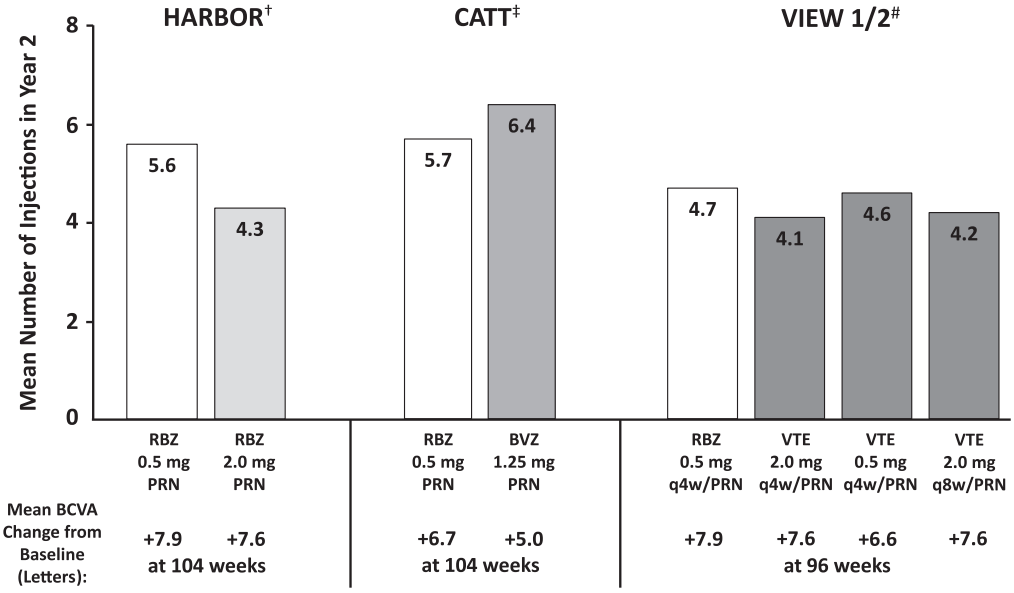

Figure 7. Bar graphs showing cross-trial comparison of the mean number of injections in year 2 with pro re nata (PRN; as needed) dosing. Numbers below bars indicate mean changes in best-corrected visual acuity (BCVA) from baseline to month 24. Cross-trial comparisons have limitations and data must be interpreted with caution. †In year 1 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 (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration (HARBOR) trial, ranibizumab (RBZ) was administered as 3 loading doses, followed by PRN dosing through year 2. ‡In year 1 of Comparison of Age-related Macular Degeneration Treatments Trials (CATT), RBZ and bevacizumab (BVZ) were administered as 1 loading dose, followed by PRN dosing through year 2. #In year 1 of VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2, RBZ and aflibercept (VTE) were administered as 3 loading doses, followed by fixed q4w (RBZ) or q8w (VTE) dosing; in VIEW 1/2 year 2, RBZ and VTE were administered PRN at least every 12 weeks. q4w = every 4 weeks; q8w = every 8 weeks; VEGF = vascular endothelial growth factor.

1/2 trials resulted in clinically meaningful and similar mean VA gains over 24 months: HARBOR, +7.9 letters at 104 weeks; CATT, +6.7 letters at 104 weeks; VIEW 1/2, +7.9 letters at 96 weeks (Fig 7). Additionally, during year 2, when injections were given PRN based on prespecified re-treatment criteria, the mean number of treatments in the ranibizumab 0.5 mg groups was similar across all 3 trials: HARBOR, 5.6 injections; CATT, 5.7 injections; VIEW 1/2, 4.7 injections (Fig 7).

In year 2 of the VIEW 1/2 studies, when the ranibizumab 0.5 mg q4w/PRN and aflibercept 2.0 mg q8w/PRN groups were dosed according to the same capped PRN treatment schedule, mean injection frequencies were similar between groups (4.7 and 4.2 injections, respectively; Fig 7). Mean vision gain at 96 weeks also was comparable between groups (+7.9 and +7.6 letters, respectively; Fig 7).

Overall, the incidence of ocular AEs observed in the study eye through month 24 of the HARBOR study was comparable among treatment groups and is consistent with previous large trials evaluating ranibizumab for wet AMD. Ocular SAEs in the study eye reported during the 2-year trial mostly were singular in nature, occurring in <4% of patients across treatment groups, with no new safety events identified. Endophthalmitis was reported in 3 patients in the monthly groups during year 2 (n = 2 with 0.5 mg and n = 1 with 2.0 mg). The incidence of retinal hemorrhage and iridocyclitis remained unchanged through the second year of the trial. An increase in intraocular pressure was reported in 1 patient in the 0.5 mg monthly group. Other SAEs reported in the study eye are shown in Table 3. The rates of systemic AEs also were comparable among ranibizumab treatment groups, indicating that there was no evident dose-response trends (0.5 mg vs. 2.0 mg) or dose-exposure trends (monthly vs. PRN) observed over 2 years in the HARBOR study.

In conclusion, the HARBOR 2-year results demonstrate that all 4 ranibizumab treatment groups maintained their visual and anatomic improvements, on average, between months 12 and 24 of the study. Over 2 years, the 2.0 mg dose did not show any clinically meaningful difference in efficacy, durability, or safety compared with the 0.5 mg ranibizumab dose. The PRN administration of ranibizumab 0.5 mg and 2.0 mg was efficacious, with safety profiles consistent with those of previous ranibizumab studies in wet AMD, and provided durable results with less frequent dosing. The VA gains achieved in the 0.5 mg PRN group had the least amount of change from months 12 to 24 (−0.3 letters) compared with the other ranibizumab treatment groups. Most patients (93%) in the 0.5 mg PRN group did not require monthly dosing over 2 years, indicating that an individualized treatment approach with ranibizumab 0.5 mg using visual acuity and SD-OCT–guided re-treatment criteria may be appropriate for most patients with wet AMD.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AE = adverse event; **AESI** = adverse event of special interest; **AMD** = age-related macular degeneration; **ANCHOR** = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related macular degeneration; **APTC** = Antiplatelet Trialists' Collaboration; **BCVA** = best-corrected visual acuity; **CATT** = Comparison of Age-related macular degeneration Treatments Trials; **CFT** = central foveal thickness; **CNV** = choroidal neovascularization; **DA** = disc area; **HARBOR** = 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 (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration; **MARINA** = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; **OCT** = optical coherence tomography; **PRN** = pro re nata (as needed); **SAE** = serious adverse event; **SD** = spectral domain; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VIEW** = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD.

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