

# Intravitreal Aflibercept Injection for Neovascular Age-Related Macular Degeneration

## Ninety-Six–Week Results of the VIEW Studies

Ursula Schmidt-Erfurth, MD,<sup>1</sup> Peter K. Kaiser, MD,<sup>2</sup> Jean-François Korobelnik, MD,<sup>3</sup> David M. Brown, MD,<sup>4</sup> Victor Chong, MD,<sup>5</sup> Quan Dong Nguyen, MD,<sup>6</sup> Allen C. Ho, MD,<sup>7</sup> Yuichiro Ogura, MD,<sup>8</sup> Christian Simader, MD,<sup>1</sup> Glenn J. Jaffe, MD,<sup>9</sup> Jason S. Slakter, MD,<sup>10</sup> George D. Yancopoulos, MD, PhD,<sup>11</sup> Neil Stahl, PhD,<sup>11</sup> Robert Vitti, MD,<sup>11</sup> Alyson J. Berliner, MD, PhD,<sup>11</sup> Yuhwen Soo, PhD,<sup>11</sup> Majid Anderesi, MD,<sup>12</sup> Olaf Sowade, MD,<sup>12</sup> Oliver Zeitz, MD,<sup>12,13</sup> Christiane Norenberg, MS,<sup>12</sup> Rupert Sandbrink, MD, PhD,<sup>12,14</sup> Jeffrey S. Heier, MD<sup>15</sup>

**Purpose:** To determine efficacy and safety of intravitreal aflibercept in patients with neovascular age-related macular degeneration (AMD) during a second year of variable dosing after a first-year fixed-dosing period.

**Design:** Two randomized, double-masked, active-controlled, phase 3 trials.

**Participants:** Two thousand four hundred fifty-seven patients with neovascular AMD.

**Methods:** From baseline to week 52, patients received 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections. During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks.

**Main Outcome Measures:** Proportion of eyes at week 96 that maintained best-corrected visual acuity (BCVA; lost <15 letters from baseline); change from baseline in BCVA.

**Results:** Proportions of eyes maintaining BCVA across treatments were 94.4% to 96.1% at week 52 and 91.5% to 92.4% at week 96. Mean BCVA gains were 8.3 to 9.3 letters at week 52 and 6.6 to 7.9 letters at week 96. Proportions of eyes without retinal fluid decreased from week 52 (60.3% to 72.4%) to week 96 (44.6% to 54.4%), and more 2q4 eyes were without fluid at weeks 52 and 96 than Rq4 eyes (difference of 10.4% [95% confidence interval {CI}, 4.9–15.9] and 9.0% [95% CI, 3.0–15.1]). Patients received on average 16.5, 16.0, 16.2, and 11.2 injections over 96 weeks and 4.7, 4.1, 4.6, and 4.2 injections during weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. The number of injections during weeks 52 through 96 was lower in the 2q4 and 2q8 groups versus the Rq4 group (differences of  $-0.64$  [95% CI,  $-0.89$  to  $-0.40$ ] and  $-0.55$  [95% CI,  $-0.79$  to  $-0.30$ ];  $P < 0.0001$ , post hoc analysis). Incidences of Antiplatelet Trialists' Collaboration–defined arterial thromboembolic events were similar across group (2.4% to 3.8%) from baseline to week 96.

**Conclusions:** All aflibercept and ranibizumab group were equally effective in improving BCVA and preventing BCVA loss at 96 weeks. The 2q8 aflibercept group was similar to ranibizumab in visual acuity outcomes during 96 weeks, but with an average of 5 fewer injections. Small losses at 96 weeks in the visual and anatomic gains seen at 52 weeks in all arms were in the range of losses commonly observed with variable dosing.

**Financial Disclosure(s):** Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2013; ■:1–9 © 2013 by the American Academy of Ophthalmology.



The introduction of antiangiogenic therapy to treat neovascular age-related macular degeneration (AMD) has vastly changed common paradigms in this important entity usually referred to as “the leading cause of legal blindness in the developed world.”<sup>1</sup> The prospective, masked, randomized, pivotal trials for ranibizumab, called the Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal

Neovascularization in AMD (ANCHOR) and the Minimally Classic/Occlud Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), showed clear superiority of monthly intravitreal ranibizumab administration compared with sham or with the previous gold standard, photodynamic therapy.<sup>2,3</sup> After approval in 2006 to treat neovascular AMD, intravitreal ranibizumab was embraced quickly by the ophthalmic

community. Odds for visual acuity loss resulting from neovascular AMD markedly decreased with fixed monthly ranibizumab therapy.<sup>4</sup> Thus, this monthly treatment regimen was included in the ranibizumab Food and Drug Administration label.

Although the visual results in the clinical trials were excellent with the monthly dosing regimens, in clinical practice, the repetitive office visits and injections represent an overwhelming management challenge for patients and their families. Evaluations of actual treatment patterns revealed that most patients were examined and treated far less frequently than recommended by the results of the studies, leading to inferior outcomes.<sup>5,6</sup> Undertreatment prevents patients from optimally benefitting from one of the major therapeutic breakthroughs in ophthalmology.

To reduce the treatment burden and still conform to a structured regimen, treatment intervals were expanded in studies such as the Phase IIIB, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Patients with AMD-Related Subfoveal Choroidal Neovascularization (CNV), with or without Classic CNV(PIER), and the Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-Related Macular Degeneration (EXCITE).<sup>7,8</sup> However, the visual acuity benefit of ranibizumab therapy was reduced markedly when treatment intervals were increased up to 3 months. It was recognized that treatment of recurrence had to take place in a timely manner to prevent functional loss.

