

Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

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Objective: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) with monthly ranibizumab.

Design: Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

Participants: Patients (n = 2419) with active, subfoveal, choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD.

Intervention: Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

Main Outcome Measures: The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart). Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

Results: All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

Conclusions: Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

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*Group members listed online in Appendix 1 (<http://aaojournal.org>).

Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness in industrialized countries.¹ The most severe vision loss occurs in the neovascular (or wet) form of AMD, involving choroidal neovascularization (CNV) and associated retinal edema. Early treatments for CNV (laser ablation, photodynamic therapy with verteporfin), although clearly better than no treatment at all, decreased severe vision loss rather than truly stabilizing vision or resulting in clinically significant improvements in visual acuity.^{2–4} The suggestion that vascular endothelial growth factor (VEGF) might be driving the CNV and associated edema seen in AMD led to a paradigm shift with the success of the first anti-VEGF therapy, pegaptanib sodium.^{5,6} Monthly intravitreal

injections of 0.5 mg ranibizumab, a humanized monoclonal antibody fragment that blocks VEGF, not only prevent vision loss in most patients but also lead to significant visual gain in approximately one-third.^{7,8} The risk of rare but serious adverse events resulting from the intravitreal procedure, together with the significant burden of making monthly visits to their retinal specialist, have led to extensive efforts to decrease injection and monitoring frequency. However, fixed quarterly^{9,10} or “as needed” (pro re nata [PRN]) dosing regimens,^{11,12} without requiring monthly monitoring visits, were not effective at maintaining vision.

The Comparison of AMD Treatments Trials (CATT)¹³ recently compared monthly ranibizumab with monthly

bevacizumab, as well as with PRN regimens that required monthly monitoring visits during which treatment decisions primarily were made on the basis of anatomic criteria. Monthly bevacizumab resulted in mean best-corrected visual acuity (BCVA) gains (8.0 letters) similar to those for monthly ranibizumab (8.5 letters), whereas PRN ranibizumab yielded a mean BCVA gain of 1.7 letters less than that of the monthly standard (with a confidence interval [CI] extending to 4.7 letters below) that achieved noninferiority, and PRN bevacizumab yielded a mean BCVA gain 2.6 letters below the monthly standard (with a CI extending to 5.9 letters below) that did not achieve noninferiority. In the CATT, monthly bevacizumab and both PRN regimens were significantly worse than monthly ranibizumab in terms of the propor-

tion of patients who had fluid-free retinas on optical coherence tomography (OCT). Although CIs were not provided for monthly and PRN regimens, switching from monthly to PRN regimens in the second year of the CATT resulted in a significant worsening of BCVA and retinal thickness, as well as a significant decrease in the proportion of patients without retinal fluid.¹⁴ The “alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization” (IVAN) study also found that the mean foveal retinal thickness and the percentage of patients with fluorescein leakage were significantly higher with the PRN regimen compared with the monthly regimen.¹⁵ In the HARBOR study (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677), PRN regimens of both the approved 0.5 mg dose and the higher 2 mg dose of

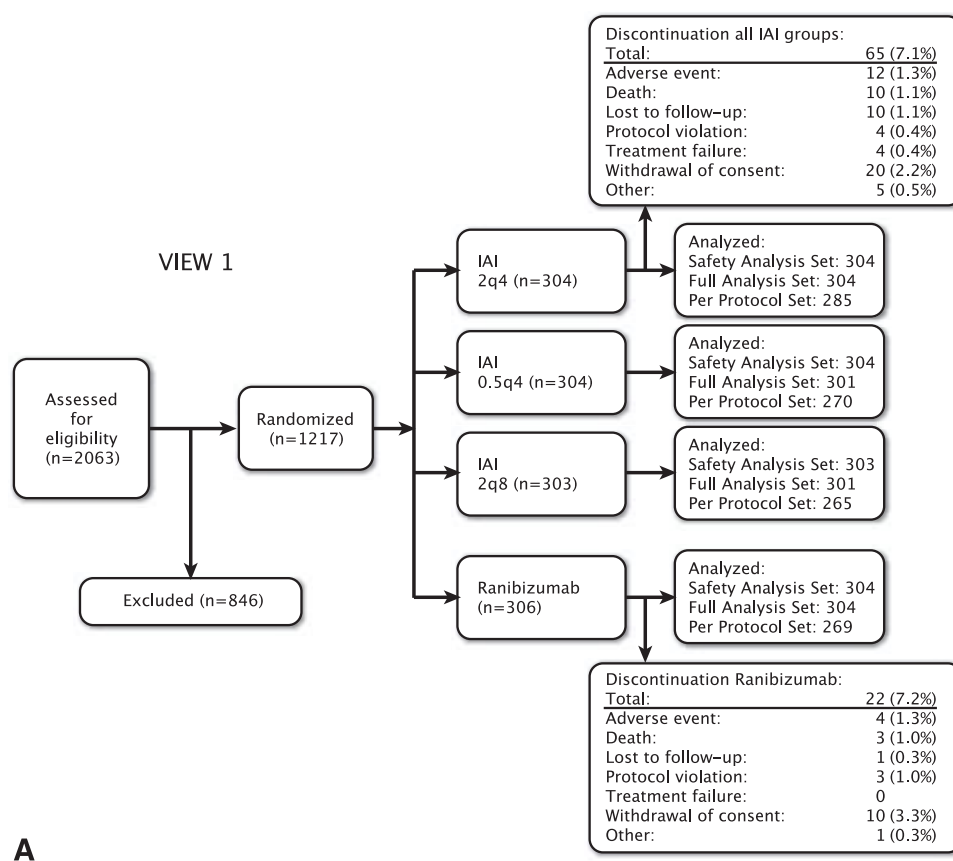


Figure 1. Flowcharts describing treatment allocation and patient disposition in VIEW 1 (**A**) and VIEW 2 (**B**). In both VIEW 1 and VIEW 2 studies, the most common reason for patients to be screened but not randomized was ineligibility based on angiographic characteristics as identified by the reading center. The second most common reason was visual acuity out of range. Discontinuations are those that occurred from the study. Two milligrams intravitreal aflibercept every 2 months (2q8) dosing was performed after 3 initial monthly doses. The numbers of patients who prematurely discontinued study medication in the 2q4, 0.5q4, 2q8, and Rq4 groups were 16 (5.3%), 30 (9.9%), 30 (9.9%), and 27 (8.8%), respectively, in VIEW 1; and 37 (11.8%), 45 (14.5%), 33 (10.5%), and 33 (10.9%), respectively, in VIEW 2. In VIEW 1, 1089 patients were included in the per protocol set (PPS), with 92.6% to 96.1% completing week-52 visual acuity assessment. A total of 128 patients were not included in the PPS for the following reasons (in order of occurrence): missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments. In VIEW 2, 1081 patients were included in the PPS with 95.9% to 97.8% completing week-52 visual acuity assessment. A total of 159 patients were not included in the PPS for the following main reasons: missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments, unmasking by investigator or Global Pharmacovigilance. 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

ranibizumab did not achieve noninferiority compared with monthly ranibizumab, with the 0.5 mg PRN regimen yielding a mean BCVA gain 2.0 letters below the monthly standard (with a CI extending to 4.5 letters below). Of note, just like the CATT PRN regimens, the HARBOR PRN regimens still depended on monthly monitoring visits. Thus, there remains a need for new therapies that will provide equivalent efficacy and anatomic disease control to monthly ranibizumab, while reducing the risk of monthly injections and the burden of mandatory monthly monitoring visits.

Intravitreal aflibercept injection (IAI) (previously known in the scientific literature as VEGF Trap-Eye, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a soluble decoy receptor fusion protein^{16,17} that is specifically purified and formulated for intraocular injection. Intravitreal aflibercept at doses of 0.5 mg and 2 mg provided the most robust outcomes in the Clinical Evaluation of Antiangiogenesis in the Retina Intravitreal Trial Phase 2 (CLEAR-IT 2) study after 4 monthly administrations followed by PRN dosing to week 52.¹⁸ The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab.¹⁷ The greater affinity could translate into a higher efficacy or, as predicted by a mathematical model, into a substantially longer duration of

action in the eye,¹⁹ allowing for less frequent dosing, as supported by early clinical trials.^{18,20} In this article, we report the first-year results of 2 phase 3 studies comparing intravitreal aflibercept, monthly or every 2 months, with monthly ranibizumab.

Materials and Methods

Study Design

The “VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD” studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at <http://aojournal.org>. Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007; NCT00509795. Accessed August 8, 2012) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008; NCT00637377. Accessed August 8, 2012) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were approved by institutional review boards or ethics committees for each clinical site; all participants provided written informed consent. All the US study sites complied with the Health Insurance

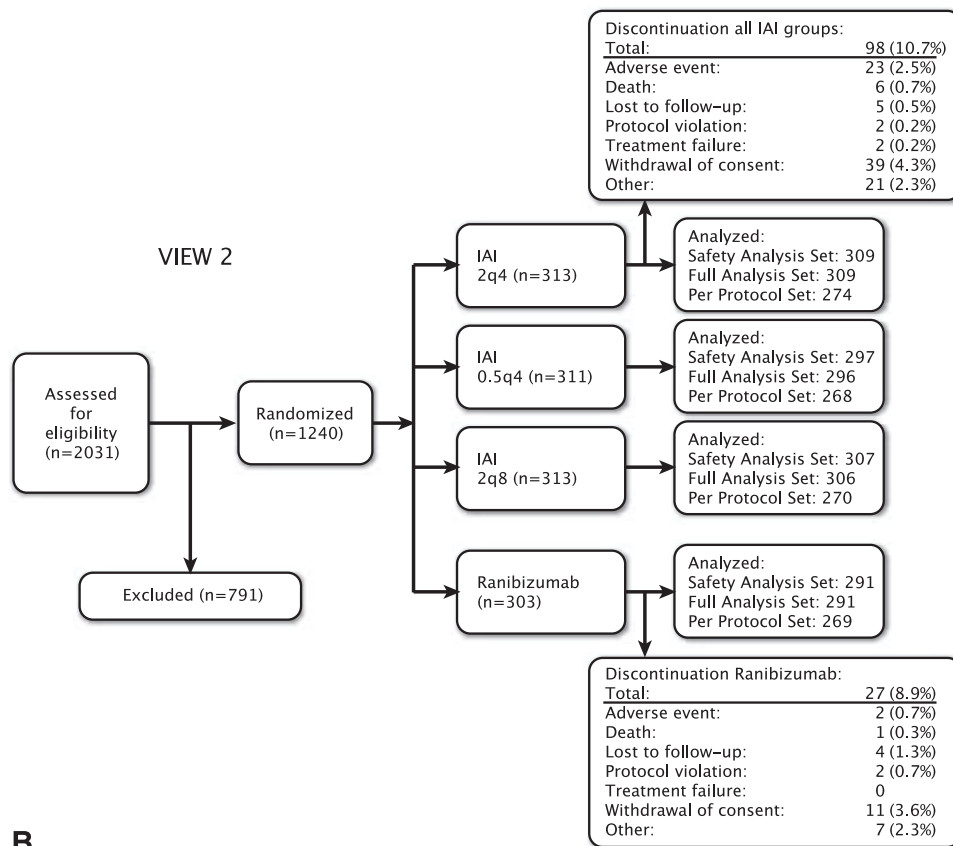


Figure 1. (Continued.)

Portability and Accountability Act. The 52-week outcomes are reported.

Participants

Inclusion and exclusion criteria were designed to maintain constancy with the pivotal trials for the reference drug ranibizumab, consistent with regulatory guidelines for noninferiority studies, and included (1) age ≥ 50 years with active subfoveal CNV lesions (any subtype) secondary to AMD; juxtafoveal lesions with leakage affecting the fovea also were allowed; (2) CNV comprising at least 50% of total lesion size; and (3) BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40–20/320 Snellen equivalent). Patients with prior treatment for AMD (including an investigational agent or anti-VEGF therapy) in the study eye were excluded. Eligibility was determined using fluorescein angiography at the reading center. Complete eligibility criteria are shown in Appendix 2 (available at <http://aaojournal.org>).

Treatment Groups and Randomization

Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2 mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5 mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system.

