# Twelve-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 12-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly and on an as-needed (PRN) basis in treatment-naïve patients with subfoveal neovascular age-related macular degeneration (wet AMD).

***Design:*** A 24-month, phase III, randomized, multicenter, double-masked, dose-response study.

***Participants:*** Patients aged ≥50 years with subfoveal wet AMD.

***Methods:*** Patients (n = 1098) were randomized to receive ranibizumab 0.5 mg or 2.0 mg intravitreal injections administered monthly or on a PRN basis after 3 monthly loading doses.

***Main Outcome Measures:*** The primary efficacy end point was the mean change from baseline in best-corrected visual acuity (BCVA) at month 12. Key secondary end points included the mean number of ranibizumab injections, the mean change from baseline in central foveal thickness (CFT) over time, and the proportion of patients who gained ≥15 letters of BCVA. Unless otherwise specified, end point analyses were performed using the last-observation-carried-forward method to impute missing data.

***Results:*** At month 12, the mean change from baseline in BCVA for the 4 groups was +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). The proportion of patients who gained ≥15 letters from baseline at month 12 in the 4 groups was 34.5%, 30.2%, 36.1%, and 33.0%, respectively. The mean change from baseline in CFT at month 12 in the 4 groups was −172.0 μm, −161.2 μm, −163.3 μm, and −172.4 μm, respectively. The mean number of injections was 7.7 and 6.9 for the 0.5-mg PRN and 2.0-mg PRN groups, respectively. Ocular and systemic safety profiles were consistent with previous ranibizumab trials in AMD and comparable between groups.

***Conclusions:*** At month 12, the ranibizumab 2.0 mg monthly group did not meet the prespecified superiority comparison and the ranibizumab 0.5 mg and 2.0 mg PRN groups did not meet the prespecified noninferiority (NI) comparison. However, all treatment groups demonstrated clinically meaningful visual improvement (+8.2 to +10.1 letters) and improved anatomic outcomes, with the PRN groups requiring approximately 4 fewer injections (6.9–7.7) than the monthly groups (11.2–11.3). No new safety events were observed despite a 4-fold dose escalation in the study. 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) study confirmed that ranibizumab 0.5 mg dosed monthly provides optimum results in patients with wet AMD.

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Age-related macular degeneration (AMD) is the leading cause of blindness among individuals aged 50 years or older in the United States and many other parts of the world.[1,2] Choroidal neovascularization (CNV), the hallmark of neovascular or wet AMD, is responsible for the majority of cases of severe vision loss due to AMD.[3] The development of CNV lesions is promoted by increased expression of vascular endothelial growth factor A (VEGF-A), with highly vascularized lesions expressing the highest levels.[4] Although the pathogenesis of neovascular AMD is not fully understood, inhibition of VEGF-A has been shown to block intraocular neovascularization in vivo.[5]

## Rationale for Higher Doses of Ranibizumab in Wet Age-Related Macular Degeneration

The pivotal phase III clinical studies, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal





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Neovascularization in Age-Related Macular Degeneration (ANCHOR)[6,7] and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA),[8] established that intravitreal administration of ranibizumab 0.3 mg and 0.5 mg (Lucentis; Genentech, Inc, South San Francisco, CA) significantly improves visual acuity (VA) in wet AMD. These 2 studies led to the US Food and Drug Administration (FDA) approval of monthly intravitreal ranibizumab 0.5 mg for the treatment of neovascular AMD in 2006. In these pivotal trials, most of the functional and anatomic outcomes favored the 0.5 mg dose of ranibizumab compared with the 0.3 mg dose. For example, in the ANCHOR[6,7] study at month 12, the mean VA improvement with ranibizumab 0.5 mg was 11.3 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (at a distance of 2 meters) versus 8.5 letters with the 0.3 mg dose. Furthermore, 40.3% and 35.7% of patients receiving ranibizumab 0.5 mg or 0.3 mg gained ≥15 ETDRS letters at month 12, respectively. Likewise, in the MARINA[8] study at month 12, 33.8% of patients treated with 0.5 mg had a ≥15-letter gain in best-corrected visual acuity (BCVA) compared with 24.8% treated with 0.3 mg. Patients in the MARINA study had a mean BCVA improvement at month 12 of 7.2 letters when treated with ranibizumab 0.5 mg and 6.5 letters when treated with ranibizumab 0.3 mg. The data from ANCHOR and MARINA suggested that treatment with higher doses of ranibizumab may lead to a further increase in efficacy.

Before the FDA approval of ranibizumab 0.5 mg for patients with wet AMD, an open-label, uncontrolled, randomized clinical study demonstrated that doses of ranibizumab up to 2.0 mg were safe and well tolerated in this patient population.[9] More recently, the investigator-sponsored double dose (DoDo) trial demonstrated trends toward higher efficacy with less frequent injections using ranibizumab 1.0 mg compared with 0.5 mg for naïve, wet AMD (Busbee B, Wu C, McCain M. Predictive factors for repeat dosing in wet AMD: results from the DoDo trial. Presented at: the American Society of Retina Specialists 29th Annual Meeting, August 20–24, 2011, Boston, MA). Further study of higher dosing revealed favorable initial results when patients previously treated with ranibizumab 0.5 mg were switched to 2.0 mg in the investigator-sponsored Super-dose Anti-VEgF (SAVE) trial.[10] These small trials suggested the potential of enhanced efficacy with higher dosing of ranibizumab.

## Rationale for As-Needed Dosing in Wet Age-Related Macular Degeneration

On the basis of results from several phase III/IIIb studies, in which VA outcomes were markedly better in patients receiving ranibizumab on a monthly basis (ANCHOR[6,7] and MARINA[8]) than in patients receiving 3 monthly loading doses, followed by prescheduled quarterly injections thereafter (Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration study [PIER]),[11,12] the ranibizumab US prescribing information recommended monthly injections for optimal VA outcomes. However, because monthly injections represent a burden on patients and their caregivers, most retina specialists use individualized dosing regimens based predominantly on optical coherence tomography (OCT) to treat patients with wet AMD (Jumper MJ, Mittra RA. American Society of Retina Specialists PAT Survey, 2011).

Quantitative and qualitative examination findings on OCT have become an integral part of the decision-making formula for treating patients on an individualized basis as opposed to monthly dosing for all patients.

Before the recent Comparison of Age-related macular degeneration Treatments Trials (CATT)[13,14] and alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization (IVAN)[15] multicenter studies, an OCT-guided treatment approach had been evaluated only in the 40-patient, phase II, open-label, nonrandomized prospective OCT imaging of patients with neovascular AMD treated with intraocular Ranibizumab (PrONTO)[16,17] trial. In this trial, patients received 3 monthly doses of ranibizumab 0.5 mg, followed by monthly evaluation and pro re nata (PRN) treatment guided by specific VA and imaging criteria for 24 months. The visual results from this small cohort were favorable and similar to the results from the ANCHOR and MARINA trials with fewer injections over the study period. The PrONTO study, along with the adoption of alternative dosing regimens by many retina specialists, supported the evaluation of PRN dosing in wet AMD.