Pro re nata (PRN) treatment, or treatment as needed, was evaluated first in the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab (PRONTO) study, a small, single-center, carefully monitored investigator-driven trial.<sup>9</sup> Physicians used an optical coherence tomography (OCT)-guided variable-dosing regimen with intravitreal ranibizumab and achieved outcomes comparable with those observed in the phase 3 clinical studies, which used a fixed monthly monitoring and dosing regimen. In contrast, the Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON) trial, a PRN extension trial after monthly ranibizumab for 2 years, reported that the initial benefit achieved by 2 years of monthly retreatment was lost progressively when switching to a PRN treatment paradigm.<sup>10</sup>

The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) group subsequently designed a large, multicenter, prospective, randomized trial that compared a fixed monthly regimen with a flexible as-needed regimen using the 2 most commonly used anti-VEGF therapies, ranibizumab and bevacizumab.<sup>11</sup> Unlike the PRONTO study,<sup>9</sup> the indication for retreatment in the CATT study was focused strictly on the presence of fluid on OCT, rather than on overall retinal thickness changes; injection was indicated whenever intraretinal, subretinal, or sub-retinal pigment epithelium fluid was identified during monthly OCT monitoring. Although the primary outcome showed noninferiority between ranibizumab and bevacizumab when administered according to similar

regimens, the visual acuity gains and morphologic improvement were greater for the monthly groups as compared with the as-needed groups, especially in year 2.<sup>11</sup> To achieve these results, the total number of injections in the as-needed ranibizumab and bevacizumab arms was high: 6.9 and 7.7 injections over the first year and 12.6 and 14.1 injections over 2 years, respectively, with monthly monitoring visits. It is also important to note that the bevacizumab as-needed group did not meet the noninferiority criteria with an as-needed dosing schedule.<sup>12</sup>

Intravitreal aflibercept, a fusion protein of key domains from human VEGF receptors 1 and 2 with the constant region (Fc) of human immunoglobulin G, recently was approved for the treatment of neovascular AMD.<sup>13</sup> As a designed molecule featuring optimal pharmacologic characteristics to inhibit intraocular VEGF, intravitreal aflibercept injection offers improved binding affinity and superior pharmacokinetics in an iso-osmotic formulation.<sup>14,15</sup>

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and 2) studies were the largest controlled trials of anti-VEGF agents in AMD ever performed, recruiting more than 2400 patients with treatment-naïve neovascular AMD from more than 360 centers worldwide.<sup>16</sup> The focus of the trials was to compare the standard of care (ranibizumab 0.5 mg at monthly intervals) with 2 doses (2 and 0.5 mg) of intravitreal aflibercept and 2 regimens (monthly and every 2 months after 3 initial monthly doses). All intravitreal aflibercept groups were clinically equivalent to monthly ranibizumab in maintaining visual acuity at week 52.<sup>16</sup> This result also was true when drug was administered every 2 months, which allowed a substantially reduced monitoring and treatment frequency, and thus introduced a novel treatment strategy to manage neovascular AMD.<sup>16</sup>

After the 52-week primary end point, a follow-up phase of the VIEW trials, up to 96 weeks, was based on a protocol that required a switch of all regimens from the fixed monthly or every 2 months regimen to a variable regimen requiring at least quarterly dosing (capped PRN); interim injections were allowed based on an assessment of anatomic and visual parameters. The aim of the current study was to investigate the safety and efficacy of an extended treatment interval after 1 year of rigorously scheduled fixed treatments. The 96-week data for the integrated VIEW studies describing characteristics and outcomes of a variable dosing regimen are presented and discussed in this article.

## Methods

### Design

The VIEW 1 and 2 studies were 2 similarly designed randomized, double-masked, active-controlled, parallel-group, multicenter, 96-week phase 3 trials comparing the efficacy and safety of intravitreal aflibercept and ranibizumab in patients with neovascular AMD.<sup>16</sup> The VIEW 1 study was carried out from July 2007 through July 2011 in the United States and Canada, and the VIEW 2 study was carried out from April 2008 through August 2011 in Europe, the Middle East, the Asia-Pacific region, and

Latin America. Patients were screened and/or randomized at 362 sites in the VIEW studies. Each institutional review board or ethics committee approved the study protocols. Both trials were registered with [ClinicalTrials.gov](http://ClinicalTrials.gov) (identifier nos. NCT00509795 and NCT00637377), and all patients signed a written consent form before initiation of the study-specific procedures. The VIEW 1 and 2 studies were conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki.

The design of VIEW studies has been described previously.<sup>16</sup> In brief, patients 50 years of age and older with active, subfoveal, CNV lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to neovascular AMD were eligible for enrollment if CNV made up at least 50% of total lesion size and BCVA was between 25 and 73 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/320–20/40 Snellen equivalent). Only 1 eye from each patient was included in the study. Patients were randomized in a 1:1:1:1 ratio to receive 1 of the following 4 regimens in the study eye for the first 52 weeks: (1) 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), (2) 2 mg intravitreal aflibercept every 4 weeks (2q4), (3) 0.5 mg intravitreal aflibercept every 4 weeks (0.5q4), and (4) 2 mg intravitreal aflibercept every 8 weeks (2q8) after 3 initial monthly injections. During the follow-up period from weeks 52 to 96, patients continued to receive the same dose of study drugs as in the first 52 weeks, but received injections at least every 12 weeks, with monthly evaluations for interim injections based on prespecified retreatment criteria (mandatory quarterly dosing with examination-guided interim injections or capped-PRN). Criteria for retreatment were new or persistent fluid on OCT, an increase in central retinal thickness of 100  $\mu$ m or more compared with the lowest previous value, loss of 5 ETDRS letters or more from the best previous score in conjunction with recurrent fluid on OCT, new-onset classic neovascularization, new or persistent leak on fluorescein angiography, new macular hemorrhage, or a time lapse of 12 weeks since the previous injection.

## Outcome Measures

The primary efficacy end point of the VIEW 1 and VIEW 2 studies was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining visual acuity (losing <15 ETDRS letters) at week 52.<sup>16</sup> Prespecified secondary efficacy end points compared the change among treatment groups in visual acuity and anatomic outcomes from baseline to week 52.<sup>16</sup> Prespecified primary and secondary efficacy outcomes of the VIEW 1 and VIEW 2 studies at week 52 have been reported previously.<sup>16</sup> Efficacy end points evaluated after week 52 all were exploratory and included the proportion of patients maintaining visual acuity (losing <15 ETDRS letters), the mean change in BCVA from baseline, the proportion of patients gaining 15 letters or more, mean change from baseline CNV size, and the proportion of patients without retinal fluid at week 96. The mean change in central retinal thickness also was determined from baseline through week 96. Additional end points during the exploratory follow-up phase were the number of study drug injections and the proportion of patients receiving fewer than 6 injections and 6 injections or more between weeks 52 and 96.