End Points and Statistical Analyses

The primary end point analysis, noninferiority margins, and definition of “clinical equivalence” were established in discussion with the Food and Drug Administration (FDA) (as part of a Special Protocol Assessment), European Medicines Agency, Pharmaceutical and Medical Device Agency and other regulatory authorities, with the intent of maintaining constancy with the previous ranibizumab pivotal trials^{7,8} and preserving the majority of the treatment effect demonstrated in these trials. The primary end point analysis was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 ETDRS letters; per protocol data set) in each study. A noninferiority margin of 10% in the individual studies was chosen to preserve approximately two-thirds of the ranibizumab effect for prevention of moderate vision loss (loss of <15 letters) demonstrated in pivotal ranibizumab studies,^{7,8} using the 2 CI approach. The FDA suggested that a margin of 5% could determine clinical equivalence. Thus, the margin of 10% was used for assessing noninferiority, and the margin of 5% was used for assessing clinical equivalence. The prespecified analysis plan also included a prospectively planned integrated analysis combining the 2 VIEW studies; in this integrated analysis, the European Medicines Agency/Committee for Medicinal Products for Human Use requested a noninferiority margin of 7%. In the individual studies, the primary end point was assessed by a prespecified hierarchical testing sequence of noninferiority to ranibizumab with the sequence of aflibercept 2q4, 0.5q4, and then 2q8 to control the 5% (4.9% for VIEW 1) overall type I error while maintaining a 5% significance level (4.9% for

VIEW 1) for each individual comparison (see Appendices 3 and 4 for details of the statistical analysis, available at <http://aaojournal.org>). If all aflibercept groups demonstrated noninferiority to ranibizumab for the primary end point, additional comparisons with ranibizumab were prespecified regarding the secondary end points, also using a hierarchical testing sequence in which each secondary end point was tested for superiority of aflibercept over ranibizumab. Prespecified secondary efficacy variables compared baseline and 52-week data regarding mean change in BCVA; gaining ≥ 15 letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on fluorescein angiography. Anatomic measures included retinal thickness and persistent fluid as assessed by OCT. Change in BCVA also was assessed as part of the prospectively planned prespecified integrated analysis combining the 2 studies.

The full analysis set included all randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment. The per protocol set (PPS) included all patients in the full analysis set who (1) received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year, (2) had not missed 2 consecutive injections before administration of the ninth injection (per patient), and (3) did not have major protocol violations. Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS included patients who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks (even if they met points 1 and 2 above). These patients were considered nonresponders for the primary end-point analysis. The last observation carried forward (LOCF) approach was used to impute missing values. When indicated, the robustness of analysis results was assessed by using the observed case or completers’ data. A completer was defined as a patient who received treatment for at least 9 months and had efficacy data for at least 9 months during the 52 weeks of study. The missing values for completers also were imputed using the LOCF approach.

Schedule of Visits and Assessments

Patients were examined on the day of treatment initiation and every 4 weeks thereafter through 52 weeks, as well as 1 week after first treatment for safety assessment (subsequent safety assessments occurred by telephone). Each 4-week visit included BCVA assessment and anterior/posterior segment examination (with intraocular pressure determination) before injection (active or sham) and posterior segment examination with intraocular pressure determination 30 to 60 minutes after injection. For the 2q8 treatment group, no treatment decisions were made at the interim monthly visits. The NEI VFQ-25 assessment occurred at screening and weeks 12, 24, 36, and 52. Adverse events were recorded at every visit.

Imaging Assessments

Fundus photography and fluorescein angiography were performed at screening and weeks 24 and 52, and evaluated by an independent center (Digital Angiography Reading Center, New York). Optical coherence tomography was performed using time domain Stratus machines (Carl Zeiss Meditec, Jena, Germany) and evaluated by an independent center (VIEW 1: OCT Reading Center at Duke, Durham, NC; VIEW 2: Vienna Reading Center, Austria). Visual acuity examiners were certified to ensure consistent measurement of BCVA. In VIEW 1, OCT was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52

(and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit. Areas of visible CNV (classic or occult) were identified when angiographic analyses showed evidence of late leakage or pooling of dye.

Masking

Patients were masked as to treatments. An unmasked investigator performed the study drug or sham injection. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose. A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment. Intravitreal aflibercept and sham kits were packaged identically. Lucentis (Genentech Inc, South San Francisco, CA) was obtained commercially but only prepared and delivered by unmasked personnel at the sites.

Results

Patient Disposition, Baseline Characteristics, and Exposure

The disposition of patients is shown in Figure 1A-B. In VIEW 1, 1217 patients were randomized, with 91.1% to 96.4% of patients completing 52 weeks. In VIEW 2, 1240 patients were randomized, with 88.1% to 91.1% completing 52 weeks. Baseline demographics and disease characteristics were evenly balanced among all treatment groups (Table 1). The mean number of active injections received by patients in all monthly treatment arms, which were scheduled to receive 13 monthly injections, was 12.1 to 12.5 in VIEW 1 and 12.2 to 12.4 in VIEW 2. The aflibercept every-2-month groups, scheduled to receive 3 initial monthly injections followed by 5 active injections over the next 10 months, received an average of 7.5 active injections in VIEW 1 and in VIEW 2.

Primary End Point Analysis

In both studies, the proportion of patients maintaining vision was similar among all treatment groups in the prespecified per-protocol analysis and the full analysis set (Table 2). All aflibercept groups achieved statistical noninferiority compared with monthly ranibizumab, with the CIs of the difference between ranibizumab and

Table 1. Patient Demographics and Baseline Characteristics

	VIEW 1				VIEW 2			
	Ranibizumab		Intravitreal Aflibercept		Ranibizumab		Intravitreal Aflibercept	
	0.5q4	2q4	0.5q4	2q8	0.5q4	2q4	0.5q4	2q8
N (full analysis set)	304	304	301	301	291	309	296	306
Age, yrs (mean ± SD)	78.2±7.6	77.7±7.9	78.4±8.1	77.9±8.4	73.0±9.0	74.1±8.5	74.7±8.6	73.8±8.6
Race								
White	296 (97.4)	295 (97.0)	291 (96.7)	287 (95.3)	213 (73.2)	226 (73.1)	219 (74.0)	217 (70.9)
Black	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.7)
Asian	0	3 (1.0)	5 (1.7)	4 (1.3)	60 (20.6)	67 (21.7)	61 (20.6)	69 (22.5)
Other	7 (2.3)	5 (1.6)	5 (1.7)	9 (3.0)	17 (5.8)	16 (5.2)	15 (5.1)	18 (5.9)
Sex								
Men, n (%)	132 (43.4)	110 (36.2)	134 (44.5)	123 (40.9)	122 (41.9)	133 (43.0)	149 (50.3)	131 (42.8)
Women, n (%)	172 (56.6)	194 (63.8)	167 (55.5)	178 (59.1)	169 (58.1)	176 (57.0)	147 (49.7)	175 (57.2)
Baseline ETDRS BCVA (mean ± SD)	54.0±13.4	55.2±13.2	55.6±13.1	55.7±12.8	53.8±13.5	52.8±13.9	51.6±14.2	51.6±13.9
Proportion of patients with ≥20/40 BCVA, % (n)	4.3% (13)	4.9% (15)	6.3% (19)	6.6% (20)	2.7% (8)	2.6% (8)	5.4% (16)	3.3% (10)
CNV area, mm ² (mean ± SD)	6.53±5.2	6.59±5.1	6.49±4.5	6.57±5.1	7.59±5.3	8.25±5.8	7.70±5.3	7.75±5.5
Lesion type								
Predominantly classic, n (%)	82 (27.0)	87 (28.6)	81 (26.9)	71 (23.6)	70 (24.1)	72 (23.3)	80 (27.0)	88 (28.8)
Minimally classic, n (%)	101 (33.2)	105 (34.5)	97 (32.2)	110 (36.5)	104 (35.7)	112 (36.2)	103 (34.8)	106 (34.6)
Occult, n (%)	115 (37.8)	110 (36.2)	121 (40.2)	118 (39.2)	116 (39.9)	123 (39.8)	113 (38.2)	110 (35.9)
Patients with juxtafoveal lesions, n (%)	15 (4.9)	13 (4.3)	17 (5.6)	17 (5.6)	20 (6.9)	15 (4.9)	11 (3.7)	14 (4.6)
Lesion size, mm ² (mean ± SD)	6.99±5.5	6.98±5.4	6.95±4.7	6.89±5.2	8.01±5.7	8.72±6.1	8.17±5.5	8.22±5.9
Central retinal thickness, μm (mean ± SD)	315.3±108.3	313.6±103.4	313.2±106.0	324.4±111.2	325.9±110.9	334.6±119.8	326.5±116.5	342.6±124.0
Baseline NEI VFQ-25 scores (mean ± SD)	71.8±17.2	70.4±16.6	71.1±17.8	69.6±16.8	72.9±19.1	70.3±19.4	74.0±18.2	71.3±19.1

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; SD = standard deviation.

Table 2. Prespecified Efficacy

	VIEW 1			
	Ranibizumab	Intravitreal Aflibercept		
	0.5q4	2q4	0.5q4	2q8
Primary end point				
N (PPS)	269	285	270	265
Proportion maintaining vision (losing <15 ETDRS letters), % (n)	94.4% (254)	95.1% (271)	95.9% (259)	95.1% (252)
N (full analysis set)	304	304	301	301
Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)	93.8% (285)	95.1% (289)	95.0% (286)	94.4% (284)
Secondary end points				
N (full analysis set)	304	304	301	301
Change in ETDRS BCVA (mean $\pm$ SD)	8.1 $\pm$ 15.3	10.9 $\pm$ 13.8	6.9 $\pm$ 13.4	7.9 $\pm$ 15.0
LS mean difference between IAI and ranibizumab (95% CI)*		3.15 (0.92 to 5.37)	-0.80 (-3.03 to 1.43)	0.26 (-1.97 to 2.49)
Proportion gaining $\geq$ 15 ETDRS letters, % (n)	30.9% (94)	37.5% (114)	24.9% (75)	30.6% (92)
LS mean difference between IAI and ranibizumab (95% CI)*		6.58 (-0.98 to 14.14)	-6.00 (-13.17 to 1.16)	-0.36 (-7.74 to 7.03)
Change in CNV area, mm ² (mean $\pm$ SD)	-4.2 $\pm$ 5.6	-4.6 $\pm$ 5.5	-3.5 $\pm$ 5.3	-3.4 $\pm$ 6.0
LS mean difference between IAI and ranibizumab (95% CI)*		-0.33 (-1.04 to 0.38)	0.71 (-0.01 to 1.42)	0.86 (0.15-1.58)
Change in total NEI VFQ-25 score (mean $\pm$ SD)	4.9 $\pm$ 14.0	6.7 $\pm$ 13.5	4.5 $\pm$ 11.9	5.1 $\pm$ 14.7
LS mean difference between IAI and ranibizumab (95% CI)*		1.28 (-0.73 to 3.28)	-0.67 (-2.69 to 1.35)	-0.60 (-2.61 to 1.42)
Exploratory end point				
Change in central retinal thickness, μ m (mean $\pm$ SD)	-116.8 $\pm$ 109.0	-116.5 $\pm$ 98.4	-115.6 $\pm$ 104.1	-128.5 $\pm$ 108.5
Post hoc end point [†]				
Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n)	63.6% (171)	64.8% (184)	56.7% (148)	63.4% (168)

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; aflibercept injection; LOCF = last observation carried forward; LS = least-squares; NEI VFQ-25 = National Eye Institute 25-Item Visual

*95.1% CI for VIEW 1.

[†]Observed case.

each aflibercept group within the prespecified 10% margin (Fig 2), and the point estimates of the differences in means favoring the aflibercept groups in all cases. All the aflibercept regimens also met the prespecified 7% noninferiority margin in the prespecified integrated analysis combining the 2 VIEW studies, as well as the prespecified 5% margin for clinical equivalence compared with ranibizumab in the individual VIEW studies. Moreover, the results of multiple imputation analyses were consistent with those using the LOCF.