Presented within are the 12-month results 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, which was conducted to evaluate the potential beneficial effects of both a higher dose and PRN dosing of ranibizumab in patients with wet AMD.

## Patients and Methods

### Study Design

HARBOR is a 24-month, phase III, randomized, multicenter, double-masked, active treatment-controlled study (ClinicalTrials.gov identifier: NCT00891735) with 100 investigator sites and 1098 randomized patients. The study was conducted in accordance with Good Clinical Practice (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E6), applicable FDA regulations, and the Health Insurance Portability and Accountability Act. The study protocol was approved by respective institutional review boards before the start of the study, and all participants provided written informed consent.

### Screening and Eligibility

Patients were eligible for the HARBOR trial if they were aged 50 years or older and fulfilled the following inclusion criteria for the

study eye: (1) BCVA of 20/40 to 20/320 (Snellen equivalent), using ETDRS charts (at a distance of 4 meters); (2) active subfoveal lesions with classic CNV, some classic CNV component, or purely occult CNV; (3) total area of lesion <12 disc areas (DA) or 30.48 $mm^2$; and (4) total CNV area constitutes ≥50% of total lesion area based on fluorescein angiography (FA). For the inclusion of purely occult or occult with some classic CNV, activity of the lesion had to be demonstrated by one of several criteria. This included a ≥10% increase in CNV lesion size on 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.

## Safety Run-in Assessment for the Ranibizumab 2.0 mg Dose

A 10-patient safety run-in assessment to determine the safety and tolerability of a single 2.0 mg dose of intravitreal ranibizumab was conducted before the 4-arm, randomized phase of the HARBOR trial. Each patient received a single injection at day 0 and had safety assessment visits scheduled on days 3, 7, 14, 28, 60, and 90. The HARBOR Data Monitoring Committee evaluated the first month of safety data for this group; they recommended no change to the study protocol, and enrollment in the randomized phase of the HARBOR trial commenced.

An additional safety assessment was performed after the first 40 evaluable patients in the 4-arm, randomized phase of the study (20 patients receiving ranibizumab 0.5 mg monthly or PRN and 20 patients receiving ranibizumab 2.0 mg monthly or PRN) received at least 2 study treatments. No dose-limiting criteria were observed for this group, and Data Monitoring Committee review of these safety data resulted in a recommendation to continue with the randomized phase of the HARBOR trial.

## Randomization

After written informed consent was obtained, and the central reading center confirmed that patients met all eligibility requirements, each patient received a computer-generated subject number on day 0, which 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, and 2.0 mg PRN. The 0.5 mg and 2.0 mg doses were both injected in a volume of 0.05 ml. Randomization was stratified by VA at day 0 (≤54 letters [approximate Snellen equivalent <20/80] vs. ≥55 letters [approximate Snellen equivalent ≥20/80]), CNV classification at baseline (predominantly classic, minimally classic, or purely occult), and study center. One eye was chosen as the study eye for each patient. 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 mg vs. 2.0 mg). Treatment frequency (ie, monthly vs. PRN dosing) was not masked to patient and site personnel.

Only the randomization provider and an external and independent statistical coordinating center responsible for performing interim analyses for the Data Monitoring Committee review, not otherwise involved in the study, had access to the unmasking code. In addition, an independent review of fundus photographs, FAs, and OCT images was performed at the central reading center to provide an objective, masked assessment of these evaluations. The central reading center review team consisted of graders and ophthalmologists experienced in clinical trials.

## Study Assessment and Treatment Schedule

The 4-arm, randomized phase of the study consisted of a screening period of up to 28 days and a 24-month treatment period. The primary efficacy end point was evaluated at month 12 (treatment period from day 0 [first intravitreal injection of ranibizumab] to month 11). Safety and ocular parameters were assessed on day 7; subsequently, all patients had scheduled monthly visits for evaluation of safety and efficacy. Patients in the monthly dosing groups had a safety evaluation before receiving the next monthly ranibizumab injection. Patients in the PRN groups also had monthly safety evaluations, but received ranibizumab monthly for the first 3 doses only. At the month 3 visit and thereafter, patients in the PRN groups received ranibizumab only if the investigating ophthalmologist determined that retreatment criteria were met (a ≥5-letter decrease in BCVA from the previous visit OR any evidence of disease activity on spectral-domain [SD OCT]; Table 1, available at http://aaojournal.org). At each monthly visit, all patients received an assessment for BCVA using the ETDRS protocol; a complete eye examination and vital signs; a review of concomitant medications; adverse events (AEs), and SD-OCT using Cirrus HD-OCT III (Carl Zeiss Meditec, Inc., Dublin, CA). Fluorescein angiography and fundus photography were performed at screening and at months 3, 6, and 12.

## Outcome Measures

The primary end point was the mean change from baseline in BCVA at month 12. Key secondary end points included the mean number of ranibizumab injections up to, but not including, month 12; the mean change from baseline in central foveal thickness (CFT) based on SD-OCT over time to month 12; the proportion of patients who gained ≥15 letters from baseline in BCVA at month 12; and the proportion of patients with a Snellen equivalent of ≥20/40.

An exploratory VA end point evaluated was the proportion of patients with a Snellen equivalent of ≤20/200, and additional VA end points included the proportion of patients who lost <15 letters from baseline in BCVA at month 12.

Safety assessments included ocular and systemic safety events through month 12. Assessments of targeted events included study eye serious adverse events (SAEs), Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events (ATEs), and SAEs potentially related to systemic VEGF-A inhibition.

## Statistical Analysis

**Efficacy Analyses.** Unless otherwise specified, the intent-to-treat principle was used for efficacy analyses, with missing data imputed using the last-observation-carried-forward method. Efficacy analyses were stratified by baseline BCVA score (≤54 letters, ≥55 letters) and baseline CNV classification (predominantly classic, minimally classic, purely occult). Patients were analyzed according to the treatment assignment at randomization. For efficacy end points using continuous variables (except for the mean number of ranibizumab injections), mean change from baseline at 12 months was compared between each treatment group and the standard treatment group (0.5 mg monthly) using the *t* test from a stratified analysis of variance or a stratified analysis of covariance model. For efficacy end points using binary variables, the proportion of patients meeting the end point was compared between each treat-

ment group and the standard treatment group using the Cochran–Mantel–Haenszel chi-square test. The mean number of injections during the first 12-month treatment period was compared between each treatment group and the standard treatment group using a stratified Wilcoxon test, and only patients who received at least 1 ranibizumab injection in the study eye were included in this analysis. Three primary end point comparisons were performed between the standard treatment group and each of the remaining 3 groups. Noninferiority (NI) tests with a prespecified NI margin of 4 letters comparing the 0.5 mg PRN with the 0.5 mg monthly group and the 2.0 mg PRN with the 0.5 mg monthly group were performed. A superiority test assessed the differences between the 2.0 mg monthly and 0.5 mg monthly groups. A Hochberg–Bonferroni approach was used to control the overall significance level for these 3 primary comparisons. The sample size of 1100 randomized patients ensured 80% power in the intent-to-treat population analysis for these 3 primary comparisons.