Patients were evaluated for BCVA at screening, at the day of treatment initiation, and every 4 weeks thereafter through week 96, as well as 1 week after the first treatment for safety reasons. In the VIEW 1 study, OCT was performed at screening, at the day of treatment initiation, and at weeks 4, 12, 24, 36, and 52 and every 4 weeks thereafter through week 96. In the VIEW 2 study, OCT was performed at every visit. The OCT images were obtained with

a time-domain Stratus instrument (Carl Zeiss Meditec, Dublin, CA) and was evaluated by an independent central reading center (VIEW 1, Duke Reading Center, Durham, NC; VIEW 2, Vienna Reading Center, Vienna, Austria). Fundus photography and fluorescein angiography were performed at screening and at weeks 24, 52, 72, and 96, and the results were evaluated by an independent central reading center (Digital Angiography Reading Center, New York, NY). Areas of visible active CNV (classic, occult, or both) were identified when angiographic analyses showed evidence of visible neovascular tissue accompanied by late leakage or pooling of dye.

## Statistical Analysis

Data from the VIEW 1 and VIEW 2 studies were pooled for the purpose of presentation in this report. The proportion of patients maintaining visual acuity (losing <15 ETDRS letters) at week 52 was analyzed in the per-protocol set as defined previously.<sup>16</sup> The proportion of patients maintaining visual acuity (losing <15 ETDRS letters) at week 96 was analyzed in the full analysis set, which included all randomized patients who received any study medication and had a baseline BCVA measurement and at least 1 BCVA assessment after baseline. All other visual and anatomic end points were analyzed in the full analysis set. The last-observation-carried-forward approach was used to impute missing data. Safety end points at weeks 52 and 96 were analyzed in the safety analysis set, which included all patients who received any study medication. Treatment experience over the 2 years of study was analyzed in the safety analysis set. Treatment experience in the second year was analyzed in patients who completed study treatments. Between-group differences in the number of injections from weeks 52 to 96 were analyzed with an analysis of variance in a post hoc analysis.

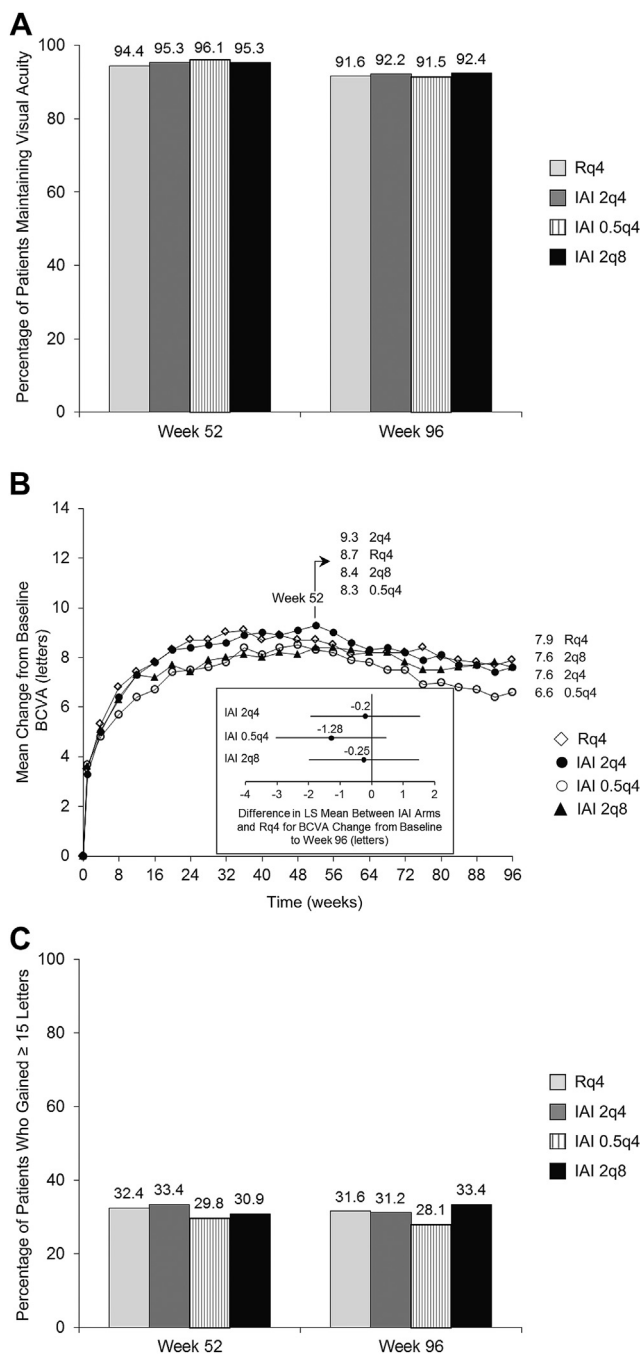
## Results

### Patient Disposition and Baseline Characteristics

The VIEW 1 and 2 studies randomized a total of 2457 patients; 2419 (98.5%) patients received at least 1 dose of study medication, and 2245 (91.4%) patients completed 52 weeks of study. A total of 2235 (91.0%) patients entered the second year, and 2063 (84.0%) patients completed 96 weeks of study. The percentage of patients completing the study was similar among treatment groups at both weeks 52 and 96 (Table 1, available at <http://aaojournal.org>). Reasons for discontinuation before week 96 included consent withdrawal occurring in 5.0% to 6.5% of patients and adverse events occurring in 2.6% to 4.9% of patients across treatment groups (Table 1, available at <http://aaojournal.org>). Baseline demographics and disease characteristics were evenly balanced among all treatment groups (Table 2).