Mean Changes in Best-Corrected Visual Acuity and Other Visual Acuity End Points

The mean change in BCVA was a clinically important secondary end point in both studies. On the basis of the hierarchical testing sequence, only the aflibercept 2q4 group was statistically superior to ranibizumab, and only in VIEW 1, with a gain of +10.9 versus +8.1 letters (Table 2). Small numeric differences between treatment groups in one study at any given timepoint were not reproduced in the other study, suggesting that they reflected random variability even in groups of this size (Fig 3A, B); this interpretation was supported by a prespecified integrated analysis that combined the 2 studies (Fig 3C), showing similar visual acuity scores

across the entire 52-week study for all treatment groups. All groups behaved similarly in this integrated analysis (Fig 3C), with rapid increases in mean visual acuity after the first injection followed by incremental gains that were durable and maintained through week 52. Regardless of whether the analysis was by LOCF, by multiple imputations, by assessing completers, or by using actual observed data, intravitreal aflibercept dosed every 2 months achieved a mean visual acuity score within 0.3 letters of monthly ranibizumab in the integrated analysis, with a CI of less than 2 letters (Fig 3C, inset).

In both studies, the secondary end point of proportions of patients gaining $\geq$ 15 ETDRS letters from baseline to week 52 was similar in all treatment groups (Table 2), as were other exploratory categorical measures of visual outcome (Appendix 5, available at <http://aaojournal.org>). Likewise, vision-related quality of life, assessed by the change of total score of the NEI VFQ-25, improved in all groups in both studies (Table 2).

Key Anatomic Measures

In both studies, all groups demonstrated a comparable decrease in the secondary end point of change in area of active CNV

Outcomes at Week 52

	VIEW 2			
	Ranibizumab	Intravitreal Aflibercept		
	0.5q4	2q4	0.5q4	2q8
Primary end point				
N (PPS)	269	274	268	270
Proportion maintaining vision (losing <15 ETDRS letters), % (n)	94.4% (254)	95.6% (262)	96.3% (258)	95.6% (258)
N (full analysis set)	291	309	296	306
Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)	94.8% (276)	94.5% (292)	95.3% (282)	95.4% (292)
Secondary end points				
N (full analysis set)	291	309	296	306
Change in ETDRS BCVA (mean $\pm$ SD)	9.4 $\pm$ 13.5	7.6 $\pm$ 12.6	9.7 $\pm$ 14.1	8.9 $\pm$ 14.4
LS mean difference between IAI and ranibizumab (95% CI)*		-1.95 (-4.10 to 0.20)	-0.06 (-2.24 to 2.12)	-0.90 (-3.06 to 1.26)
Proportion gaining $\geq$ 15 ETDRS letters, % (n)	34.0% (99)	29.4% (91)	34.8% (103)	31.4% (96)
LS mean difference between IAI and ranibizumab (95% CI)*		-4.57 (-12.02 to 2.88)	0.78 (-6.91 to 8.46)	-2.65 (-10.18 to 4.88)
Change in CNV area, mm ² (mean $\pm$ SD)	-4.2 $\pm$ 5.9	-6.0 $\pm$ 6.1	-4.2 $\pm$ 6.1	-5.2 $\pm$ 5.9
LS mean difference between IAI and ranibizumab (95% CI)*		-1.18 (-1.98 to -0.38)	0.17 (-0.63 to 0.97)	-0.73 (-1.53 to 0.07)
Change in total NEI VFQ-25 score (mean $\pm$ SD)	6.3 $\pm$ 14.8	4.5 $\pm$ 15.0	5.1 $\pm$ 13.7	4.9 $\pm$ 14.7
LS mean difference between IAI and ranibizumab (95% CI)*		-2.79 (-4.90 to -0.68)	-0.93 (-3.07 to 1.20)	-1.95 (-4.07 to 0.17)
Exploratory end point				
Change in central retinal thickness, μ m (mean $\pm$ SD)	-138.5 $\pm$ 122.2	-156.8 $\pm$ 122.8	-129.8 $\pm$ 114.8	-149.2 $\pm$ 119.7
Post hoc end point [†]				
Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n)	60.4% (162)	80.3% (220)	63.9% (170)	71.9% (197)

CNV = choroidal neovascularization; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal Functioning Questionnaire; OCT = optical coherence tomography; PPS = per protocol set; SD = standard deviation.

(Table 2). Likewise, all aflibercept groups in both studies had reductions in central retinal thickness similar to those for monthly ranibizumab as assessed by OCT, with a large and rapid reduction evident by week 4 (with retinal thickness approaching normal levels) that was maintained to week 52 (Table 2, Fig 4). Minor fluctuations in central retinal thickness were seen in the 2q8 group after sham injections in the VIEW 2 study; these fluctuations attenuated over time, starting at 17 μ m and decreasing to 8 μ m over the year, with no apparent negative impact on visual acuity outcomes.

Because of the inability of other regimens in the CATT¹³ to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, a post hoc analysis was performed to determine the percentage of patients who had fluid-free retinas, which were defined, on OCT, by the absence of both cystic intraretinal edema and subretinal fluid. All intravitreal aflibercept groups were similar to the monthly ranibizumab group in terms of this end point, with numerically higher percentages of dry retinas seen in the 2q4 and 2q8 regimens largely driven by VIEW 2 (Table 2; Appendix 6, available at <http://aaajournal.org>). Integrated analysis combining both studies for proportions of patients with dry retinas for ranibizumab and the aflibercept regimens of 2q4, 0.5q4, and 2q8 showed percentages of 62.0%, 72.4%, 60.3%, and 67.7%, respectively.

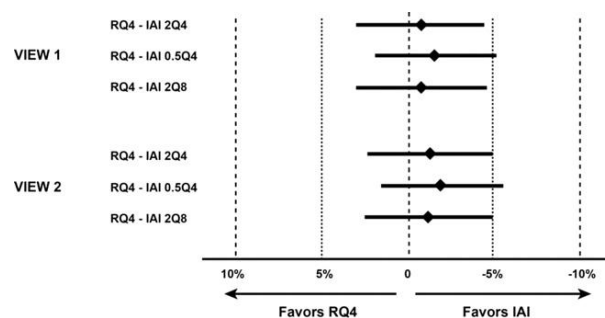


Figure 2. Difference in proportions of patients who maintained vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) at week 52 in the VIEW studies (per protocol set [PPS]). The diamond symbol denotes the difference between the treatment arms, and the horizontal bars indicate 95% confidence interval (CI) range. The CI within the left 10% (dashed vertical lines) indicates that all intravitreal aflibercept arms were noninferior to ranibizumab. The CI within the left 5% (dotted vertical line) indicates clinical equivalence to ranibizumab. The last observation carried forward (LOCF) was used for imputing the missing values. RQ4 = 0.5 mg ranibizumab monthly; 0.5Q4 = 0.5 mg IAI monthly; 2Q4 = 2 mg IAI monthly; 2Q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

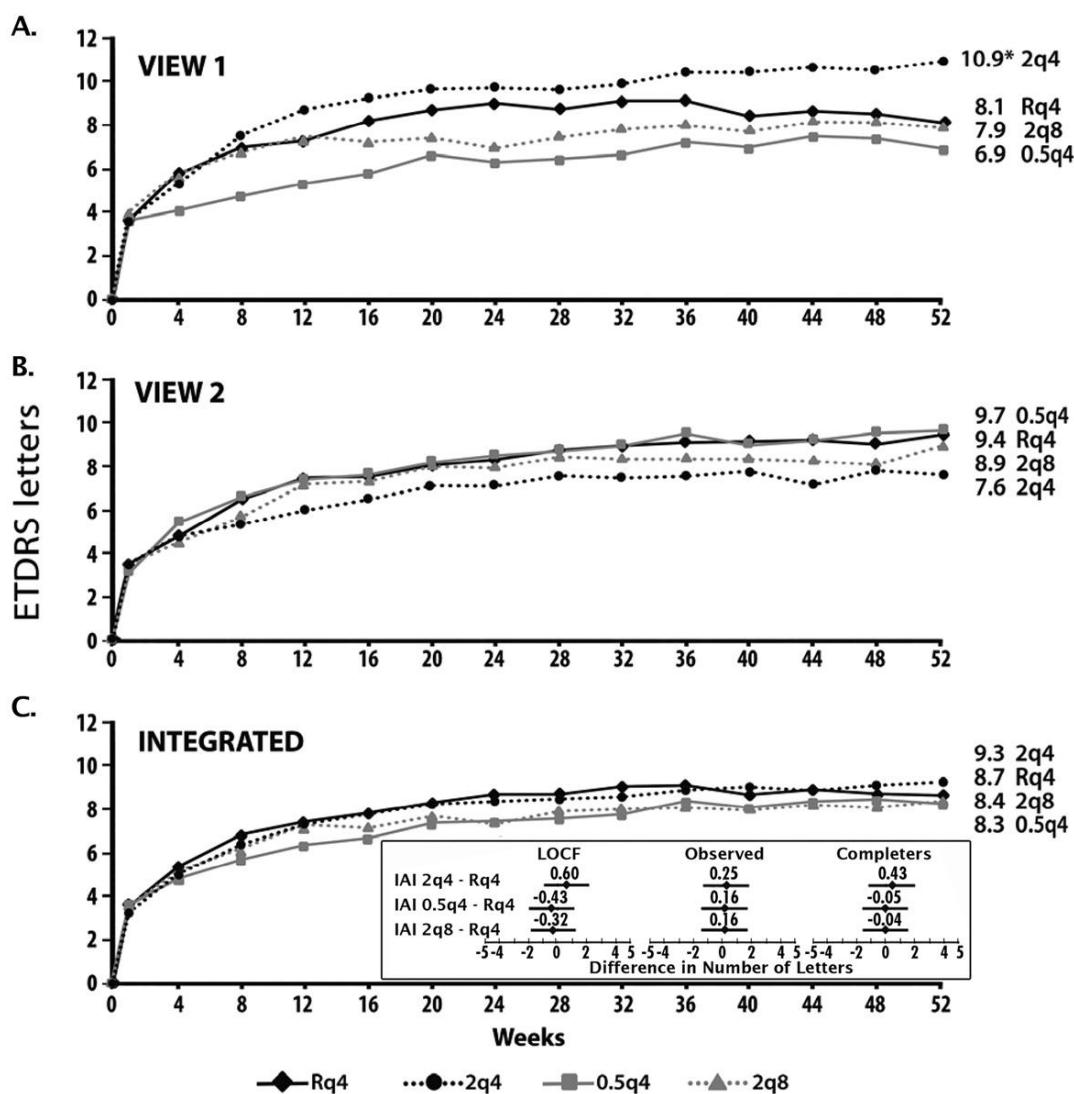


Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis. Values in the line graphs refer to mean changes in the number of letters from baseline at week 52. Only the intravitreal aflibercept 2q4 arm in VIEW 1 was significantly different from ranibizumab (* $P = 0.005$ for the difference). The panel inset (integrated analysis) shows the difference in visual acuity between each intravitreal aflibercept arm and ranibizumab (least-square mean with 95% confidence interval [CI]) at week 52, using 3 different analyses: by last observation carried forward (LOCF), using observed case data, and by assessing completers. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection.

Safety

Intravitreal aflibercept was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to those for monthly ranibizumab (Table 3; Appendix 7, available at <http://aaojournal.org>). Differences were noted in the prespecified analyses of intraocular pressure: Fewer patients treated with aflibercept had increases in intraocular pressure over the 52 weeks of the VIEW 1 and VIEW 2 studies (Appendix 7, available at <http://aaojournal.org>). There were few ocular injection-related treatment-emergent serious adverse events in the study eye. The combined data for both studies showed a rate of events/1000 injections of 1.1, 0.8, 0.1, and 0.2 for the ranibizumab 0.5q4 and intravitreal aflibercept 2q4,

0.5q4, and 2q8 groups, respectively. These events included eye disorders, endophthalmitis, procedural complications, and increased intraocular pressure.

There was a similar overall incidence of systemic (nonocular) adverse events (Appendix 7, available at <http://aaojournal.org>), serious systemic adverse events, specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration, and deaths between intravitreal aflibercept and ranibizumab (Table 3). Among the aflibercept treatment groups, there was no evidence of a dose-response for adverse events: The group with the highest exposure, the aflibercept 2q4 group, generally had the lowest rates of adverse events. There was little to no immunogenicity associated with intravitreal aflibercept (Appendix 8, available at <http://aaojournal.org>).