**Safety Analyses.** Safety was assessed through collection and summary of ocular and nonocular AEs, SAEs, ocular assessments, deaths, laboratory results, vital signs, and antibodies to ranibizumab. At each study visit, nondirective questioning was used to elicit AE reports from patients. All AEs and SAEs, whether volunteered by the patient, discovered by study site personnel during questioning, or detected by examination, laboratory testing, or other means, were recorded in the patient record and case report forms. Safety analyses included all patients receiving ≥1 ranibizumab injection. Patients were analyzed according to actual treatment received.

# Results

## Patient Characteristics and Disposition

Between July 2009 and August 2010, recruitment of HARBOR included 1098 patients in 100 study centers across the United States and assigned to ranibizumab 0.5 mg monthly (n = 276), 0.5 mg PRN (n = 275), 2.0 mg monthly (n = 274), or 2.0 mg PRN (n = 273). Overall, 1097 patients were eligible for the study; 1 patient was randomized before screen failure, and no baseline or post-baseline data were reported for this patient; therefore, the patient was excluded from analysis. In total, 94.5% of patients remained in the study through month 12; 5.5% of patients discontinued the study; the most common reason for study discontinuation was based on the patient's decision to withdraw (Table 2). Discontinuation rates were balanced among the 4 treatment groups. All but 2 patients received the study drug in the study eye (before the first injection, 1 patient withdrew from the study and 1 patient was lost to follow-up).

The mean age of patients was 79 years; 59% were female, and the majority was Caucasian. The mean baseline VA was between 53.5 and 54.5 letters (approximate Snellen equivalent of 20/80) and mean baseline CFT ranged from 333 to 348 $\mu$m among the 4 cohorts (Table 3). Overall, approximately 46% of patients had minimally classic CNV lesions, 16% had predominantly classic lesions, and 38% had purely occult CNV. The total area of CNV lesion size was 3.0 to 3.3 DA. All variables were well balanced among the 4 treatment groups.

## Efficacy Outcomes

**Visual Acuity End Points.** The HARBOR study did not meet its primary end point, which comprised 3 comparisons: a superiority comparison (2.0 mg monthly vs. 0.5 mg monthly) and 2 NI comparisons (2.0 mg PRN and 0.5 mg PRN vs. 0.5 mg monthly; Fig 1). There was no evidence that the 2.0 mg monthly dosing regimen was superior to the 0.5 mg monthly regimen (model-adjusted mean difference, −1.1 letters; 95.1% confidence interval [CI], −3.4 to 1.3; $P = 0.8145$). The 0.5 mg PRN and 2.0 mg PRN regimens failed to meet the 4-letter NI margin when compared with the 0.5 mg monthly regimen. The NI comparison between 0.5 mg PRN and 0.5 mg monthly had a model-adjusted mean difference of −2.0 letters (97.5% CI, −4.5 to 0.6), and the NI comparison between 2.0 mg PRN and 0.5 mg monthly had a model-adjusted mean difference of −1.6 letters (98.4% CI, −4.4 to 1.1).

Although the primary end point was not met, all 4 treatment groups demonstrated significant and clinically meaningful increases in BCVA at month 12 compared with baseline. This improvement from baseline BCVA was observed starting at day 7, with further improvements over the course of the study that were sustained through month 12. The mean gains in BCVA (ETDRS letters) from baseline to 12 months were 10.1 (0.5 mg monthly), 8.2 (0.5 mg PRN), 9.2 (2.0 mg monthly), and 8.6 (2.0 mg PRN). The BCVA gains were achieved with an average of 11.3 (0.5 mg monthly), 7.7 (0.5 mg PRN), 11.2 (2.0 mg monthly), and 6.9 (2.0 mg PRN) injections over 12 months (Fig 2).

Table 2. Patient Disposition

| Status/Primary Reason for Discontinuation, n (%) | Ranibizumab Treatment Groups | | | |
|---|---|---|---|---|
| | *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 before month 12 | 274 (99.6) | 275 (100.0) | 274 (100.0) | 272 (99.6) |
| Discontinued study before month 12 (total) | 17 (6.2) | 12 (4.4) | 16 (5.8) | 15 (5.5) |
| AE | 2 (0.7) | 2 (0.7) | 0 | 0 |
| Death | 8 (2.9) | 4 (1.5) | 5 (1.8) | 5 (1.8) |
| Lost to follow-up | 2 (0.7) | 2 (0.7) | 2 (0.7) | 2 (0.7) |
| Physician's decision to withdraw patient from study | 1 (0.4) | 0 | 0 | 0 |
| Patient's decision to withdraw | 4 (1.5) | 4 (1.5) | 9 (3.3) | 8 (2.9) |
| Discontinued treatment before month 12 (total) | 21 (7.6) | 16 (5.8) | 18 (6.6) | 18 (6.6) |
| AE | 2 (0.7) | 1 (0.4) | 0 | 1 (0.4) |
| Death | 8 (2.9) | 4 (1.5) | 5 (1.8) | 4 (1.5) |
| Lost to follow-up | 2 (0.7) | 2 (0.7) | 3 (1.1) | 3 (1.1) |
| Physician's decision to discontinue treatment | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Patient's decision to discontinue treatment | 8 (2.9) | 9 (3.3) | 9 (3.3) | 10 (3.7) |

AE = adverse event; PRN = pro re nata.

Table 3. Patient Demographics and Baseline Ocular Characteristics (Study Eye)