### Efficacy

The proportion of patients maintaining visual acuity ranged from 94.4% to 96.1% at week 52 (Fig 1A). Both monthly and every 2 months intravitreal aflibercept regimens were statistically noninferior (with a margin within 5%) to monthly ranibizumab at week 52 (mean of Rq4 minus intravitreal aflibercept,  $-0.9%$  [95% confidence interval (CI),  $-3.5$  to  $1.7$ ] for 2q4;  $-1.7%$  [95% CI,  $-4.2$  to  $0.9$ ] for 0.5q4; and  $-0.9%$  [95% CI,  $-3.5$  to  $1.7$ ] for 2q8). Largely similar proportions of patients (91.5% to 92.4%) maintained visual acuity across all treatment groups at week 96 (Fig 1A). The mean increase in BCVA from baseline was largely similar among treatment groups throughout the 96 weeks of the study (Fig 1B). At week 96, the mean BCVA gains were 7.9 letters, 7.6 letters, 6.6 letters, and 7.6 letters in the Rq4,



**Figure 1.** Graphs showing visual acuity outcomes in the total study cohort. **A**, Proportion of patients maintaining visual acuity (losing  $<15$  Early Treatment Diabetic Retinopathy Study letters). Per-protocol and full analysis sets were used for weeks 52 and 96, respectively. At week 52,  $n = 538$ ,  $n = 559$ ,  $n = 538$ , and  $n = 535$  for Rq4, 2q4, 0.5q4, and 2q8, respectively. At week 96,  $n = 595$ ,  $n = 613$ ,  $n = 597$ , and  $n = 607$  for Rq4, 2q4, 0.5q4, and 2q8, respectively. **B**, Mean change from baseline best-corrected visual acuity (BCVA). The inset shows the difference in least square (LS) mean (with 95% confidence interval) between intravitreal aflibercept arms and ranibizumab (aflibercept minus ranibizumab) for BCVA change from baseline to week 96, full analysis set. **C**, Proportion of patients who gained 15 letters or more, full analysis set. At weeks 52 and 96,  $n = 595$ ,  $n = 613$ ,  $n = 597$ , and  $n = 607$  for Rq4, 2q4, 0.5q4, and 2q8, respectively. Missing values were imputed using the

2q4, 0.5q4, and 2q8 groups, respectively; these gains represented a 1- to 2-letter loss in all groups during the capped PRN (modified quarterly dosing) phase, compared with the gains observed at week 52 (8.7, 9.3, 8.3, and 8.4 letters, respectively). Overall, 29.8% to 33.4% of patients in all treatment groups gained 15 letters or more from baseline to week 52 (Fig 1C). The proportions of patients who gained 15 letters or more from baseline to week 96 were similar and ranged from 28.1% to 33.4% (Fig 1C). Across treatment groups, largely similar proportions of patients had a BCVA of 20/40 or better or had an improvement from baseline BCVA of 0 letters or more, 10 letters or more, and 30 letters or more at weeks 52 and 96 (Table 3, available at <http://aoajournal.org>).

During the capped PRN phase (requiring at least quarterly dosing), there was a minor loss in the anatomic improvements that had been seen at week 52. At week 96, patients had an average increase in central retinal thickness of 10  $\mu\text{m}$ , 10  $\mu\text{m}$ , 10  $\mu\text{m}$ , and 6  $\mu\text{m}$  from week 52 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively (Fig 2A). The proportion of patients with no retinal fluid on time-domain OCT (observed cases) ranged from 60.3% to 72.4% at week 52, with higher percentages of 2q4 and 2q8 patients having no retinal fluid compared with Rq4 patients (mean of aflibercept minus Rq4, 10.4% [95% CI, 4.9–15.9] for 2q4 and 5.7% [95% CI, 0–11.4] for 2q8). The percentage of patients with no retinal fluid decreased from week 52 to week 96 in all treatment groups. Nevertheless, a higher percentage of 2q4 patients had no retinal fluid at week 96 compared with Rq4 patients (mean of 2q4 minus Rq4, 9.0% [95% CI, 3.0–15.1]; Fig 2B). In contrast, the mean decreases in CNV area were maintained from week 52 (range, 3.9–5.3  $\text{mm}^2$ ) to week 96 (range, 3.7–5.1  $\text{mm}^2$ ) in all treatment groups. A lower CNV area observed at week 52 for 2q4 in comparison with Rq4 (least squares mean of 2q4 minus Rq4,  $-0.74 \text{ mm}^2$  [95% CI,  $-1.27$  to  $-0.21$ ]), but was not maintained at week 96.

## Number of Injections

The mean number of injections from week 0 to week 96 was 16.5 (standard deviation [SD], 3.7), 16.0 (SD, 3.2), 16.2 (SD, 4.0), and 11.2 (SD, 2.9) in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. The mean number of injections from week 52 to week 96 was 4.7 (SD, 2.2), 4.1 (SD, 1.8), 4.6 (SD, 2.2), and 4.2 (SD, 1.7) in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. In a post hoc analysis, this number of injections from week 52 to week 96 was lower in the 2q4 and 2q8 groups versus the Rq4 group: mean of aflibercept minus Rq4,  $-0.64$  (95% CI,  $-0.89$  to  $-0.40$ ) for 2q4 and  $-0.55$  (95% CI,  $-0.79$  to  $-0.30$ ) for 2q8 ( $P < 0.0001$  for both). The proportion of patients who received fewer than 6 injections and 6 injections or more during weeks 52 to 96 are shown in Figure 3A. Overall, higher percentages of 2q4 and 2q8 patients received fewer than 6 injections compared with Rq4 patients, whereas a higher percentage of Rq4 patients received 6 injections or more compared with 2q4 and 2q8 patients (Fig 3A, B).

## Safety

Safety profiles of both intravitreal aflibercept and ranibizumab were favorable. Ocular adverse events occurring in 10% or more of

last-observation-carried-forward method in (A), (B), and (C). The outcomes for the aflibercept and ranibizumab groups were similar in (A), (B), and (C) at both weeks 52 and 96. IAI = intravitreal aflibercept injection; Rq4 = 0.5-mg intravitreal ranibizumab every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q4 = 0.5 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 3 initial monthly injections.