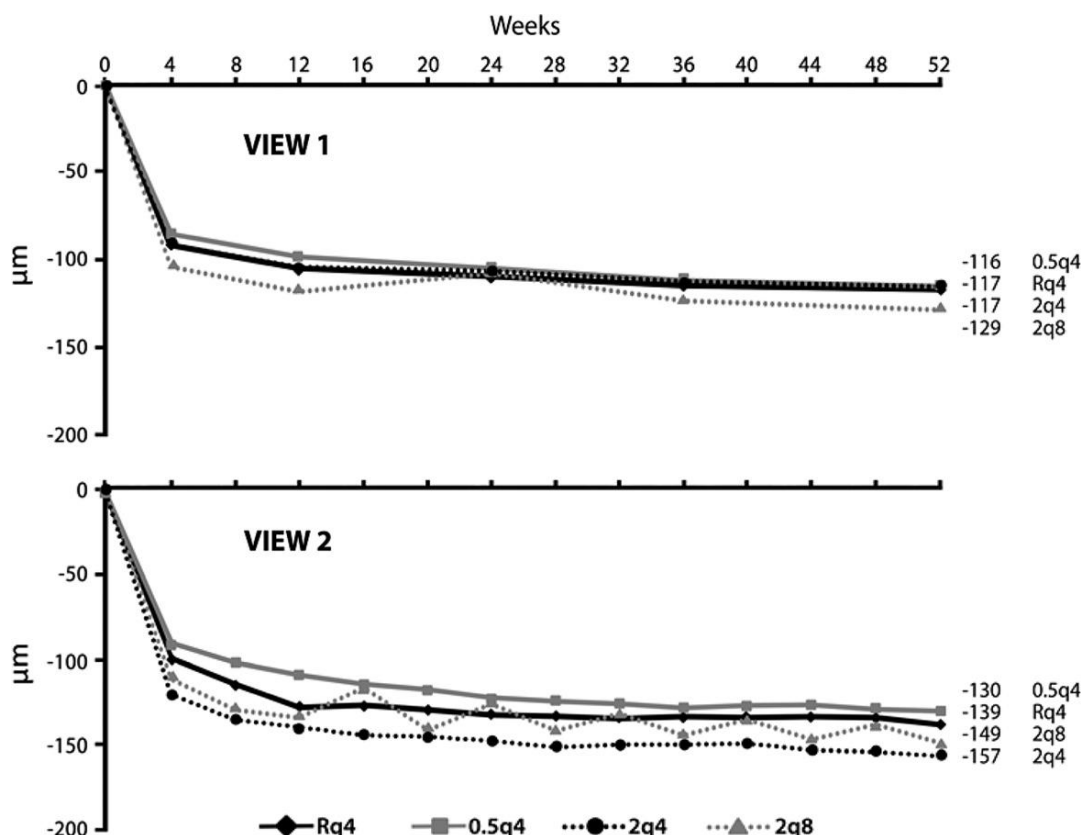


Figure 4. Mean change from baseline in central retinal thickness (full analysis set). As described in the “Materials and Methods” section, in VIEW 1, optical coherence tomography (OCT) was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52 (and was optional at the investigators’ discretion at other study visits). In VIEW 2, OCT was performed at every study visit. The last observation carried forward (LOCF) was used for imputing the missing values. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg intravitreal aflibercept injection (IAI) monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses.

Discussion

We have described 2 large and similarly designed clinical trials involving more than 2400 patients with neovascular AMD. In both trials, all 3 aflibercept treatment regimens (including the every-2-month regimen after 3 initial monthly loading doses) were statistically noninferior to monthly ranibizumab in preventing moderate visual acuity loss at 1 year, meeting the primary outcome of the trials; all the aflibercept regimens also met the stricter margin of 5% for clinical equivalence compared with monthly ranibizumab. In terms of mean change in BCVA over time, all aflibercept regimens behaved similarly to monthly ranibizumab, with rapid increases after the first treatment followed by incremental gains that were durable and maintained through week 52. Mean visual acuity scores were within 1 letter of each other at week 52 in the prespecified integrated analysis combining the 2 studies; of note, aflibercept dosed every 2 months achieved a visual acuity score within 0.3 letters of monthly ranibizumab, with a CI of less than 2 letters, regardless of the analysis set used. Because the CATT¹³ highlighted the inability of other regimens, including monthly be-

vacizumab and PRN ranibizumab or bevacizumab, to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, it is notable that all 3 aflibercept regimens behaved similarly to monthly ranibizumab in terms of these anatomic measures.

Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits. The CATT and HARBOR studies used noninferiority margins of change from baseline BCVA of 5 letters and 4 letters, respectively, to evaluate the efficacy of PRN regimens (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677).¹³ The CATT¹³ generated much interest, in part because it showed that PRN ranibizumab and bevacizumab regimens approached the visual acuity outcomes achieved with monthly ranibizumab; however, these PRN regimens produced numerically smaller gains in BCVA at 52 weeks (by 1.7–2.6 letters) with poorer anatomic outcomes. Switching from a monthly to a PRN regimen during the second year of the CATT significantly worsened visual and anatomic out-

Table 3. Serious Ocular Adverse Events in the Study Eye and Other Key Nonocular Events Occurring in $\geq 0.5\%$ * of Patients in Any Study Arm

	VIEW 1				VIEW 2			
	Ranibizumab		Intravitreal Aflibercept		Ranibizumab		Intravitreal Aflibercept	
	0.5q4	2q4	0.5q4	2q8	0.5q4	2q4	0.5q4	2q8
N (safety analysis set)	304	304	304	303	291	309	297	307
Patients with at least 1 ocular SAE, n (%)	10 (3.3)	7 (2.3)	6 (2.0)	3 (1.0)	9 (3.1)	6 (1.9)	5 (1.7)	9 (2.9)
Serious ocular adverse event, n (%)								
Endophthalmitis	3 (1.0)	3 (1.0)	0	0	0	0	0	0
Visual acuity reduced	2 (0.7)	1 (0.3)	2 (0.7)	0	1 (0.3)	1 (0.3)	1 (0.3)	5 (1.6)
Retinal hemorrhage	2 (0.7)	0	0	2 (0.7)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Posterior capsule opacification	—	—	—	—	2 (0.7)	0	0	0
Serious systemic (or nonocular) adverse event	57 (18.8)	40 (13.2)	50 (16.4)	51 (16.8)	26 (8.9)	36 (11.7)	37 (12.5)	38 (12.4)
APTC ATE events								
Any APTC ATE event	5 (1.6)	2 (0.7)	7 (2.3)	6 (2.0)	5 (1.7)	4 (1.3)	5 (1.7)	8 (2.6)
Vascular death	1 (0.3)	0	1 (0.3)	4 (1.3)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)
Nonfatal myocardial infarction	4 (1.3)	1 (0.3)	4 (1.3)	1 (0.3)	2 (0.7)	2 (0.6)	2 (0.7)	5 (1.6)
Nonfatal stroke	0	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.7)
Any AE of hypertension	29 (9.5)	25 (8.2)	26 (8.6)	31 (10.2)	29 (10.0)	31 (10.0)	22 (7.4)	28 (9.1)
SAEs of interest occurring in any patient								
Venous thromboembolic event	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Congestive heart failure event	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (1.0%)	1 (0.3%)	0	0	1 (0.3%)
GI perforation or fistula event	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)
Nonocular hemorrhagic event	1 (0.3%)	1 (0.3%)	3 (1.0%)	3 (1.0%)	0	2 (0.6%)	0	1 (0.3%)
Delayed wound healing	0	0	0	0	0	0	0	0

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; AE = adverse event; APTC ATE = Anti-platelet Trialists' Collaboration Arteriothrombotic Event; GI = gastrointestinal; SAE = serious adverse event.

*For SAEs of interest, occurrence in any patient is reported.

comes and resulted in a decrease in the proportion of patients without retinal fluid.¹⁴ The results from the HARBOR study showed that PRN regimens of ranibizumab (including a higher 2 mg dose) did not achieve noninferiority compared with monthly ranibizumab (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677). Moreover, the PRN regimens in both CATT and HARBOR still required mandatory monthly visits, during which treatment decisions had to be made largely on the basis of anatomic measures. The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians. The FDA has approved intravitreal aflibercept injection for AMD and recommended the regimen of 2 mg once every 2 months after 3 initial monthly doses (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: <http://www.regeneron.com/Eylea/eylea-fpi.pdf>. Accessed August 8, 2012). This approval was based on the evaluation that this regimen provided the best benefit/risk; the approved label notes that aflibercept can be dosed as often as every 4 weeks, although additional efficacy was not reported with such frequent dosing. By halving the need for monthly visits, the every-2-month regimen of aflibercept may markedly decrease the treatment burden experienced by patients and their families. Less frequent

injections also should provide an ocular safety benefit. Although the VIEW studies were not powered to see differences in rare but serious intraocular complications (e.g., endophthalmitis and retinal detachment), it is likely that fewer injections may substantially decrease the cumulative population risk of such events, considering that millions of injections are given each year.

After the 1-year primary end point of VIEW 1/VIEW 2 presented in this article, all treatment groups' dosing intervals were changed to a common protocol of modified quarterly dosing with their originally randomized dose and drug (all patients were monitored monthly and received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections). The results of this second year were recently presented (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 6962) and reveal 81.6% to 85.7% patient retention in all groups with comparable visual acuity maintenance (91%–92%) in each group at the 96-week time point. The total number of active injections (baseline to week 96) was 16.0 to 16.2 in the monthly intravitreal aflibercept groups, 16.5 in the monthly ranibizumab group, and 11.2 in the original 2q8 group. The finding that visual acuity maintenance can be achieved for up to 96 weeks in the 2q8 group with similar gains in BCVA compared with ranibizumab despite more than 5 fewer doses is encouraging and implies that the treatment burden of neovascular AMD may be meaningfully reduced with this 2q8 intravitreal aflibercept regimen.

The sustained durability of intravitreal aflibercept as demonstrated by the every-2-month regimen is consistent

with the rationale that a higher binding affinity could lead to increased durability.¹⁷ It is encouraging that the increased affinity of intravitreal aflibercept did not result in an observed increase in ocular or systemic adverse events. In the VIEW 1 and VIEW 2 trials, no differences in systemic or ocular safety were noted between any of the doses or dosing regimens of intravitreal aflibercept. Systemic exposure of aflibercept injected intravitreally is extremely low (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: <http://www.regeneron.com/Eylea/eylea-fpi.pdf>. Accessed August 8, 2012). After intravitreal administration of 2 mg per eye of aflibercept to patients with wet AMD, the mean maximum concentration of free aflibercept in the plasma was 0.02 µg/ml (range, 0–0.054 µg/ml) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable 2 weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families, and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events.

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Footnotes and Financial Disclosures

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Appendix 1. VIEW 1 and VIEW 2 Study Investigator List.

VIEW 1 Study Investigator List		
Principal Investigator	Study Site	Location/Address
Abraham, Prema	Black Hills Regional Eye Institute	Rapid City, SD
Adelman, Ron	Yale University School of Medicine	New Haven, CT
Adrean, Sean	Retina Consultants of Orange County	Fullerton, CA
Ali, Fareed	Canadian Centre for Advanced Eye Therapeutics	Mississauga, Ontario
Altaweel, Michael	University of Wisconsin	Madison, WI
Antworth, Michael	Retina Consultants of Carolina	Greenville, SC
Appa, Suri	Kaiser Permanente	Yorba Linda, CA
Arend, Laurence	Ochsner Clinic Foundation	New Orleans , LA
Arroyo, Jorge	Beth Israel Deaconess Medical Center	Boston, MA
Baker, Carl W.	Paducah Retinal Center	Paducah, KY
Bakri, Sophie J.	Mayo Clinic - Rochester	Rochester, MN
Beer, Paul	Retina Consultants PLLC	Slingerlands, NY
Benz, Matthew	Vitreo Retinal Consultants	Houston, TX
Berger, Brian B.	Retina Research Center	Austin, TX
Berinstein, Daniel	Retina Group of Washington	Chevy Chase, MD
Bertolucci, George A.	Eye Medical Center of Fresno	Fresno, CA
Bhavsar, Abdhish	Retina Center	Minneapolis, MN
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Chan, Clement	Southern California Desert Retina Consultants	Palm Desert, CA
Chang, Stanley	Harkness Eye Institute at Columbia University Department of Ophthalmology	New York, NY
Chang, Tom	Retina Institute of California	Arcadia, CA
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Chen, Sanford	Orange County Retina Medical Group	Santa Ana, CA
Chiu, Mark	Eye Associates of New Mexico	Albuquerque, NM
Cirino, Anthony	Kaiser Permanente Northwest	Portland, OR
Ciulla, Thomas	Midwest Eye Insititute	Indianapolis, IN
Clark, W. L.	Palmetto Retina Center, LLC	West Columbia, SC
Colquhoun, Peter J.	Southwest Michigan Eye Center	Battle Creek, MI
Combs, James	Virginia Eye Institute	Richmond, VA
Conway, Brian P.	University of Virginia	Charlottesville, VA
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Dugel, Pravin U.	Retinal Consultants of Arizona	Phoenix, AZ
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Erasmus, Murray J.	Retina Consultants of Victoria	Victoria, British Columbia
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APPENDIX 2: Eligibility Criteria

Inclusion Criteria

- Men and women ≥ 50 years of age.
- Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye
- CNV must be at least 50% of total lesion size
- ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
- Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
- Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.
- Signed informed consent form

Exclusion Criteria:

- Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
- Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
- Prior treatment with anti-VEGF agents as follows:
 - Prior treatment with anti VEGF therapy in the study eye is not allowed.
 - Prior treatment with anti VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. Prior treatment with an FDA/Health Canada approved anti VEGF therapy in the fellow eye is allowed.