| | Ranibizumab Treatment Groups | | | |
|---|---|---|---|---|
| | *0.5 mg Monthly (n = 275)* | *0.5 mg PRN (n = 275)* | *2.0 mg Monthly (n = 274)* | *2.0 mg PRN (n = 273)* |
| Age (yrs) | | | | |
| Mean (SD) | 78.8 (8.4) | 78.5 (8.3) | 79.3 (8.3) | 78.3 (8.3) |
| Range | 53.0–97.0 | 53.0–97.0 | 50.0–96.0 | 54.0–98.0 |
| Sex, n (%) | | | | |
| Male | 113 (41.1) | 112 (40.7) | 104 (38.0) | 117 (42.9) |
| Female | 162 (58.9) | 163 (59.3) | 170 (62.0) | 156 (57.1) |
| Race, n (%) | | | | |
| White | 265 (96.4) | 268 (97.5) | 268 (97.8) | 261 (95.6) |
| VA (No. of letters, 0–100) | | | | |
| Mean (SD)* | 54.2 (13.3) | 54.5 (11.7) | 53.5 (13.1) | 53.5 (13.2) |
| Range | 3–78 | 26–73 | 19–74 | 15–77 |
| ≤54 letters, n (%) | 126 (45.8) | 128 (46.5) | 134 (48.9) | 134 (49.1) |
| ≥55 letters, n (%) | 149 (54.2) | 147 (53.5) | 140 (51.1) | 139 (50.9) |
| CFT (μm) | | | | |
| Mean (SD) | 348.3 (146.3) | 347.8 (143.8) | 332.9 (138.7) | 347.9 (142.9) |
| CNV lesion type, n (%) | | | | |
| Minimally classic | 127 (46.2) | 128 (46.5) | 126 (46.0) | 128 (46.9) |
| Predominantly classic | 42 (15.3) | 47 (17.1) | 40 (14.6) | 41 (15.0) |
| Purely occult | 106 (38.5) | 100 (36.4) | 108 (39.4) | 104 (38.1) |
| Total area of lesion (DA) | | | | |
| Mean (SD) | 3.39 (2.17) | 3.21 (2.08) | 3.46 (2.29) | 3.33 (2.29) |
| Range | 0.13–11.74 | 0.09–10.65 | 0.08–13.73 | 0.23–10.88 |
| Total area of CNV (DA) | | | | |
| Mean (SD) | 3.27 (2.12) | 3.04 (1.97) | 3.29 (2.22) | 3.17 (2.17) |
| Range | 0.13–11.74 | 0.05–10.31 | 0.08–13.73 | 0.21–10.88 |
| Total area of CNV leakage (DA) | | | | |
| Mean (SD) | 3.48 (2.08) | 3.31 (1.93) | 3.51 (2.10) | 3.43 (2.17) |
| Range | 0.33–11.74 | 0.37–10.31 | 0.28–13.73 | 0.23–10.88 |

CFT = central foveal thickness; CNV = choroidal neovascularization; DA = disc areas; PRN = pro re nata; SD = standard deviation; VA = visual acuity.
*Approximate Snellen equivalent of 20/80.

Other key efficacy end points are summarized in Table 4. The proportion of patients who gained ≥15 letters (~3 lines) from baseline in BCVA at month 12 was 34.5% (0.5 mg monthly), 30.2% (0.5 mg PRN), 36.1% (2.0 mg monthly), and 33.0% (2.0 mg PRN). The proportion of patients who had a Snellen equivalent of ≥20/40 at month 12 was 52.4% (0.5 mg monthly), 46.2% (0.5 mg PRN), 50.0% (2.0 mg monthly), and 43.6% (2.0 mg PRN). The proportion of patients with a Snellen equivalent of ≤20/200 at month 12 was 7.3% (0.5 mg monthly), 8.4% (0.5 mg PRN), 11.3% (2.0 mg monthly), and 12.1% (2.0 mg PRN).

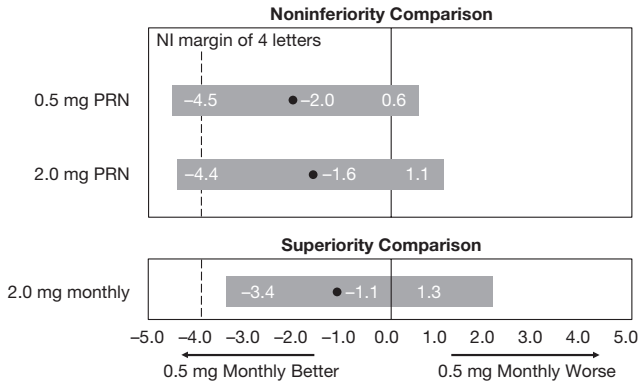


**Figure 1.** Mean change from baseline in best-corrected visual acuity (BCVA) at month 12 using Hochberg-adjusted confidence intervals (CIs)* (adjusted difference in mean change in BCVA compared with 0.5 mg monthly†). *Prespecified in HARBOR statistical analysis plan. †Adjusted for baseline BCVA score (≤54 letters, ≥55 letters) and choroidal neovascularization (CNV) classification; the last-observation-carried-forward (LOCF) method was used to impute missing data. NI = noninferiority; PRN = pro re nata.

Another commonly reported VA end point, the proportion of patients who lost <15 letters from baseline at month 12, was explored post hoc. At month 12, the proportion of patients who lost <15 letters from baseline at month 12 was 97.8% (0.5 mg monthly), 94.5% (0.5 mg PRN), 93.4% (2.0 mg monthly), and 94.9% (2.0 mg PRN) (Table 4).

## Anatomic End Points and Pro Re Nata Cohort Analysis

**Optical Coherence Tomography End Points.** The mean change from baseline in CFT by SD-OCT over time up to month 12 is depicted in Figure 3. All groups showed a rapid decrease in CFT at day 7 that continued through month 3 and was sustained from month 3 to 12. At month 12, the mean reduction from baseline was 172.0 μm (0.5 mg monthly), 161.2 μm (0.5 mg PRN), 163.3 μm (2.0 mg monthly), and 172.4 μm (2.0 mg PRN).

**Optical Coherence Tomography Analysis in the Pro Re Nata Groups.** Further exploratory analyses of the criteria for retreatment in the PRN groups revealed that between 51% and 62% of patients in the 0.5 mg PRN group met criteria for retreatment at

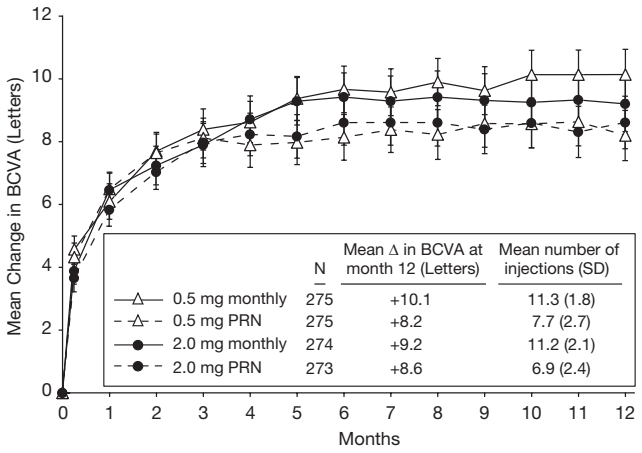


**Figure 2.** Mean change from baseline to month 12 in best-corrected visual acuity (BCVA).* Vertical bars are ±1 standard error of the unadjusted mean. The last-observation-carried-forward (LOCF) method was used to impute missing data. *Mean number of injections was analyzed for patients who received at least 1 ranibizumab injection in the study eye (n = 274 treated patients in 0.5 mg monthly group, n = 275 treated patients in 0.5 mg pro re nata (PRN) group, n = 274 treated patients in the 2.0 mg monthly group, and n = 272 treated patients in the 2.0 mg PRN group). SD = standard deviation.