Table 2. Patient Demographics and Baseline Characteristics, Full Analysis Set

	0.5 mg Intravitreal Ranibizumab Every 4 Weeks (n = 595)	Intravitreal Aflibercept Injection 2 mg Every 4 Weeks (n = 613)	Intravitreal Aflibercept Injection 0.5 mg Every 4 Weeks (n = 597)	Intravitreal Aflibercept Injection 2 mg Every 8 Weeks after 3 Initial Monthly Injections (n = 607)
Female, n (%)	341 (57.3)	370 (60.4)	314 (52.6)	353 (58.2)
Race, n (%)				
White	509 (85.5)	521 (85.0)	510 (85.4)	504 (83.0)
Asian	60 (10.1)	70 (11.4)	66 (11.1)	73 (12.0)
Other*	26 (4.4)	22 (3.6)	21 (3.5)	30 (5.0)
Age (SD), yrs	75.6 (8.7)	75.9 (8.4)	76.5 (8.5)	75.8 (8.8)
BCVA (SD), letters	53.9 (13.4)	54.0 (13.6)	53.6 (13.8)	53.6 (13.5)
Central retinal thickness (SD), $\mu\text{m}$	296 (123) <sup>†</sup>	299 (126) <sup>‡</sup>	296 (132) <sup>†</sup>	306 (134) <sup>§</sup>
Area of CNV (SD), $\text{mm}^2$	7.1 (5.3) <sup>  </sup>	7.4 (5.5) <sup>¶</sup>	7.1 (4.9) <sup>¶</sup>	7.2 (5.4)**
Type of CNV, n (%)				
Minimally classic	205 (34.5)	217 (35.4)	200 (33.5)	216 (35.6)
Occult	231 (38.8)	233 (38.0)	234 (39.2)	228 (37.6)
Predominantly classic	152 (25.5)	159 (25.9)	161 (27.0)	159 (26.2)
Missing	7 (1.2)	4 (0.7)	2 (0.3)	4 (0.7)
Total lesion size (SD), $\text{mm}^2$	7.5 (5.6) <sup>  </sup>	7.9 (5.8) <sup>¶</sup>	7.5 (5.2) <sup>¶</sup>	7.6 (5.6)**
Total NEI VFQ score (SD)	72.4 (18.1) <sup>†</sup>	70.3 (18.1) <sup>††</sup>	72.6 (18.0) <sup>‡‡</sup>	70.4 (18.0) <sup>§§</sup>

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; NEI VFQ = National Eye Institute Visual Function Questionnaire; SD = standard deviation.

\*Included American Indian or Alaska Native, Black or African American, Native Hawaiian or other Pacific Islander, multiracial patients, and those who did not report their race.

<sup>†</sup>n = 594.

<sup>‡</sup>n = 611.

<sup>§</sup>n = 603.

<sup>||</sup>n = 589.

<sup>¶</sup>n = 610.

<sup>¶</sup>n = 596.

\*\*n = 605.

<sup>††</sup>n = 609.

<sup>‡‡</sup>n = 592.

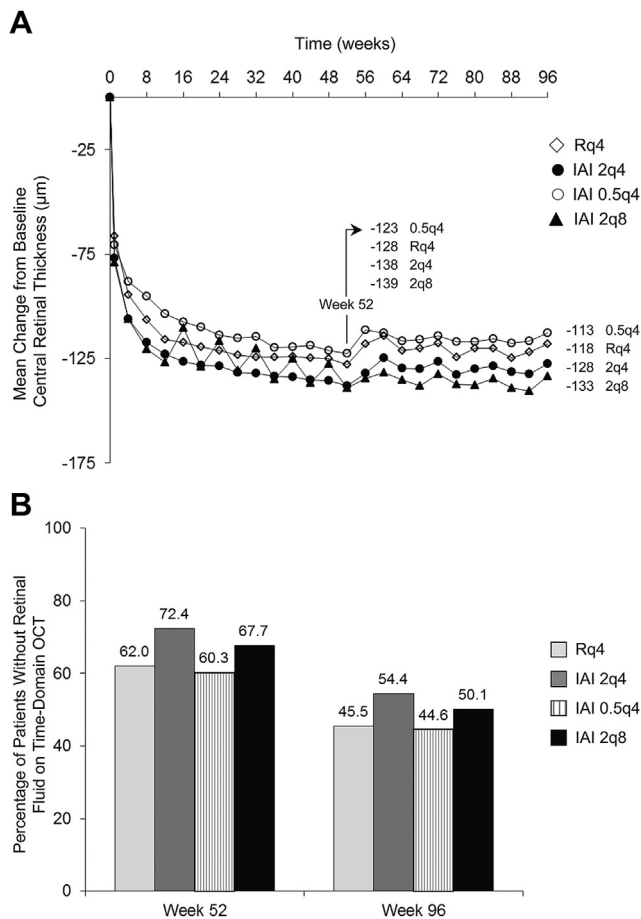
<sup>§§</sup>n = 599.

patients across treatment groups were conjunctival hemorrhage (range, 21.7%–28.1%) and eye pain (range, 7.0%–10.8%) from baseline to week 52, and conjunctival hemorrhage (range, 23.7%–29.9%), retinal hemorrhage (range, 13.6%–16.2%), reduced visual acuity (range, 11.3%–13.0%), eye pain (range, 8.9%–12.1%), vitreous detachment (range, 7.7%–10.0%), and increased intraocular pressure (range, 6.2%–10.8%) from baseline to week 96. Any intraocular inflammatory response (predefined adverse event of interest) was reported in 0.8%, 0.7%, 0.3%, and 0.2% of patients from baseline to week 52 and in 1.5%, 1.1%, 0.8%, and 0.5% of patients from baseline to week 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. Serious ocular adverse events were infrequent and occurred with a similar rate across all treatment groups (Table 4). Major serious systemic adverse events were fall and pneumonia from baseline to week 52, and fall, pneumonia, atrial fibrillation, and myocardial infarction from baseline to week 96 (Table 5, available at <http://aaojournal.org>). In general, serious systemic adverse events were typical of those reported in this population of elderly patients who receive intravitreal treatment for neovascular AMD. The incidence of arterial thromboembolic events as defined by the Antiplatelet Trialists' Collaboration criteria was similar among treatment groups from both baseline to week 52 and from baseline to week 96 (Table 6). The percentage of deaths was 1.2%, 0.7%, 0.5%, and 1.5% from baseline to week 52 and 2.7%, 2.1%, 3.2%, and 3.3% from baseline to week 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups,

respectively. The incidences and patterns of deaths were not different among treatment groups.