- Prior systemic anti VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study.
- Total lesion size > 12 disc areas (30.5 mm²), including blood, scars and neovascularization) as assessed by FA in the study eye.
- Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
- Scar or fibrosis, making up > 50% of total lesion in the study eye.
- Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
- History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
- Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
- History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye.
- Prior vitrectomy in the study eye.
- History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
- Any history of macular hole of stage 2 and above in the study eye.
- Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.
- Prior trabeculectomy or other filtration surgery in the study eye.
- Uncontrolled glaucoma (defined as intraocular pressure $\geq$ 25 mmHg despite treatment with antiglaucoma medication) in the study eye.

- Active intraocular inflammation in either eye.
- Active ocular or periocular infection in either eye.
- Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.
- Any history of uveitis in either eye.
- Presence or history of scleromalacia in either eye.
- Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye.
- Previous therapeutic radiation in the region of the study eye.
- History of corneal transplant or corneal dystrophy in the study eye.
- Significant media opacities, including cataract, in the study eye that might interfere with visual acuity, assessment of safety, or fundus photography.
- Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period.
- Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications.
- Participation as a patient in any clinical study within the 12 weeks prior to Day 1.
- Any systemic or ocular treatment with an investigational agent in the past 12 weeks prior to Day 1.
- The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1.
- Any history of allergy to povidone iodine.

- Known serious allergy to the fluorescein sodium for injection in angiography.
- Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®; Genentech Inc., South San Francisco, CA).
- Females who are pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera® (Pfizer, Inc. New York); Norplant® System (Pfizer, Inc. New York) implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

APPENDIX 3: Summary of Statistical Analysis

The primary endpoint analysis was chosen to preserve constancy with the ranibizumab pivotal trials^{7,8} and was non-inferiority of the intravitreal aflibercept treatment regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 ETDRS letters, per protocol data). Prespecified secondary efficacy variables compared baseline and 52-week data regarding: mean change in BCVA; gaining ≥ 15 letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on FA. Anatomic measures included retinal thickness and persistent fluid as assessed by OCT. Mean change in BCVA was also assessed in data pooled between the studies.

The full analysis set (FAS) included all randomized patients who received any study medication and had a baseline and at least one post-baseline BCVA assessment. The per protocol set (PPS) includes all patients in the FAS who:

1. Received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year;
2. Had not missed two consecutive injections before administration of the 9th injection (per patient); and
3. Did not have major protocol violations.

Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS included patients who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks (even if they met points 1 and 2 above). These patients were considered non-responders for the primary endpoint analysis.

A non-inferiority margin of 10% was chosen to preserve ~61% of the ranibizumab effect for prevention of moderate vision loss (loss of <15 letters) demonstrated in MARINA study,⁷ using the two confidence interval approach. The non-inferiority for the primary endpoint was assessed by a pre-specified hierarchical testing sequence to control the overall type I error with the sequence of intravitreal aflibercept 2q4, 0.5q4, and then 2q8 as compared with ranibizumab. If all intravitreal aflibercept groups demonstrated non-inferiority to ranibizumab for the primary endpoint, additional comparisons to ranibizumab were prespecified regarding the secondary endpoints, also using a hierarchical testing sequence in which each secondary endpoint was tested for superiority of intravitreal aflibercept over ranibizumab. For the primary endpoint

analysis, a margin of 5% was used to determine clinical equivalence. To control the 5% (4.9% for VIEW 1) overall type I error for all these assessments while maintaining a 5% significance level (4.9% for VIEW1) for the primary comparisons, the hierarchical testing procedure was used. The order of testing was pre-specified in the study protocols. It was also agreed to by the U.S. regulatory agency that, for the primary endpoint analysis, a margin of 5% could be used to determine clinical equivalence.

Sample sizes were determined assuming that 90% of patients treated with 0.5 mg ranibizumab or with intravitreal aflibercept would maintain vision, and defining the non-inferiority margin to be 10%. In VIEW 1, 191 patients per group per study were estimated to provide a 90% power to demonstrate non-inferiority assuming a two-sided alpha level = 0.049. In VIEW 2, 190 patients per group were estimated to provide a 90% power to demonstrate non-inferiority assuming two-sided alpha level = 0.05. To account for dropout or per-protocol set ineligibility rate of 30% and to ensure sufficient number of patients for safety assessment, 300 patients per group were planned.

The primary analysis (using last observation carried forward under pre-specified conditions) was conducted on the per protocol dataset and comprised a hierarchical sequence of evaluations of non-inferiority of intravitreal aflibercept arms to 0.5 mg ranibizumab to control the overall type I error. The hierarchical sequence of comparisons was: 2q4, 0.5q4, and then 2q8. 95.1% confidence intervals (VIEW1) and 95% confidence intervals (VIEW2) were estimated for the difference between ranibizumab and each intravitreal aflibercept arm in the proportion of patients who maintained vision. Intravitreal aflibercept was considered to be non-inferior to ranibizumab if the confidence interval of the difference lay below 10%, where a positive difference favored ranibizumab.

If all intravitreal aflibercept groups demonstrated non-inferiority to ranibizumab, additional comparisons to ranibizumab would be made with respect to the secondary endpoints in a hierarchical sequence of analyses (Appendix 4). The comparison between 2q4 and Rq4 in the primary endpoint was made, and only if non-inferiority was demonstrated at the 5% level (4.9% for VIEW 1), or 95% confidence interval (95.1% CI for VIEW 1), the analysis moved on to the next comparison between 0.5q4 and Rq4 at the 5% level (4.9% for VIEW1). Otherwise, the testing procedure would be interrupted and no subsequently formal statistical testing could be

performed. If all aflibercept groups demonstrated non-inferiority to ranibizumab for the primary endpoint, additional comparisons to ranibizumab were performed on the secondary endpoints, also using a hierarchical testing sequence in which each secondary endpoint was tested for superiority of aflibercept over ranibizumab at the 5% level (4.9% for VIEW 1). Each secondary endpoint was tested using the full analysis set (all randomized patients who received any study medication and had a baseline and at least one post baseline BCVA assessment), using last observation carried forward. Analyses of proportions were conducted using Pearson's Chi-Square test (in VIEW 1) and the Cochran-Mantel-Haenszel test adjusted for region (in VIEW 2) for the pairwise comparisons of 2q4, 0.5q4, and 2q8 to Rq4. Analyses of continuous variables utilized analysis of covariance with a main-effects model with baseline measure as a covariate and treatment as the main factor. Region is included in the model as an additional factor in VIEW 2. Statistical analyses were conducted by Regeneron Pharmaceuticals, Inc and Bayer Healthcare.

APPENDIX 4: Hierarchy of Statistical Inference for Secondary Endpoints

The secondary endpoint analyses were tested for superiority of Intravitreal aflibercept over ranibizumab. The hierarchical sequence of statistical hypothesis tests utilized for control of multiplicity was as follows:

1. Intravitreal aflibercept 2q4 compared to ranibizumab relative to mean change in BCVA as measured by ETDRS letter score from baseline to week 52.
2. Intravitreal aflibercept 2q4 compared to ranibizumab relative to the proportions of patients who gain 15 or more letters of vision from baseline to week 52.
3. Intravitreal aflibercept 2q4 compared to ranibizumab relative to mean change in total NEI-VFQ-25 score from baseline to week 52.
4. Intravitreal aflibercept 0.5q4 compared to ranibizumab relative to mean change in BCVA as measured by ETDRS letter score from baseline to week 52.
5. Intravitreal aflibercept 0.5q4 compared to ranibizumab relative to the proportions of patients who gain 15 or more letters of vision from baseline to week 52.
6. Intravitreal aflibercept 0.5q4 compared to ranibizumab relative to mean change in total NEI-VFQ-25 score from baseline to week 52.
7. Intravitreal aflibercept 2q8 compared to ranibizumab relative to mean change in BCVA as measured by ETDRS letter score from baseline to week 52.
8. Intravitreal aflibercept 2q8 compared to ranibizumab relative to the proportions of patients who gain 15 or more letters of vision from baseline to week 52.
9. Intravitreal aflibercept 2q8 compared to ranibizumab relative to mean change in total NEI-VFQ-25 score from baseline to week 52.
10. Intravitreal aflibercept 2q4 compared to ranibizumab relative to mean change in CNV area from baseline to week 52
11. Intravitreal aflibercept 0.5q4 compared to ranibizumab relative to mean change in CNV area from baseline to week 52
12. Intravitreal aflibercept 2q8 compared to ranibizumab relative to mean change in CNV area from baseline to week 52

APPENDIX 5. Additional Visual Acuity Endpoints

	VIEW 1				VIEW 2			
	Ranibizumab		Intravitreal Afibercept		Ranibizumab	Intravitreal Afibercept		
	Rq4	2q4	0.5q4	2q8	Rq4	2q4	0.5q4	2q8
N (full analysis set)	304	304	301	301	291	309	296	306
Exploratory endpoints								
Proportion losing ≥ 30 ETDRS letters, % (n)	3.0% (9)	1.0% (3)	1.0% (3)	3.0% (9)	0.7% (2)	1.0% (3)	1.7% (5)	1.6% (5)
Proportion gaining ≥ 0 ETDRS letters, % (n)	78.9% (240)	83.6% (254)	78.1% (235)	79.7% (240)	79.0% (230)	78.0% (241)	83.1% (246)	81.7% (250)
Proportion gaining ≥ 30 ETDRS letters, % (n)	5.6% (17)	7.6% (23)	3.7% (11)	7.0% (21)	5.5% (16)	2.9% (9)	5.7% (17)	4.9% (15)
Proportion with best-corrected visual acuity (BCVA) of 20/40 or better, % (n)	34.5% (105)	45.7% (139)	34.9% (105)	37.9% (114)	35.7% (104)	32.7% (101)	32.4% (96)	27.5% (84)

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months following 3 initial monthly doses; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; Rq4 = 0.5 mg ranibizumab monthly.

APPENDIX 6. Proportion of Patients with Dry Retina^a at Week 52 (Post-hoc Analysis)^b

	Ranibizumab	Intravitreal Aflibercept		
	0.5q4	2q4	0.5q4	2q8
VIEW1, % (n)	63.6% (171/269)	64.8% (184/284)	56.7% (148/261)	63.4% (168/265)
VIEW2, % (n)	60.4% (162/268)	80.3% (220/274)	63.9% (170/266)	71.9% (197/274)
Integrated (combined VIEW1 and VIEW2), % (n)	62.0% (333/537)	72.4% (404/558)	60.3% (318/527)	67.7% (365/539)

^aDefined as absence of cystic intra-retinal edema and sub-retinal fluid on optical coherence tomography.

^bObserved case, Full analysis set.

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months following 3 initial monthly doses.