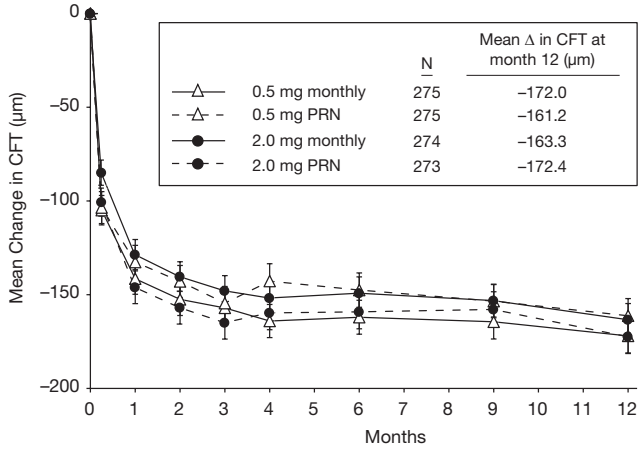


**Figure 3.** Mean change from baseline to month 12 in central foveal thickness (CFT) by spectral-domain optical coherence tomography (SD-OCT). Vertical bars are ±1 standard error of the unadjusted mean. The last-observation-carried-forward (LOCF) method was used to impute missing data. PRN = pro re nata.

any given monthly time point after month 2. The majority of these patients (>70% at each time point) met criteria on SD-OCT examination alone (did not have a concomitant ≥5-letter BCVA loss). A smaller percentage of patients (5.3%–13.8%) met retreatment criteria based on BCVA loss of ≥5 letters alone at any given monthly time point. This trend also was observed in the 2.0 mg PRN group. At every time point with 1 exception, the percentage of patients meeting retreatment criteria based on vision loss alone was higher in the 2.0 mg group (11.0%–21.0%) compared with the 0.5 mg group.

**Angiographic End Points.** At 12 months, all 4 treatment groups demonstrated a decrease from baseline in total area of CNV and total area of CNV leakage. The change from baseline in total area of CNV (DA) was a decrease of 2.14 (0.5 mg monthly), 1.74 (0.5 mg PRN), 2.42 (2.0 mg monthly), and 1.98 (2.0 mg PRN). The change from baseline in total area of CNV leakage (DA) was a decrease of 2.35 (0.5 mg monthly), 2.01 (0.5 mg PRN), 2.63 (2.0 mg monthly), and 2.22 (2.0 mg PRN).

## Safety

**Ocular Adverse Events.** Ocular safety results are summarized in Table 5. Serious ocular AEs in the study eye were rare across all treatment groups (endophthalmitis was reported by 2 patients [0.7%] in the 0.5 mg monthly group, and iridocyclitis and retinal tear were reported by 1 patient [0.4%] each in the 2.0 mg monthly group). No new safety events were identified in any of the 4 treatment groups. There were no ocular SAEs of glaucoma. There were also no ocular SAEs of increased intraocular pressure (IOP), which was measured before injection, 30 (±5) minutes after injection, and again at 60 (±10) minutes post-injection if IOP was increased by ≥10 mmHg compared with the pre-injection measurement.

Ocular AEs (including those that were considered an SAE) in the study eyes were balanced among all 4 treatment groups. Conjunctival hemorrhage was the most common ocular AE, with an overall rate of 19% among the 4 treatment groups. Adverse events of increased IOP were reported in 4.0% (0.5 mg monthly), 1.8% (0.5 mg PRN), 2.6% (2.0 mg monthly), and 2.2% (2.0 mg PRN) of patients. Post-dose IOP values of ≥30 mmHg occurred in 3.7%, 1.5%, 2.6%, and 1.9% of patients in the 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, and 2.0 mg PRN treatment groups, respectively. Other AEs of interest included glaucoma (0.4% in each treatment group) and iritis (0.6% overall). There was no trend observed for dose relationship (0.5 mg vs. 2.0 mg) or exposure (monthly vs. PRN) (Table 6, available at http://aaojournal.org).

**Systemic Adverse Events.** Systemic safety results are summarized in Table 5, categorized by APTC ATE and AE of special interest (AESI) related to VEGF-A inhibition as defined in Genentech-sponsored bevacizumab (Avastin) oncology trials and previously

Table 4. Key Visual Acuity End Points at Month 12

| | Ranibizumab Treatment Groups | | | |
|---|---|---|---|---|
| | *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) | 10.1 (13.3) | 8.2 (13.3) | 9.2 (14.6) | 8.6 (13.8) |
| Proportion of patients gaining ≥15 letters from baseline, n (%) | 95 (34.5) | 83 (30.2) | 99 (36.1) | 90 (33.0) |
| Proportion of patients losing <15 letters from baseline, n (%) | 269 (97.8) | 260 (94.5) | 256 (93.4) | 259 (94.9) |
| Proportion of patients with Snellen ≥20/40, n (%) | 144 (52.4) | 127 (46.2) | 137 (50.0) | 119 (43.6) |
| Proportion of patients with Snellen ≤20/200, n (%) | 20 (7.3) | 23 (8.4) | 31 (11.3) | 33 (12.1) |

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = pro re nata; SD = standard deviation.

Table 5. Adverse Events

| | Ranibizumab Treatment Groups | | | |
|---|---|---|---|---|
| | *0.5 mg Monthly (n = 274)* | *0.5 mg PRN (n = 275)* | *2.0 mg Monthly (n = 274)* | *2.0 mg PRN (n = 272)* |
| Serious ocular AE in the study eye, n (%) | | | | |
| Any SAE* | 3 (1.1) | 3 (1.1) | 6 (2.2) | 1 (0.4) |
| Reduced VA | 0 | 2 (0.7) | 3 (1.1) | 0 |
| Retinal hemorrhage | 0 | 1 (0.4) | 1 (0.4) | 1 (0.4) |
| Endophthalmitis | 2 (0.7) | 0 | 0 | 0 |
| Corneal edema | 0 | 1 (0.4) | 0 | 0 |
| Iridocyclitis | 0 | 0 | 1 (0.4) | 0 |
| Macular degeneration | 1 (0.4) | 0 | 0 | 0 |
| Retinal artery occlusion | 1 (0.4) | 0 | 0 | 0 |
| Retinal tear | 0 | 0 | 1 (0.4) | 0 |
| Retinal vein occlusion | 1 (0.4) | 0 | 0 | 0 |
| Vitreous floaters | 0 | 0 | 1 (0.4) | 0 |
| APTC ATEs, n (%) | | | | |
| Total APTC events† | 12 (4.4) | 4 (1.5) | 6 (2.2) | 8 (2.9) |
| Deaths, overall | 8 (2.9) | 4 (1.5) | 5 (1.8) | 5 (1.8) |
| Vascular | 6 (2.2) | 3 (1.1) | 2 (0.7) | 1 (0.4) |
| Unknown cause | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Nonfatal myocardial infarction | 4 (1.5) | 0 | 2 (0.7) | 4 (1.5) |
| Nonfatal CVA, overall | 2 (0.7) | 1 (0.4) | 2 (0.7) | 2 (0.7) |
| Hemorrhagic CVA | 1 (0.4) | 0 | 0 | 0 |
| Ischemic CVA | 1 (0.4) | 1 (0.4) | 2 (0.7) | 2 (0.7) |
| Serious AESI, n (%) | | | | |
| Any AESI‡ | 16 (5.8) | 13 (4.7) | 16 (5.8) | 13 (4.8) |
| ATE | 7 (2.6) | 5 (1.8) | 6 (2.2) | 7 (2.6) |
| Bleeding/hemorrhage (CNS) | 2 (0.7) | 2 (0.7) | 1 (0.4) | 2 (0.7) |
| Bleeding/hemorrhage (non-CNS) | 2 (0.7) | 2 (0.7) | 4 (1.5) | 4 (1.5) |
| Congestive heart failure | 6 (2.2) | 2 (0.7) | 2 (0.7) | 2 (0.7) |
| Fistulae | 0 | 1 (0.4) | 1 (0.4) | 0 |
| Gastrointestinal perforation | 0 | 0 | 1 (0.4) | 0 |
| Hypertension | 0 | 1 (0.4) | 1 (0.4) | 2 (0.7) |
| Venous thrombotic events | 1 (0.4) | 1 (0.4) | 2 (0.7) | 0 |
| Wound healing complications | 0 | 1 (0.4) | 0 | 0 |