## Discussion

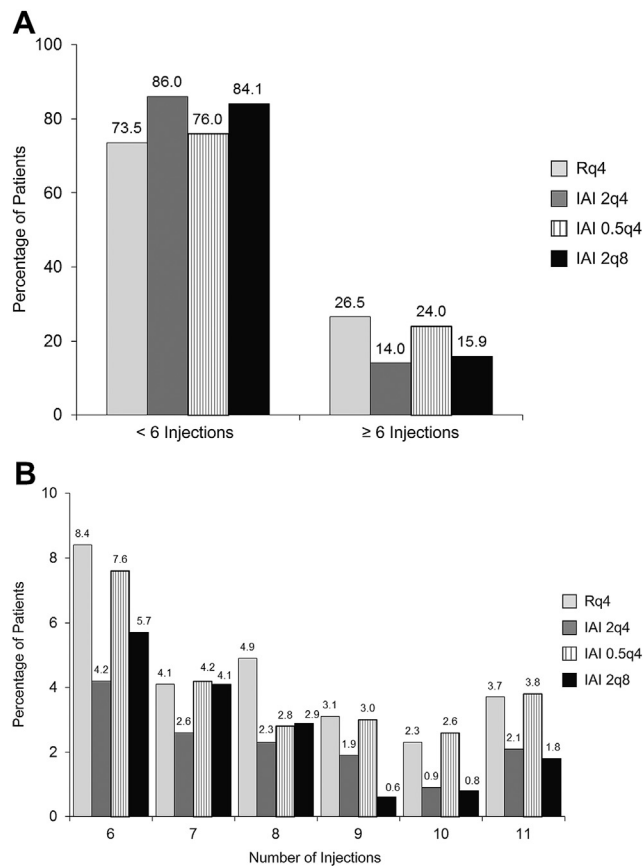
The results from the follow-up regimen of mandatory quarterly dosing with intervening as-needed injections (capped PRN) in the second year of the VIEW studies confirm the sustained improvements in visual acuity, central retinal thickness, and CNV size achieved by fixed dosing regimens of intravitreal aflibercept and ranibizumab during the first year.<sup>16</sup> All intravitreal aflibercept regimens were as effective as ranibizumab in increasing visual acuity and reducing retinal thickness and CNV size over 2 years of the VIEW studies. Small decreases in visual and anatomic improvements from week 52 to 96 were observed in all treatment groups, similar to declines seen in other randomized clinical trials when switching to treatment regimens with a variable component.<sup>11</sup> Of note was a decrease in the proportion of patients with no retinal fluid from week 52 to 96 after switching to a more variable dosing regimen in all treatment groups. Nevertheless, more patients in the 2q4 group had no



**Figure 2.** Graphs showing anatomic outcomes in total study cohort. **A**, Mean change from baseline central retinal thickness, full analysis set. Missing values were imputed using the last-observation-carried-forward method. The outcomes for the aflibercept and ranibizumab groups were similar at both weeks 52 and 96. **B**, Proportion of patients without fluid on time-domain optical coherence tomography (OCT) images. Observed values in full analysis set. Number of patients included in the Rq4, 2q4, 0.5q4, and 2q8 groups were 537, 558, 527, and 539 at week 52, and 508, 522, 493, and 505 at week 96, respectively. IAI = intravitreal aflibercept injection; Rq4 = 0.5-mg intravitreal ranibizumab every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q4 = 0.5 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 3 initial monthly injections.

retinal fluid at week 96, as did both the 2q4 and 2q8 groups at week 52, compared with the Rq4 group. Subtle decreases in the visual and anatomic improvements from week 52 to 96 are likely the result of the variable dosing regimen used. A fixed dosing regimen may provide predictable visual and anatomic outcomes and may mitigate loss of visual and anatomic improvements.

Patients in the 2q8 group achieved visual and anatomic improvements similar to those in the Rq4 and 2q4 groups, but with a mean of 5 fewer injections over 2 years. The significantly fewer average number of injections (post hoc analysis) in the follow-up phase in both 2q4 and 2q8 groups compared with the Rq4 group was driven by more patients in the Rq4 arm receiving the most intense therapy ( $\geq 6$  injections; 14.0% and 15.9% vs. 26.5%, respectively). These findings suggest that patients with greater disease



**Figure 3.** Graphs showing proportion of patients by the number of injections during weeks 52 to 96. **A**, Percentages of patients who received fewer than 6 injections and 6 or more injections. **B**, Percentage of patients who received 6 to 11 injections. The maximum number of injections was 11 in all treatment groups. Patients who completed the second year follow-up phase medications were included in the analyses shown in (A) and (B). Number of patients included in the Rq4, 2q4, 0.5q4, and 2q8 groups were 513, 529, 499, and 511, respectively, in (A) and (B). IAI = intravitreal aflibercept injection; Rq4 = 0.5-mg intravitreal ranibizumab every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q4 = 0.5 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 3 initial monthly injections.

activity may require fewer injections using intravitreal aflibercept.

Over the 2 years of treatment, a generally favorable safety profile was observed for both intravitreal aflibercept and ranibizumab. No unexpected safety signals were observed with intravitreal aflibercept. The incidence of ocular treatment-emergent adverse events was balanced across all treatment groups, with the most frequent events associated with the injection procedure, the underlying disease, the aging process, or a combination thereof. The incidences of arterial thromboembolic events and death were similar across all treatment groups.

At the time the VIEW studies were designed, the efficacy of variable regimens of anti-VEGF agents was being evaluated as a recommended standard of care in several studies. Current clinical evidence shows that variable regimens, which are unpredictable and require monthly monitoring, are less effective to maintain visual and anatomic

Table 4. Serious Ocular Adverse Events in the Study Eye Occurring in More Than 1 Patient in Any Treatment Group, Safety Analysis Set

Serious Adverse Event	Baseline to Week 52				Baseline to Week 96			
	0.5 mg Intravitreal Ranibizumab Every 4 Weeks (n = 595)	2 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 613)	0.5 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 601)	2 mg Intravitreal Aflibercept Injection Every 8 Weeks after 3 Initial Monthly Injections (n = 610)	0.5 mg Intravitreal Ranibizumab Every 4 Weeks (n = 595)	2 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 613)	0.5 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 601)	2 mg Intravitreal Aflibercept Injection Every 8 Weeks after 3 Initial Monthly Injections (n = 610)
Total patients with at least 1 ocular SAE, n (%)	19 (3.2)	13 (2.1)	11 (1.8)	12 (2.0)	26 (4.4)	22 (3.6)	19 (3.2)	24 (3.9)
Macular hole	0	0	2 (0.3)	0	0	0	2 (0.3)	0
Posterior capsule opacification	2 (0.3)	0	0	0	2 (0.3)	0	0	0
Retinal detachment	1 (0.2)	0	2 (0.3)	0	3 (0.5)	1 (0.2)	2 (0.3)	0
Retinal hemorrhage	3 (0.5)	2 (0.3)	1 (0.2)	3 (0.5)	4 (0.7)	3 (0.5)	5 (0.8)	5 (0.8)
Retinal pigment epithelial tear	1 (0.2)	0	1 (0.2)	2 (0.3)	1 (0.2)	0	1 (0.2)	3 (0.5)
Reduced visual acuity	3 (0.5)	2 (0.3)	3 (0.5)	5 (0.8)	5 (0.8)	4 (0.7)	3 (0.5)	7 (1.1)
Endophthalmitis	3 (0.5)	3 (0.5)	0	0	5 (0.8)	4 (0.7)	1 (0.2)	0
Cataract	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	4 (0.7)	3 (0.5)	4 (0.7)
Macular degeneration	0	0	0	1 (0.2)	0	0	0	2 (0.3)
Increased intraocular pressure	1 (0.2)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	1 (0.2)	2 (0.3)

SAE = serious adverse event.

improvements gained by fixed dosing regimens. Debate continues as to whether the losses in visual acuity are offset by the reductions in treatment and monitoring burden, especially if monitoring is not maintained at the monthly frequency mandated in our study and in the CATT study. Proponents of the treat-and-extend regimen, a treatment

strategy involving gradual extension of the treatment and monitoring intervals after initial treating monthly until the macula is dry, suggest that this regimen may result in visual acuity outcomes similar to those seen with monthly therapy, but this has not been demonstrated in a large, randomized clinical trial.<sup>17,18</sup> The 1-year outcomes of the VIEW studies

Table 6. Antiplatelet Trialists' Collaboration-Defined Arterial Thromboembolic Events, Safety Analysis Set

Any APTC event, n (%)	Baseline to Week 52					Baseline to Week 96				
	0.5 mg Intravitreal Ranibizumab Every 4 Weeks (n = 595)	2 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 613)	0.5 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 601)	2 mg Intravitreal Aflibercept Injection Every 8 Weeks after 3 Initial Monthly Injections (n = 610)	All Intravitreal Aflibercept Injections (n = 1824)	0.5 mg Intravitreal Ranibizumab Every 4 Weeks (n = 595)	2 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 613)	0.5 mg Intravitreal Aflibercept Injection Every 4 Weeks (n = 601)	2 mg Intravitreal Aflibercept Injection Every 8 Weeks after 3 Initial Monthly Injections (n = 610)	All Intravitreal Aflibercept Injections (n = 1824)
Any APTC event, n (%)	9 (1.5)	6 (1.0)	12 (2.0)	14 (2.3)	32 (1.8)	19 (3.2)	15 (2.4)	23 (3.8)	22 (3.6)	60 (3.3)
Nonfatal MI	6 (1.0)	3 (0.5)	6 (1.0)	6 (1.0)	15 (0.8)	12 (2.0)	6 (1.0)	12 (2.0)	7 (1.1)	25 (1.4)
Nonfatal stroke	1 (0.2)	2 (0.3)	3 (0.5)	3 (0.5)	8 (0.4)	5 (0.8)	5 (0.8)	3 (0.5)	5 (0.8)	13 (0.7)
Vascular death	2 (0.3)	1 (0.2)	3 (0.5)	5 (0.8)	9 (0.5)	3 (0.5)	5 (0.8)	8 (1.3)	11 (1.8)	24 (1.3)

APTC = Antiplatelet Trialists' Collaboration; MI = myocardial infarction.

demonstrate that the average patient can obtain results clinically equivalent to monthly ranibizumab with 2 mg intravitreal aflibercept administered every 8 weeks after 3 initial monthly injections.<sup>16</sup> It is conceivable that a continuation of the every-2-months fixed-dosing regimen using intravitreal aflibercept into the second year would have maintained more effectively the visual and anatomic improvements achieved during the first year. Such a fixed-dosing regimen thus would allow for better outcomes with a substantially lower number of monitoring visits. In addition, a fixed, every-2-months dosing regimen with aflibercept (requiring 5 injections) would approximate the 4.2 injections given with the capped PRN (modified quarterly dosing) regimen in the second year of the VIEW studies. Future studies may shed additional light on the benefit of continuing with an every-2-months fixed-dosing regimen instead of using variable dosing regimens.

**Acknowledgments.** The authors thank Hadi Moini, PhD, and S. Balachandra Dass, PhD, of Regeneron Pharmaceuticals, Inc, for editorial and administrative assistance to the authors who wrote the manuscript.

## References

1. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122:477–85.
2. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–44.
3. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–31.
4. Bressler NM, Doan QV, Varma R, et al. Estimated cases of legal blindness and visual impairment avoided using ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. *Arch Ophthalmol* 2011;129:709–17.
5. Cohen SY, Dubois L, Tadayoni R, et al. Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. *Am J Ophthalmol* 2009;148:409–13.
6. Dadgostar H, Ventura AA, Chung JY, et al. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology* 2009;116:1740–7.
7. Regillo CD, Brown DM, Abraham P, et al; PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol* 2008;145:239–48.
8. Schmidt-Erfurth U, Eldem B, Guymer R, et al; EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology* 2011;118:831–9.
9. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO study. *Am J Ophthalmol* 2009;148:43–58.
10. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2012;119:1175–83.
11. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388–98.
12. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364:1897–908.
13. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012;15:171–85.
14. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A* 2002;99:11393–8.
15. Stewart MW, Rosenfeld PJ, Penha FM, et al. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina* 2012;32:434–57.
16. Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119:2537–48.
17. Engelbert M, Zweifel SA, Freund KB. Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified “treat and extend” dosing regimen of intravitreal antivascular endothelial growth factor therapy. *Retina* 2010;30:1368–75.
18. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;117:2134–40.