AE = adverse event; AESI = adverse event of special interest; APTC = Antiplatelet Trialists' Collaboration; ATE = arterial thromboembolic event; CNS = central nervous system; CVA = cerebrovascular accident; PRN = pro re nata; SAE = serious adverse event; VA = visual acuity.

AESI Classification: AEs related to VEGF-A inhibition as defined in Genentech Inc (South San Francisco, CA) bevacizumab (Avastin) oncology trials.

*Denotes total number of patients with ≥1 SAE. An AE was classified as an SAE if it cause or led to death, required prolonged hospitalization, resulted in persistent or significant disability, or was considered a significant medical event by the investigating physician.

†Denotes total number of patients with ≥1 APTC event (including vascular deaths, deaths of unknown cause, nonfatal myocardial infarctions, and nonfatal CVAs).

‡Denotes total number of patients with ≥1 serious AESI.

described by Chen and Cleck.[18] There was no obvious imbalance across all 4 treatment groups in the rates of APTC ATEs and AESIs.

The total rates of APTC-defined ATEs were low among the treatment groups, ranging from 12 patients (4.4%) in the 0.5 mg monthly group to 4 patients (1.5%) in the 0.5 mg PRN group, 6 patients (2.2%) in the 2.0 mg monthly group, and 8 patients (2.9%) in the 2.0 mg PRN group. At year 1, 22 of the 1095 ranibizumab-treated patients (2.0%) had died: 8 of 274 (2.9%) in the 0.5 mg monthly group, 4 of 275 (1.5%) in the 0.5 mg PRN group, 5 of 274 (1.8%) in the 2.0 mg monthly group, and 5 of 272 (1.8%) in the 2.0 mg PRN group. The overall rates of nonfatal cerebrovascular accidents were low (0.4%–0.7%) and similar among the 4 treatment groups.

The overall rates of serious AESIs were similar among the 4 treatment groups, ranging from 4.7% to 5.8%. 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, 2 patients (0.7%) in the 0.5 mg PRN group, 1 patient (0.4%) in the 2.0 mg monthly group, and 2 patients (0.7%) in the 2.0 mg PRN group. Serious AEs of hypertension also were uncommon, with 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 2 patients (0.7%) in the 2.0 mg PRN group.

## Discussion

The first objective of the HARBOR study was to assess the efficacy of a higher ranibizumab dose in wet AMD, which was evaluated by a superiority comparison between the 2.0

mg monthly and 0.5 mg monthly treatment groups. The 1-year results demonstrate that in patients with previously untreated wet AMD, the ranibizumab 2.0 mg dose was not superior to the 0.5 mg dose and did not offer any incremental improvement in efficacy outcomes. However, both doses resulted in significant and clinically meaningful improvements in mean BCVA. The increase in BCVA was 10.1 letters for the 0.5 mg monthly group and 9.2 letters for the 2.0 mg monthly group, with a model-adjusted mean difference of −1.1 letters (95.1% CI, −3.4 to 1.3; $P = 0.8145$). This result was unexpected, because several trials have shown trends of a dose response with ranibizumab.[6–8] Most of the functional and anatomic outcomes favored the 0.5 mg dose compared with the 0.3 mg dose of ranibizumab in the pivotal phase III ANCHOR[6,7] and MARINA[8] studies. Subsequent trials, such as the DoDo study and the SAVE[10] trial, also showed trends in which higher ranibizumab doses led to improved VA and anatomic outcomes. In the present study, the robust results of the 0.5 mg monthly group (among the highest gains seen in previous phase III studies) and the lack of increased efficacy in the 2.0-mg group suggest that the 0.5 mg monthly dose seems to be at the top of the dose response for treatment-naïve patients with wet AMD.

The second objective of HARBOR was to evaluate a PRN dosing regimen with monthly evaluations. The 1-year data resulted in a failure to meet NI (using a 4-letter margin) for the 0.5 mg PRN and 2.0 mg PRN dose groups compared with the 0.5 mg monthly dose group, with a model-adjusted mean difference of −2.0 letters (97.5% CI, −4.5 to 0.6) and −1.6 letters (98.4% CI, −4.4 to 1.1), respectively. However, the VA outcomes for the PRN groups were clinically meaningful, especially in the context of less-than-monthly dosing. The 0.5 mg PRN group had an 8.2-letter gain that was achieved using a mean of 7.7 injections over the 12 months, and the 2.0 mg PRN group had, on average, an 8.6-letter gain using a mean of 6.9 injections over the same time period.

The HARBOR 1-year PRN data appear similar to the ranibizumab PRN data published in year 1 of the CATT[13] study. The CATT study was the first large, multicenter, randomized, masked, NI trial designed to assess the relative efficacy and safety of ranibizumab and bevacizumab and to determine whether a PRN regimen would compromise long-term VA outcomes compared with a monthly regimen. One primary analysis in CATT was a comparison between ranibizumab 0.5 mg monthly and ranibizumab 0.5 mg PRN. In CATT, the PRN group was evaluated on a monthly basis and retreated after the first loading dose when signs of active neovascularization (defined as fluid on time-domain OCT, new or persistent hemorrhage, decreased VA compared with the preceding examination, dye leakage, or increased lesion size on FA) were present.[13] By using an NI margin of 5 letters, the CATT investigators concluded that ranibizumab 0.5 mg administered PRN with a monthly evaluation had effects on vision at year 1 that were noninferior to those of ranibizumab administered monthly. The CATT investigators reported gains of 8.5 letters (ranibizumab 0.5 mg monthly) and 6.8 letters (ranibizumab 0.5 mg PRN), with the mean difference of −1.7 letters (2-sided Bonferroni-adjusted 99.2% CI, −4.7 to 1.3). The CATT ranibizumab 0.5 mg PRN regimen achieved these gains with a mean of 6.9 injections over 1 year.

Although cross-trial comparisons have obvious limitations, and data must be interpreted with caution, it is interesting to note that CATT and HARBOR had different conclusions on NI despite having similar study populations, retreatment criteria, end points, and mean differences in BCVA at month 12 between the 0.5 mg monthly and 0.5 mg PRN groups. There were some differences between the trials; for instance, CATT included patients with a Snellen VA between 20/25 and 20/320 (HARBOR inclusion was Snellen 20/40–20/320), featured a single loading dose (HARBOR had 3 loading doses), and used time-domain OCT (HARBOR used SD-OCT). However, a key difference between the 2 trials was the NI margin used in each study. The HARBOR study was designed as an FDA registrational trial, as well as to satisfy a post-marketing commitment, and used a 4-letter NI margin. In contrast, the CATT study was designed to compare the relative efficacy and safety of ranibizumab with bevacizumab, and used a 5-letter NI margin, which was determined by the investigators to be the maximum clinically acceptable true difference for new treatments compared to active controls in the NI trials. This 1-letter difference in the NI margins used in these 2 studies may have contributed to the different conclusions at year 1 regarding the NI of 0.5 mg PRN compared with 0.5 mg monthly. However, regardless of which NI margin was chosen, both of these studies showed that less-than-monthly treatment regimens can decrease treatment burden and still result in clinically meaningful VA gains over 12 months.

Another recent set of studies evaluating ranibizumab PRN dosing were the VIEW 1/2 studies, which compared aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY) with ranibizumab in wet AMD for 2 years (Heier JS. 96-week results from the VIEW 1 and VIEW 2 studies: intravitreal aflibercept injection versus ranibizumab for neovascular AMD shows sustained improvements in visual acuity. Paper presented at: ARVO Annual Meeting, May 10, 2012, Fort Lauderdale, FL). The VIEW 1/2 studies evaluated different dosing regimens between the first and second years of the trials. During the first year of the trial, patients were treated with 3 different dosing regimens of aflibercept: 0.5 mg every 4 weeks, 2.0 mg every 4 weeks, or 2.0 mg every 8 weeks (after 3 monthly loading doses) and were compared with patients treated with ranibizumab 0.5 mg every 4 weeks. In the second year, all patients continued on their assigned treatment drug and dose and were switched to a modified PRN treatment regimen in which they were evaluated monthly with a mandatory retreatment at least every 12 weeks.

The 1-year results of the VIEW 1/2 studies found that aflibercept 2.0 mg dosed every 8 weeks after 3 initial monthly loading doses was noninferior to ranibizumab 0.5 mg dosed monthly. Patients receiving aflibercept 2.0 mg dosed every 8 weeks gained 8.4 letters from baseline at week 52 with an average of 7.5 injections,[19] and finished the study with an increase of 7.6 letters from baseline at week 96 with an average of 4.2 injections in the second year (modified PRN period) (Heier JS. 96-week results from the VIEW 1 and VIEW 2 studies: intravitreal aflibercept injec-

tion versus ranibizumab for neovascular AMD shows sustained improvements in visual acuity. Paper presented at: ARVO Annual Meeting, May 10, 2012, Fort Lauderdale, FL). In comparison, the ranibizumab 0.5 mg group (dosed every 4 weeks) gained 8.7 letters from baseline at week 52 with an average of 12.3 injections,[19] and ended the study with a gain of 7.9 letters from baseline at week 96 with an average of 4.7 injections in the second year (Heier JS. 96-week results from the VIEW 1 and VIEW 2 studies: intravitreal aflibercept injection versus ranibizumab for neovascular AMD shows sustained improvements in visual acuity. Paper presented at: ARVO Annual Meeting, May 10, 2012, Fort Lauderdale, FL). Results from the second year of the VIEW 1/2 studies suggest that ranibizumab and aflibercept are capable of producing similar visual outcomes using a less-than-monthly treatment approach. Additional studies would be warranted to definitely conclude the similarity between these 2 anti-VEGF treatments.

In the context of historic, less-than-monthly dosing regimens with ranibizumab, the HARBOR PRN groups resulted in similar visual outcomes as those of the CATT ranibizumab PRN group and better visual outcomes than the quarterly dosing regimens of PIER[11,12] and Safety Assessment of Intravitreous Lucentis for AMD (SAILOR)[20] (cohort 1). The HARBOR PRN groups also had similar results to visual outcomes observed in the fixed monthly dose trials in MARINA[8] and ANCHOR.[6,7] By looking at the evaluation intervals of the 4 clinical trials with less-than-monthly ranibizumab dosing groups (HARBOR, CATT, PIER and SAILOR; Fig 4), it is evident that the durability of effect with ranibizumab can be extended in many patients using a closely monitored PRN regimen that incorporates prompt recognition of recurrent OCT activity or decrease in VA in contrast to loss of VA gains in a quarterly fixed-dose regimen.

The HARBOR PRN data for both ranibizumab doses suggest that prompt treatment of OCT fluid or visual decline allows for sustained visual improvements over a 12-month period. However, 2 points must be taken into account when considering the PRN approach. First, the PRN groups did not meet NI compared with the 0.5 mg monthly group in the HARBOR trial. The results showed that treatment-naïve patients with wet AMD treated monthly in the first year gained, on average, approximately 2 letters more than patients treated PRN. In addition, patients in the 0.5 mg monthly group also performed better on all secondary and exploratory VA end points relative to the PRN groups (Table 4). Physicians and patients will need to take into consideration this benefit/risk in the context of decreased injection frequency when deciding to treat with ranibizumab 0.5 mg monthly versus PRN. Second, the durability of the VA gains achieved with PRN dosing beyond 12 months in HARBOR is unknown, but this will be answered at the completion of the HARBOR trial.

The third objective of the HARBOR trial was to evaluate the safety of the 0.5 mg and 2.0 mg doses administered on a monthly and PRN schedule. Overall, the incidence of ocular AEs observed in HARBOR was consistent with previous ranibizumab trials in wet AMD and was comparable among groups. There were no apparent dose-related trends between the 0.5 mg and 2.0 mg groups. Moreover, there were no apparent dose-exposure–related trends between the monthly and the PRN groups. Serious ocular AEs in the study eye were rare for both the 0.5 mg and 2.0 mg treatment groups, with endophthalmitis reported in 2 patients (0.5 mg monthly group), retinal hemorrhage reported in 3 patients (1 patient each in the 0.5 mg PRN, 2.0 mg monthly, and 2.0 mg PRN groups), and iridocyclitis and retinal tear reported in 1 patient each in the 2.0 mg monthly group. Other serious ocular AEs reported in the study eye are shown in Table 5.