## Footnotes and Financial Disclosures

Originally received: May 15, 2013.

Final revision: July 18, 2013.

Accepted: August 8, 2013.

Available online: ■■■■.

Manuscript no. 2013-782.

<sup>1</sup> Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

<sup>2</sup> Department of Ophthalmology, Cole Eye Institute, Cleveland, Ohio.

<sup>3</sup> Department of Ophthalmology, Centre Hospitalier Universitaire de Bordeaux, Université Bordeaux 2, Bordeaux, France.

<sup>4</sup> Retina Consultants of Houston, Houston, Texas.

<sup>5</sup> Oxford Eye Hospital, University of Oxford, Oxford, United Kingdom.

<sup>6</sup> Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland.

<sup>7</sup> Wills Eye Hospital and Mid Atlantic Retina, Philadelphia, Pennsylvania.

<sup>8</sup> Department of Ophthalmology, Nagoya City University, Nagoya, Japan.

<sup>9</sup> Department of Ophthalmology, Duke University, Durham, North Carolina.

<sup>10</sup> Vitreous-Retina-Macula Consultants of New York, New York, New York.

<sup>11</sup> Regeneron Pharmaceuticals, Inc, Tarrytown, New York.

<sup>12</sup> Bayer HealthCare, Berlin, Germany.

<sup>13</sup> Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Augenheilkunde, Hamburg, Germany.



<sup>14</sup> Department of Neurology, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany.

<sup>15</sup> Ophthalmic Consultants of Boston and Tufts University School of Medicine, Boston, Massachusetts.

Presented at: American Academy of Ophthalmology Annual Meeting, November 2012.

#### Financial Disclosure(s):

The author(s) have made the following disclosure(s): Ursula Schmidt-Erfurth: Consultant – Bayer HealthCare, Alcon, Allergan, Boehringer, Novartis; Financial support – Bayer HealthCare; Advisory board – Alcon, Allergan, Boehringer, Novartis; Lecturer – Alcon, Allergan, Boehringer, Novartis

Peter K. Kaiser: Consultant – Alcon, Bayer HealthCare, Genentech, Novartis, Regeneron Pharmaceuticals

Jean-Francois Korobelnik: Consultant – Bayer HealthCare, Carl Zeiss Meditec, Novartis, Roche, Thea; Advisory board – Alcon, Allergan; Financial support – Regeneron Pharmaceuticals

David M. Brown: Consultant and Financial support – Alcon, Allergan, Bayer HealthCare, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, Thrombogenics

Victor Chong: Consultant – Allergan, Bayer HealthCare, Novartis, Quantel; Financial support – Allergan, Novartis, Bayer HealthCare; Lecturer – Bayer HealthCare, Heidelberg, Novartis; Travel – Bayer Healthcare.

Quan Dong Nguyen: Consultant – Bausch & Lomb, Santen; Financial support – Genentech, Pfizer, Regeneron Pharmaceuticals

Allen C. Ho: Consultant – Regeneron Pharmaceuticals; Financial support – Regeneron Pharmaceuticals, Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, Second Sight; Lecturer – Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, Second Sight

Yuichiro Ogura: Consultant – Alcon, Bayer HealthCare, Santen; Lecturer – Alcon, Santen, Novartis; Financial support – Bayer HealthCare

Christian Simader: the author's institution, the Medical University of Vienna, has received funding from Bayer Healthcare for data monitoring/reviewing, statistical analysis, and travel

Glenn J. Jaffe: the author's institution, Duke University, has received research funding from Regeneron Pharmaceuticals to serve as a masked reading center  
Jason S. Slakter: Consultant – Lpath, Ohr, Oraya, Regeneron Pharmaceuticals; Financial support and Lecturer – Regeneron Pharmaceuticals; the author's institution, Vitreous-Retina-Macula Consultants of New York, has received research funding from Bayer HealthCare, Centor, Genentech, Genzyme, GlaxoSmithKline, Kanghong Biotech, Lpath, NeoVista, Ohr, Oraya, Regeneron Pharmaceuticals, and Santen to serve as an Angiography Reading Center

George D. Yancopoulos: Employee – Regeneron Pharmaceuticals

Neil Stahl: Employee – Regeneron Pharmaceuticals

Robert Vitti: Employee – Regeneron Pharmaceuticals

Alyson J. Berliner: Employee – Regeneron Pharmaceuticals

Yuhwen Soo: Employee – Regeneron Pharmaceuticals

Majid Anderesi: Employee – Bayer HealthCare

Olaf Sowade: Employee – Bayer HealthCare

Oliver Zeitz: Employee – Bayer HealthCare

Christiane Norenberg: Employee – Bayer HealthCare

Rupert Sandbrink: Employee – Bayer HealthCare

Jeffrey S. Heier: Consultant – Acucela, Aerpio, Alimera, Allergan, Bausch & Lomb, Bayer HealthCare, Dutch Ophthalmic, Endo Optiks, Forsight, Genzyme, Heidelberg Engineering, Kala Pharmaceuticals, Kanghong, LPath, Nicox, Notal Vision, Ohr Pharmaceutical, Ophthotech, Oraya, QLT, Regeneron Pharmaceuticals, Roche, Sequenom, Thrombogenics, Vertex, Xcovery; Financial support – Acucela, Aerpio, Alcon, Alimera, Allergan, Bayer HealthCare, Fovea, Genentech, Genzyme, GlaxoSmithKline, LPath, Neovista, Notal Vision, Novartis, Ohr Pharmaceutical, Ophthotech, Paloma, Regeneron Pharmaceuticals

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) studies were funded by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin, Germany. The sponsor-authors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript.

#### Correspondence:

Jeffrey S. Heier, MD, Ophthalmic Consultants of Boston, 50 Staniford Street, Suite 600, Boston, MA 02114. E-mail: [jsheier@eyeboston.com](mailto:jsheier@eyeboston.com).