The IOP events in HARBOR are of particular interest because there have been recent reports of increased pre-dose IOP in a subset of wet AMD patients treated with ranibizumab[21] (Bakri S, Moshfeghi DM, Francom S, et al. Intraocular pressure (IOP) in eyes receiving monthly intravitreal ranibizumab in the MARINA and ANCHOR trials. Paper presented at: AAO Annual Meeting, October 24, 2011, Orlando, FL; Bakri S, Moshfeghi DM, Francom S, et al.

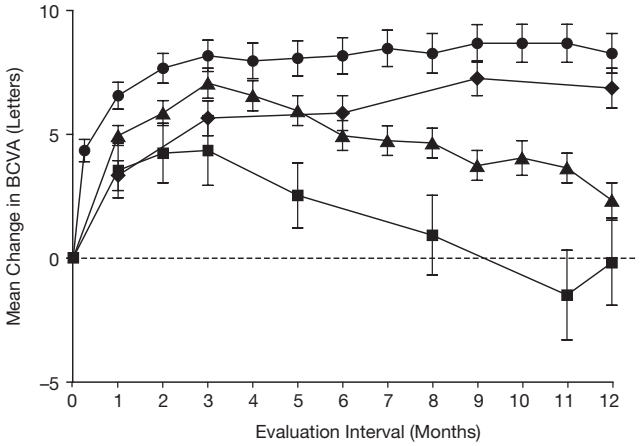


**Figure 4.** Mean change in best-corrected visual acuity (BCVA) from baseline at month 12 across select wet age-related macular degeneration (AMD) trials evaluating less-than-monthly ranibizumab dosing regimens. *Ranibizumab 0.5 mg administered as 3 monthly loading doses followed by pro re nata (PRN) dosing. Vertical bars are ±1 standard error of the unadjusted mean. The last-observation-carried-forward (LOCF) method was used to impute missing data. †Ranibizumab 0.5 mg administered as 1 loading dose, followed by PRN dosing. Vertical bars are ±1 standard error of the mean. ‡Treatment-naïve patients in cohort 1 received 3 monthly loading doses of ranibizumab 0.5 mg followed by protocol-defined retreatment. Vertical bars are ±1 standard error of the unadjusted mean. The LOCF method was used to impute missing data. #Ranibizumab 0.5 mg administered at day 0 and months 1, 2, 5, 8, and 11. Vertical bars are ±1 standard error of the unadjusted mean. The LOCF method was used to impute missing data. CATT = comparison of age-related macular degeneration treatments trials; 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; PIER = phase IIIb, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal choroidal neovascularization with or without classic choroidal neovascularization (CNV) secondary to age-related macular degeneration study; SAILOR = safety assessment of intravitreous lucentis for AMD. ●, HARBOR*; ◆, CATT†; ▲, SAILOR‡; and ■, PIER#.

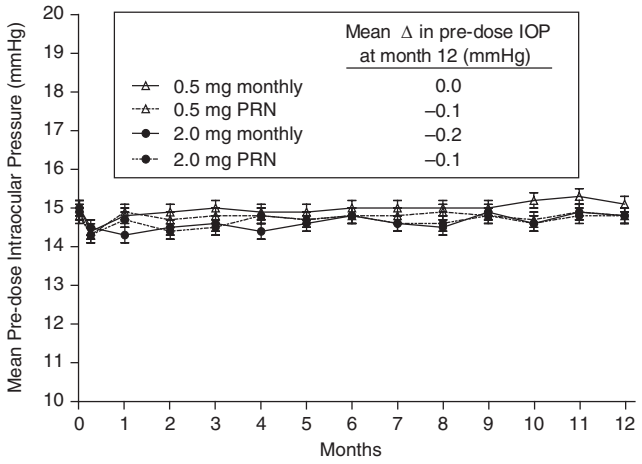


**Figure 5.** Mean pre-dose intraocular pressure (IOP) in the study eye during the first 12-month treatment period. The mean pre-dose IOP in the study eye over the first 12 months was in the range of 14.3 to 15.3 mmHg, and the standard error was 0.2 at each visit. PRN = pro re nata.

Analysis of intraocular pressure in eyes receiving monthly intravitreal ranibizumab in the MARINA and ANCHOR Trials. Paper presented at: ASRS Annual Meeting, August 22, 2011, Boston, MA). No serious ocular AEs of increased IOP were reported in HARBOR. The percentage of patients with nonserious ocular AEs of increased IOP ranged from 1.8% to 4.0% and was highest in the 0.5 mg monthly group, demonstrating that there was no increase of IOP-related AEs at higher ranibizumab doses. Furthermore, none of the 4 treatment groups showed an increase in mean pre-dose IOP from baseline to month 12 (Fig 5). In terms of glaucoma, no serious ocular AEs of glaucoma were reported and the incidence of reported ocular AEs of glaucoma was low, with 0.4% in each of the 4 treatment groups. From these data, it seems that during the first year of HARBOR, IOP and glaucoma events were not of obvious concern for the standard or the higher dose of ranibizumab.

Systemic AEs also were consistent with previous ranibizumab trials in wet AMD. Similar to the ocular AEs, the rates of systemic AEs were comparable between groups, with no apparent dose-related or dose-exposure trends observed even with a 4-fold higher dose. Ranibizumab appeared safe when used at the standard or the higher dose, as well as when administered monthly or PRN during the HARBOR trial.

There are several limitations of the HARBOR study. One limitation is a fairly homogenous US study population. A second limitation is that the 1-year data from HARBOR cannot predict visual outcomes in future years. However, HARBOR is an ongoing, 2-year study and will provide data on the long-term durability of ranibizumab with a PRN regimen. Third, although no new safety events were detected, the HARBOR study was not powered to detect statistical differences between treatment groups. Finally, although the PRN dosing regimen decreased treatment burden and produced clinically relevant visual gains, monthly monitoring was required to achieve these gains. Investigations around treatment approaches that decrease both injection and visit frequency (e.g., treat and extend or sustained delivery) are of continued interest in the treatment of wet AMD.

In conclusion, the HARBOR study adds to the growing body of clinical trial data that are available for ranibizumab in wet AMD. Although the PRN cohorts did not meet the prespecified NI comparison and the 2.0 mg monthly group did not meet the prespecified superiority comparison, the HARBOR Study 1-year results demonstrate clinically meaningful improvements in VA and anatomic outcomes across all 4 treatment groups. The HARBOR study demonstrated that the 2.0 mg dose of intravitreal ranibizumab has an acceptable safety profile comparable to that of the standard dose. Although less effective than monthly dosing, PRN dosing using SD-OCT–guided retreatment criteria decreased treatment burden and produced clinically meaningful VA gains in patients with wet AMD. The HARBOR results ultimately confirmed that the current, commercially available preparation of ranibizumab (0.5 mg), when dosed monthly, provides optimum results.

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