APPENDIX 7: Ocular and Non-ocular Treatment-Emergent Adverse and Serious Adverse Events

Table 1. VIEW 1. Ocular TEAEs in the Study Eye Occurring in at Least 5% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab 0.5q4 (N=304)	Intravitreal Aflibercept			Combined (N=911)
		2q4 (N=304)	0.5q4 (N=304)	2q8 (N=303)	
Number of patients with at least 1 Ocular TEAE in study eye	246 (80.9%)	228 (75.0%)	226 (74.3%)	238 (78.5%)	692 (76.0%)
Eye disorders	238 (78.3%)	224 (73.7%)	224 (73.7%)	233 (76.9%)	681 (74.8%)
Conjunctival haemorrhage	144 (47.4%)	109 (35.9%)	120 (39.5%)	131 (43.2%)	360 (39.5%)
Vitreous floaters	33 (10.9%)	40 (13.2%)	23 (7.6%)	21 (6.9%)	84 (9.2%)
Eye pain	26 (8.6%)	33 (10.9%)	27 (8.9%)	22 (7.3%)	82 (9.0%)
Vitreous detachment	24 (7.9%)	26 (8.6%)	23 (7.6%)	19 (6.3%)	68 (7.5%)
Visual acuity reduced	20 (6.6%)	24 (7.9%)	23 (7.6%)	20 (6.6%)	67 (7.4%)
Retinal haemorrhage	19 (6.3%)	9 (3.0%)	17 (5.6%)	23 (7.6%)	49 (5.4%)
Retinal pigment epitheliopathy	11 (3.6%)	16 (5.3%)	15 (4.9%)	13 (4.3%)	44 (4.8%)
Macular degeneration	16 (5.3%)	16 (5.3%)	17 (5.6%)	10 (3.3%)	43 (4.7%)
Intraocular pressure increased	22 (7.2%)	14 (4.6%)	12 (3.9%)	15 (5.0%)	41 (4.5%)
Eye irritation	16 (5.3%)	13 (4.3%)	13 (4.3%)	12 (4.0%)	38 (4.2%)
Maculopathy	19 (6.3%)	10 (3.3%)	20 (6.6%)	8 (2.6%)	38 (4.2%)
Foreign body sensation in eyes	9 (3.0%)	8 (2.6%)	9 (3.0%)	16 (5.3%)	33 (3.6%)
Investigations	23 (7.6%)	15 (4.9%)	15 (4.9%)	16 (5.3%)	46 (5.0%)
Intraocular pressure increased	22 (7.2%)	14 (4.6%)	12 (3.9%)	15 (5.0%)	41 (4.5%)

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks.

TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table 2. VIEW 1. Non-Ocular TEAEs Occurring in at Least 2% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab 0.5q4 (N = 304)	Intravitreal Afibercept		
		2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)
Number of patients with at least 1 non-ocular TEAE	234 (77.0%)	220 (72.4%)	231 (76.0%)	223 (73.6%)
674 (74.0%)				
Infections and infestations	123 (40.5%)	96 (31.6%)	102 (33.6%)	104 (34.3%)
				302 (33.2%)
Nasopharyngitis	23 (7.6%)	33 (10.9%)	24 (7.9%)	26 (8.6%)
				83 (9.1%)
Upper respiratory tract infection	13 (4.3%)	11 (3.6%)	14 (4.6%)	18 (5.9%)
				43 (4.7%)
Urinary tract infection	17 (5.6%)	14 (4.6%)	15 (4.9%)	13 (4.3%)
				42 (4.6%)
Bronchitis	16 (5.3%)	12 (3.9%)	11 (3.6%)	17 (5.6%)
				40 (4.4%)
Sinusitis	8 (2.6%)	7 (2.3%)	11 (3.6%)	11 (3.6%)
				29 (3.2%)
Influenza	9 (3.0%)	7 (2.3%)	3 (1.0%)	7 (2.3%)
				17 (1.9%)
Pneumonia	14 (4.6%)	5 (1.6%)	4 (1.3%)	6 (2.0%)
				15 (1.6%)
Gastroenteritis viral	3 (1.0%)	5 (1.6%)	6 (2.0%)	3 (1.0%)
				14 (1.5%)
Cystitis	6 (2.0%)	5 (1.6%)	5 (1.6%)	3 (1.0%)
				13 (1.4%)
Cellulitis	7 (2.3%)	3 (1.0%)	6 (2.0%)	2 (0.7%)
				11 (1.2%)
Investigations	48 (15.8%)	57 (18.8%)	59 (19.4%)	60 (19.8%)
				176 (19.3%)
Blood glucose increased	8 (2.6%)	9 (3.0%)	11 (3.6%)	7 (2.3%)
				27 (3.0%)
Protein urine present	7 (2.3%)	7 (2.3%)	7 (2.3%)	10 (3.3%)
				24 (2.6%)
Urine protein/creatinine ratio increased	3 (1.0%)	6 (2.0%)	9 (3.0%)	6 (2.0%)
				21 (2.3%)
Blood urine present	4 (1.3%)	7 (2.3%)	5 (1.6%)	6 (2.0%)
				18 (2.0%)
Blood pressure increased	4 (1.3%)	5 (1.6%)	3 (1.0%)	9 (3.0%)
				17 (1.9%)
Nervous system disorders	35 (11.5%)	40 (13.2%)	47 (15.5%)	47 (15.5%)
				134 (14.7%)
Headache	19 (6.3%)	11 (3.6%)	11 (3.6%)	12 (4.0%)
				34 (3.7%)
Dizziness	5 (1.6%)	8 (2.6%)	6 (2.0%)	7 (2.3%)
				21 (2.3%)
Transient ischaemic attack	0	2 (0.7%)	6 (2.0%)	1 (0.3%)
				9 (1.0%)
Injury, poisoning and procedural complications	42 (13.8%)	33 (10.9%)	47 (15.5%)	45 (14.9%)
				125 (13.7%)
Fall	15 (4.9%)	14 (4.6%)	12 (3.9%)	16 (5.3%)
				42 (4.6%)
Contusion	4 (1.3%)	1 (0.3%)	7 (2.3%)	3 (1.0%)
				11 (1.2%)
Gastrointestinal disorders	52 (17.1%)	39 (12.8%)	37 (12.2%)	40 (13.2%)
				116 (12.7%)
Nausea	13 (4.3%)	12 (3.9%)	10 (3.3%)	7 (2.3%)
				29 (3.2%)
Diarrhoea	9 (3.0%)	11 (3.6%)	7 (2.3%)	5 (1.7%)
				23 (2.5%)
Gastroesophageal reflux disease	6 (2.0%)	2 (0.7%)	8 (2.6%)	6 (2.0%)
				16 (1.8%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab		Intravitreal Aflibercept		
	0.5q4 (N = 304)	2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)
Insomnia	6 (2.0%)	1 (0.3%)	5 (1.6%)	3 (1.0%)	9 (1.0%)
Immune system disorders	8 (2.6%)	10 (3.3%)	12 (3.9%)	16 (5.3%)	38 (4.2%)
Seasonal allergy	4 (1.3%)	6 (2.0%)	9 (3.0%)	9 (3.0%)	24 (2.6%)
Blood and lymphatic system disorders	10 (3.3%)	6 (2.0%)	14 (4.6%)	9 (3.0%)	29 (3.2%)
Anaemia	6 (2.0%)	3 (1.0%)	6 (2.0%)	6 (2.0%)	15 (1.6%)
Ear and labyrinth disorders	7 (2.3%)	7 (2.3%)	6 (2.0%)	11 (3.6%)	24 (2.6%)
Vertigo	4 (1.3%)	5 (1.6%)	3 (1.0%)	8 (2.6%)	16 (1.8%)

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks.

TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table 3. VIEW 1. Number of Patients with Ocular Serious Treatment Emergent Adverse Events of Study Eye by Primary System Organ Class and Preferred Term (Safety Analysis Set)

	Ranibizumab	Intravitreal Aflibercept				
Primary System Organ Class Preferred Term MedDRA Version 13.0	0.5q4 (N=304)	2q4 (N=304)	0.5q4 (N=304)	2q8 (N=303)	Combined (N=911)	Total (N=1215)
Number of patients with at least one such Adverse Event	10 (3.3%)	7 (2.3%)	6 (2.0%)	3 (1.0%)	16 (1.8%)	26 (2.1%)
Eye disorders	6 (2.0%)	4 (1.3%)	6 (2.0%)	3 (1.0%)	13 (1.4%)	19 (1.6%)
Visual acuity reduced	2 (0.7%)	1 (0.3%)	2 (0.7%)	0	3 (0.3%)	5 (0.4%)
Retinal haemorrhage	2 (0.7%)	0	0	2 (0.7%)	2 (0.2%)	4 (0.3%)
Angle closure glaucoma	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Cataract	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Keratitis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Macular hole	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Retinal degeneration	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Retinal detachment	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Retinal oedema	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Retinal pigment epithelial tear	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Retinal tear	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Infections and infestations	3 (1.0%)	3 (1.0%)	0	0	3 (0.3%)	6 (0.5%)
Endophthalmitis	3 (1.0%)	3 (1.0%)	0	0	3 (0.3%)	6 (0.5%)
Injury, poisoning and procedural complications	1 (0.3%)	0	0	0	0	1 (<0.1%)
Incorrect dose administered	1 (0.3%)	0	0	0	0	1 (<0.1%)
Investigations	1 (0.3%)	0	0	0	0	1 (<0.1%)
Intraocular pressure increased	1 (0.3%)	0	0	0	0	1 (<0.1%)
Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered as 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 weeks, respectively. Ranibizumab administered as 0.5 mg every 4 weeks. At each level of subject summarization, a patient was counted once if the patient reported one or more events						

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered as 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 weeks, respectively. Ranibizumab administered as 0.5 mg every 4 weeks. At each level of subject summarization, a patient was counted once if the patient reported one or more events.

TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table 4. VIEW 1. Number of Patients with Non-Ocular Serious Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab 0.5q4 (N = 304)	Intravitreal Aflibercept				Total (N = 1215)
		2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)	
Number of patients with at least one such Adverse Event	57 (18.8%)	40 (13.2%)	50 (16.4%)	51 (16.8%)	141 (15.5%)	198 (16.3%)
Infections and infestations	15 (4.9%)	6 (2.0%)	11 (3.6%)	12 (4.0%)	29 (3.2%)	44 (3.6%)
Pneumonia	7 (2.3%)	3 (1.0%)	2 (0.7%)	5 (1.7%)	10 (1.1%)	17 (1.4%)
Bronchitis	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)
Cellulitis	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	4 (0.3%)
Gastroenteritis	1 (0.3%)	0	0	2 (0.7%)	2 (0.2%)	3 (0.2%)
Urinary tract infection	1 (0.3%)	2 (0.7%)	0	0	2 (0.2%)	3 (0.2%)
Arthritis bacterial	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Clostridial infection	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Clostridium difficile colitis	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Endocarditis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Escherichia urinary tract infection	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Lobar pneumonia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Pyelonephritis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Septic shock	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Sinusitis	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Sinusitis fungal	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Staphylococcal bacteraemia	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Urinary tract infection bacterial	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Vestibular neuronitis	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Viral infection	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Device related infection	1 (0.3%)	0	0	0	0	1 (<0.1%)
Diverticulitis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Lung infection	1 (0.3%)	0	0	0	0	1 (<0.1%)
Pharyngitis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Scrotal abscess	1 (0.3%)	0	0	0	0	1 (<0.1%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab	Intravitreal Aflibercept				Total (N = 1215)
	0.5q4 (N = 304)	2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)	
Viral pericarditis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Cardiac disorders	14 (4.6%)	7 (2.3%)	10 (3.3%)	11 (3.6%)	28 (3.1%)	42 (3.5%)
Atrial fibrillation	2 (0.7%)	2 (0.7%)	3 (1.0%)	3 (1.0%)	8 (0.9%)	10 (0.8%)
Cardiac failure congestive	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (1.0%)	6 (0.7%)	8 (0.7%)
Myocardial infarction	3 (1.0%)	1 (0.3%)	3 (1.0%)	2 (0.7%)	6 (0.7%)	9 (0.7%)
Coronary artery disease	4 (1.3%)	0	4 (1.3%)	0	4 (0.4%)	8 (0.7%)
Acute myocardial infarction	0	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	2 (0.2%)
Acute coronary syndrome	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Aortic valve stenosis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Arrhythmia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Bradycardia	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Cardiac arrest	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Coronary artery occlusion	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)
Intracardiac thrombus	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Mitral valve incompetence	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Sick sinus syndrome	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Tachycardia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Ventricular fibrillation	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Ventricular tachycardia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Angina unstable	1 (0.3%)	0	0	0	0	1 (<0.1%)
Cardiac failure chronic	1 (0.3%)	0	0	0	0	1 (<0.1%)
Supraventricular tachycardia	1 (0.3%)	0	0	0	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (3.3%)	9 (3.0%)	10 (3.3%)	9 (3.0%)	28 (3.1%)	38 (3.1%)
Squamous cell carcinoma of skin	3 (1.0%)	2 (0.7%)	1 (0.3%)	3 (1.0%)	6 (0.7%)	9 (0.7%)
Bladder transitional cell carcinoma	0	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	2 (0.2%)
Breast cancer	0	0	2 (0.7%)	0	2 (0.2%)	2 (0.2%)
Prostate cancer	1 (0.3%)	0	2 (0.7%)	0	2 (0.2%)	3 (0.2%)
Prostate cancer metastatic	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)
Breast cancer in situ	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Bronchioloalveolar carcinoma	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Chronic lymphocytic leukaemia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab 0.5q4 (N = 304)	Intravitreal Aflibercept				Total (N = 1215)
		2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)	
Colon cancer	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Leukaemia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Lung neoplasm	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Malignant melanoma	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Non-small cell lung cancer stage IV	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Rectosigmoid cancer	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Renal cell carcinoma	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Salivary gland cancer recurrent	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Thyroid cancer	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Tonsil cancer	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Transitional cell carcinoma	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Atypical fibroxanthoma	1 (0.3%)	0	0	0	0	1 (<0.1%)
Hepatic neoplasm malignant	1 (0.3%)	0	0	0	0	1 (<0.1%)
Lung neoplasm malignant	1 (0.3%)	0	0	0	0	1 (<0.1%)
Oesophageal adenocarcinoma	1 (0.3%)	0	0	0	0	1 (<0.1%)
Tumour perforation	1 (0.3%)	0	0	0	0	1 (<0.1%)
Nervous system disorders	1 (0.3%)	6 (2.0%)	13 (4.3%)	6 (2.0%)	25 (2.7%)	26 (2.1%)
Transient ischaemic attack	0	2 (0.7%)	5 (1.6%)	1 (0.3%)	8 (0.9%)	8 (0.7%)
Cerebrovascular accident	0	0	1 (0.3%)	3 (1.0%)	4 (0.4%)	4 (0.3%)
Syncope	1 (0.3%)	1 (0.3%)	2 (0.7%)	0	3 (0.3%)	4 (0.3%)
Carotid artery stenosis	0	2 (0.7%)	0	0	2 (0.2%)	2 (0.2%)
Subarachnoid haemorrhage	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)
Balance disorder	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cerebral artery thrombosis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Cerebral haemorrhage	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Cerebral infarction	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Ischaemic cerebral infarction	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Metabolic encephalopathy	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Spinal cord compression	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Injury, poisoning and procedural complications	5 (1.6%)	6 (2.0%)	5 (1.6%)	8 (2.6%)	19 (2.1%)	24 (2.0%)
Fall	5 (1.6%)	6 (2.0%)	4 (1.3%)	6 (2.0%)	16 (1.8%)	21 (1.7%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab		Intravitreal Aflibercept				Total (N = 1215)
	0.5q4 (N = 304)	2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)		
Hip fracture	1 (0.3%)	2 (0.7%)	2 (0.7%)	0	4 (0.4%)	5 (0.4%)	
Subdural haematoma	1 (0.3%)	0	1 (0.3%)	2 (0.7%)	3 (0.3%)	4 (0.3%)	
Humerus fracture	0	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	2 (0.2%)	
Rib fracture	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)	
Femur fracture	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Incisional hernia, obstructive	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Pubis fracture	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)	
Snake bite	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Subcutaneous haematoma	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Traumatic brain injury	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Upper limb fracture	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Lumbar vertebral fracture	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Spinal fracture	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Gastrointestinal disorders	5 (1.6%)	4 (1.3%)	4 (1.3%)	3 (1.0%)	11 (1.2%)	16 (1.3%)	
Gastritis	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	
Colitis ischaemic	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Constipation	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Diarrhoea	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Duodenal ulcer haemorrhage	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)	
Gastric ulcer	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Gastrointestinal motility disorder	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Gastroesophageal reflux disease	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Haematochezia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Hiatus hernia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Ileus	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Lower gastrointestinal haemorrhage	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Colonic polyp	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Gastritis erosive	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Haemorrhoids	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Intestinal obstruction	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Respiratory, thoracic and mediastinal disorders	4 (1.3%)	4 (1.3%)	3 (1.0%)	4 (1.3%)	11 (1.2%)	15 (1.2%)	

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab	Intravitreal Aflibercept				Total (N = 1215)
	0.5q4 (N = 304)	2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)	
Chronic obstructive pulmonary disease	2 (0.7%)	3 (1.0%)	2 (0.7%)	2 (0.7%)	7 (0.8%)	9 (0.7%)
Pneumonitis	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)
Pleural effusion	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Pneumonia aspiration	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	2 (0.2%)
Pulmonary embolism	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Pulmonary fibrosis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Respiratory failure	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Apnoeic attack	1 (0.3%)	0	0	0	0	1 (<0.1%)
Metabolism and nutrition disorders	2 (0.7%)	3 (1.0%)	3 (1.0%)	3 (1.0%)	9 (1.0%)	11 (0.9%)
Hyponatraemia	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)	4 (0.3%)
Dehydration	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)
Diabetes mellitus	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Diabetes mellitus inadequate control	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Hyperkalaemia	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Hypokalaemia	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)
Malnutrition	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Shock hypoglycaemic	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Vascular disorders	5 (1.6%)	2 (0.7%)	3 (1.0%)	4 (1.3%)	9 (1.0%)	14 (1.2%)
Deep vein thrombosis	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)
Aortic aneurysm	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)
Aortic stenosis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Arteriosclerosis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Hypertension	2 (0.7%)	0	1 (0.3%)	0	1 (0.1%)	3 (0.2%)
Iliac artery occlusion	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Peripheral artery aneurysm	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Shock haemorrhagic	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Aortic aneurysm rupture	1 (0.3%)	0	0	0	0	1 (<0.1%)
Orthostatic hypotension	1 (0.3%)	0	0	0	0	1 (<0.1%)
General disorders and administration site conditions	1 (0.3%)	2 (0.7%)	2 (0.7%)	2 (0.7%)	6 (0.7%)	7 (0.6%)
Asthenia	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Catheter site haematoma	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab 0.5q4 (N = 304)	Intravitreal Aflibercept				Total (N = 1215)
		2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)	
Chest pain	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)
Drug withdrawal syndrome	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Non-cardiac chest pain	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Pyrexia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Musculoskeletal and connective tissue disorders	5 (1.6%)	1 (0.3%)	0	3 (1.0%)	4 (0.4%)	9 (0.7%)
Back pain	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Intervertebral disc degeneration	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Intervertebral disc protrusion	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Lumbar spinal stenosis	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	2 (0.2%)
Osteoarthritis	3 (1.0%)	0	0	0	0	3 (0.2%)
Spinal column stenosis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Spinal osteoarthritis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Spondylolisthesis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Ear and labyrinth disorders	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)	3 (0.2%)
Vertigo	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)
Meniere's disease	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Hepatobiliary disorders	3 (1.0%)	2 (0.7%)	0	1 (0.3%)	3 (0.3%)	6 (0.5%)
Cholecystitis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cholecystitis chronic	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Cholelithiasis	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)
Bile duct stone	1 (0.3%)	0	0	0	0	1 (<0.1%)
Portal vein thrombosis	1 (0.3%)	0	0	0	0	1 (<0.1%)
Renal and urinary disorders	1 (0.3%)	0	2 (0.7%)	1 (0.3%)	3 (0.3%)	4 (0.3%)
Renal failure acute	0	0	2 (0.7%)	1 (0.3%)	3 (0.3%)	3 (0.2%)
Calculus ureteric	1 (0.3%)	0	0	0	0	1 (<0.1%)
Investigations	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)
Blood glucose increased	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Blood pressure increased	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Psychiatric disorders	2 (0.7%)	0	0	2 (0.7%)	2 (0.2%)	4 (0.3%)
Confusional state	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Psychotic disorder	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab 0.5q4 (N = 304)	Intravitreal Aflibercept				Total (N = 1215)
		2q4 (N = 304)	0.5q4 (N = 304)	2q8 (N = 303)	Combined (N = 911)	
Mental status changes	2 (0.7%)	0	0	0	0	2 (0.2%)
Blood and lymphatic system disorders	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Anaemia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Congenital, familial and genetic disorders	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Arteriovenous malformation	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Reproductive system and breast disorders	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Cystocele	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered as 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 weeks, respectively. Ranibizumab administered as 0.5 mg every 4 weeks. At each level of patient summarization, a patient was counted once if the patient reported one or more events.

TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table 5. VIEW 2. Ocular TEAEs in the Study Eye Occurring in $\geq 5.0\%$ of the Patients in any Treatment Group (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab	Intravitreal Aflibercept			
	0.5q4 (N = 291) n (%)	2q4 (N = 309) n (%)	0.5q4 (N = 297) n (%)	2q8 (N = 307) n (%)	Combined (N = 913) n (%)
Any ocular TEAE (study eye)	187 (64.3%)	191 (61.8%)	182 (61.3%)	198 (64.5%)	571 (62.5%)
Eye disorders	181 (62.2%)	180 (58.3%)	169 (56.9%)	190 (61.9%)	539 (59.0%)
Visual acuity reduced	20 (6.9%)	26 (8.4%)	34 (11.4%)	33 (10.7%)	93 (10.2%)
Conjunctival haemorrhage	23 (7.9%)	24 (7.8%)	37 (12.5%)	30 (9.8%)	91 (10.0%)
Retinal haemorrhage	29 (10.0%)	27 (8.7%)	30 (10.1%)	27 (8.8%)	84 (9.2%)
Macular degeneration	23 (7.9%)	27 (8.7%)	23 (7.7%)	30 (9.8%)	80 (8.8%)
Eye pain	27 (9.3%)	33 (10.7%)	22 (7.4%)	21 (6.8%)	76 (8.3%)
Intraocular pressure increased	19 (6.5%)	24 (7.8%)	15 (5.1%)	15 (4.9%)	54 (5.9%)
Detachment of retinal pigment epithelium	15 (5.2%)	18 (5.8%)	15 (5.1%)	12 (3.9%)	45 (4.9%)
Vitreous detachment	9 (3.1%)	18 (5.8%)	9 (3.0%)	15 (4.9%)	42 (4.6%)
Cataract	15 (5.2%)	16 (5.2%)	12 (4.0%)	12 (3.9%)	40 (4.4%)
Ocular hyperaemia	18 (6.2%)	12 (3.9%)	13 (4.4%)	9 (2.9%)	34 (3.7%)
Retinal degeneration	11 (3.8%)	17 (5.5%)	9 (3.0%)	7 (2.3%)	33 (3.6%)

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks. Preferred terms are sorted in descending order by frequency in the aflibercept combined group.

TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table 6. VIEW 2. Non-ocular TEAEs Occurring in $\geq 2.0\%$ of the Patients in any Treatment Group (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab	Intravitreal Aflibercept			
	0.5q4 (N = 291) n (%)	2q4 (N = 309) n (%)	0.5q4 (N = 297) n (%)	2q8 (N = 307) n (%)	Combined (N = 913) n (%)
Any non-ocular TEAE	181 (62.2)	231 (74.8%)	206 (69.4%)	213 (69.4%)	650 (71.2%)
Infections and infestations	77 (26.5%)	72 (23.3%)	67 (22.6%)	73 (23.8%)	212 (23.2%)
Nasopharyngitis	25 (8.6%)	14 (4.5%)	25 (8.4%)	19 (6.2%)	58 (6.4%)
Influenza	7 (2.4%)	14 (4.5%)	8 (2.7%)	17 (5.5%)	39 (4.3%)
Bronchitis	7 (2.4%)	13 (4.2%)	9 (3.0%)	9 (2.9%)	31 (3.4%)
Urinary tract infection	9 (3.1%)	7 (2.3%)	6 (2.0%)	5 (1.6%)	18 (2.0%)
Cystitis	3 (1.0%)	6 (1.9%)	6 (2.0%)	2 (0.7%)	14 (1.5%)
Upper respiratory tract infection	6 (2.1%)	3 (1.0%)	5 (1.7%)	5 (1.6%)	13 (1.4%)
Investigations	43 (14.8%)	63 (20.4%)	55 (18.5%)	61 (19.9%)	179 (19.6%)
Blood glucose increased	1 (0.3%)	12 (3.9%)	8 (2.7%)	8 (2.6%)	28 (3.1%)
Electrocardiogram T wave inversion	5 (1.7%)	9 (2.9%)	2 (0.7%)	7 (2.3%)	18 (2.0%)
Cardiac disorders	32 (11.0%)	48 (15.5%)	35 (11.8%)	40 (13.0%)	123 (13.5%)
Atrioventricular block first degree	10 (3.4%)	20 (6.5%)	14 (4.7%)	9 (2.9%)	43 (4.7%)
Atrial fibrillation	3 (1.0%)	7 (2.3%)	1 (0.3%)	5 (1.6%)	13 (1.4%)
Gastrointestinal disorders	30 (10.3%)	40 (12.9%)	34 (11.4%)	45 (14.7%)	119 (13.0%)
Diarrhoea	10 (3.4%)	8 (2.6%)	10 (3.4%)	14 (4.6%)	32 (3.5%)
Vomiting	6 (2.1%)	4 (1.3%)	3 (1.0%)	2 (0.7%)	9 (1.0%)
Musculoskeletal and connective tissue disorders	31 (10.7%)	36 (11.7%)	33 (11.1%)	39 (12.7%)	108 (11.8%)
Back pain	13 (4.5%)	14 (4.5%)	9 (3.0%)	11 (3.6%)	34 (3.7%)
Arthralgia	8 (2.7%)	7 (2.3%)	10 (3.4%)	3 (1.0%)	20 (2.2%)
Osteoarthritis	4 (1.4%)	5 (1.6%)	5 (1.7%)	6 (2.0%)	16 (1.8%)
Nervous system disorders	27 (9.3%)	33 (10.7%)	26 (8.8%)	35 (11.4%)	94 (10.3%)
Headache	11 (3.8%)	9 (2.9%)	12 (4.0%)	17 (5.5%)	38 (4.2%)
Dizziness	9 (3.1%)	5 (1.6%)	1 (0.3%)	9 (1.0%)	9 (1.0%)
Vascular disorders	27 (9.3%)	33 (10.7%)	24 (8.1%)	23 (7.5%)	80 (8.8%)
Hypertension	22 (7.6%)	22 (7.1%)	18 (6.1%)	16 (5.2%)	56 (6.1%)
Respiratory, thoracic and	24 (8.2%)	25 (8.1%)	25 (8.4%)	24 (7.8%)	74 (8.1%)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab	Intravitreal Aflibercept		
	0.5q4 (N = 291) n (%)	2q4 (N = 309) n (%)	0.5q4 (N = 297) n (%)	2q4 (N = 307) n (%)
mediastinal disorders				
Cough	7 (2.4%)	2 (0.6%)	7 (2.4%)	3 (1.0%)
Injury, poisoning and procedural complications	19 (6.5%)	18 (5.8%)	26 (8.8%)	27 (8.8%)
Fall	9 (3.1%)	3 (1.0%)	4 (1.3%)	2 (0.7%)
General disorders and admi- nistration site conditions	18 (6.2%)	22 (7.1%)	29 (9.8%)	13 (4.2%)
Pyrexia	8 (2.7%)	8 (2.6%)	15 (5.1%)	5 (1.6%)
Metabolism and nutrition disorders	12 (4.1%)	19 (6.1%)	16 (5.4%)	23 (7.5%)
Diabetes mellitus	4 (1.4%)	7 (2.3%)	2 (0.7%)	7 (2.3%)
Hyperglycemia	2 (0.7%)	2 (0.6%)	6 (2.0%)	2 (0.7%)
Blood and lymphatic system disorders	11 (3.8%)	5 (1.6%)	12 (4.0%)	10 (3.3%)
Anemia	6 (2.1%)	4 (1.3%)	8 (2.7%)	7 (2.3%)
Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q4 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks. System organ classes (SOCs) are sorted in descending order by frequency in the VEGF Trap-Eye combined group, preferred terms are sorted within each SOC in descending order by frequency in the VEGF Trap-Eye combined group. TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities				
				19 (2.1%)
				27 (3.0%)

Table 7. VIEW 2. Number of Patients with Ocular Treatment-Emergent Serious Adverse Events of Study Eye by Primary System Organ Class and Preferred Term (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab		Intravitreal Aflibercept				Total N=1204 (100%)
	0.5q4 N=291 (100%)	2q4 N=309 (100%)	0.5q4 N=297 (100%)	2q8 N=307 (100%)	Combined N=913 (100%)		
Number of patients with at least one of such adverse events	9 (3.1%)	6 (1.9%)	5 (1.7%)	9 (2.9%)	20 (2.2%)	29 (2.4%)	
Eye disorders							
Cataract	9 (3.1%)	6 (1.9%)	4 (1.3%)	8 (2.6%)	18 (2.0%)	27 (2.2%)	
Cataract cortical	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	3 (0.2%)	
Cataract nuclear	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Cataract nuclear	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Hyphaema	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Macular cyst	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Macular degeneration	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Macular hole	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Posterior capsule opacification	2 (0.7%)	0	0	0	0	2 (0.2%)	
Retinal degeneration	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Retinal detachment	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	2 (0.2%)	
Retinal haemorrhage	1 (0.3%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	4 (0.4%)	5 (0.4%)	
Retinal pigment epithelial tear	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	3 (0.2%)	
Retinal pigment epitheliopathy	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Visual acuity reduced	1 (0.3%)	1 (0.3%)	1 (0.3%)	5 (1.6%)	7 (0.8%)	8 (0.7%)	
Injury, poisoning and procedural complications	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Macular scar	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Investigations	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)	
Intraocular pressure increased	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)	
Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks. At each level of patient summarization, a patient was counted once if the patient reported one or more events.							

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks. At each level of patient summarization, a patient was counted once if the patient reported one or more events.

MedDRA = Medical Dictionary for Regulatory Activities .

Table 8. VIEW 2. Number of Patients with Non-ocular Treatment-Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term (Safety Analysis Set)

	Ranibizumab	Intravitreal Aflibercept				Combined N = 913 (100%)	Total N = 1204 (100%)
Primary System Organ Class Preferred Term MedDRA Version 13.0	0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)			
Number of patients with at least one of such adverse events	26 (8.9%)	36 (11.7%)	37 (12.5%)	38 (12.4%)	111 (12.2%)	137 (11.4%)	
Blood and lymphatic system disorders	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)	3 (0.2%)	
Anaemia	0	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	2 (0.2%)	
Febrile neutropenia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Cardiac disorders	5 (1.7%)	8 (2.6%)	7 (2.4%)	11 (3.6%)	26 (2.8%)	31 (2.6%)	
Acute coronary syndrome	0	2 (0.6%)	2 (0.7%)	1 (0.3%)	5 (0.5%)	5 (0.4%)	
Acute myocardial infarction	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	2 (0.2%)	
Angina pectoris	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	3 (0.2%)	
Arteriosclerosis coronary artery	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Atrial fibrillation	2 (0.7%)	1 (0.3%)	0	3 (1.0%)	4 (0.4%)	6 (0.5%)	
Atrial flutter	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Atrioventricular block	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Cardiac arrest	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Cardiac failure	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Cardiovascular insufficiency	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Coronary artery disease	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Myocardial infarction	2 (0.7%)	0	3 (1.0%)	3 (1.0%)	6 (0.7%)	8 (0.7%)	
Myocardial ischaemia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Palpitations	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Pericarditis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Supraventricular tachycardia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Ear and labyrinth disorders	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Tympanic membrane disorder	1 (0.3%)	0	0	0	1 (0.1%)	2 (0.2%)	
Vertigo	0	0	1 (0.3%)	0	0	1 (<0.1%)	

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab		Intravitreal Aflibercept				Combined N = 913 (100%)	Total N = 1204 (100%)
	0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)				
Gastrointestinal disorders	0	4 (1.3%)	6 (2.0%)	6 (2.0%)	16 (1.8%)	16 (1.3%)		
Anal fistula	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Colitis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Constipation	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Diverticulum intestinal	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Gastric ulcer	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Gastritis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Gastritis erosive	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)		
Inguinal hernia	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)	3 (0.2%)		
Intestinal obstruction	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Large intestine perforation	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Lower gastrointestinal haemorrhage	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Pancreatitis acute	0	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	2 (0.2%)		
Small intestinal obstruction	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
General disorders and administration site conditions	3 (1.0%)	4 (1.3%)	1 (0.3%)	1 (0.3%)	6 (0.7%)	9 (0.7%)		
Chest pain	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)		
Death	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Device dislocation	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)		
Device malfunction	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Oedema peripheral	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	2 (0.2%)		
Pyrexia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Hepatobiliary disorders	0	2 (0.6%)	1 (0.3%)	0	3 (0.3%)	3 (0.2%)		
Cholecystitis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Cholecystitis acute	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Cholelithiasis	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab		Intravitreal Aflibercept				Combined N = 913 (100%)	Total N = 1204 (100%)
	0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)				
Infections and infestations	6 (2.1%)	4 (1.3%)	0	8 (2.6%)	12 (1.3%)	18 (1.5%)		
Appendicitis	1 (0.3%)	0	0	0	0	1 (<0.1%)		
Bronchitis	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	3 (0.2%)		
Dysentery	1 (0.3%)	0	0	0	0	1 (<0.1%)		
Dysentery	1 (0.3%)	0	0	0	0	1 (<0.1%)		
Escherichia sepsis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Gastroenteritis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Gastroenteritis norovirus	1 (0.3%)	0	0	0	0	1 (<0.1%)		
Nervous system disorders	2 (0.7%)	8 (2.6%)	2 (0.7%)	3 (1.0%)	13 (1.4%)	15 (1.2%)		
Brain oedema	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Cerebral infarction	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Pneumonia pneumococcal	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Postoperative wound infection	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Respiratory tract infection	1 (0.3%)	0	0	0	0	1 (<0.1%)		
Septic shock	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Urinary tract infection	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	2 (0.2%)		

Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab	Intravitreal Aflibercept				Combined N = 913 (100%)	Total N = 1204 (100%)
	0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)			
Injury, poisoning and procedural complications	2 (0.7%)	1 (0.3%)	7 (2.4%)	6 (2.0%)	14 (1.5%)	16 (1.3%)	
Accident	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Ankle fracture	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Burns second degree	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Clavicle fracture	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Concussion	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Contusion	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Fall	2 (0.7%)	0	1 (0.3%)	0	1 (0.1%)	3 (0.2%)	
Femoral neck fracture	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Femur fracture	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Graft thrombosis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Head injury	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Injury	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Joint injury	1 (0.3%)	0	0	0	0	1 (<0.1%)	
Lower limb fracture	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Lumbar vertebral fracture	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Meniscus lesion	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Post procedural complication	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Radius fracture	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Road traffic accident	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	
Skull fractured base	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Subdural haematoma	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Lumbar vertebral fracture	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Meniscus lesion	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	
Post procedural complication	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)	
Radius fracture	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Road traffic accident	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	
Skull fractured base	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Subdural haematoma	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)	
Upper limb fracture	0	0	2 (0.7%)	0	2 (0.2%)	2 (0.2%)	
Wound haemorrhage	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)	

	Ranibizumab	Intravitreal Aflibercept				
Primary System Organ Class Preferred Term MedDRA Version 13.0	0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)	Combined N = 913 (100%)	Total N = 1204 (100%)
Investigations	0	2 (0.6%)	0	0	2 (0.2%)	2 (0.2%)
Blood osmolarity decreased	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Electrocardiogram QT prolonged	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Metabolism and nutrition disorders	2 (0.7%)	0	0	0	0	2 (0.2%)
Dehydration	1 (0.3%)	0	0	0	0	1 (<0.1%)
Diabetes mellitus	1 (0.3%)	0	0	0	0	1 (<0.1%)
Hyperglycaemia	1 (0.3%)	0	0	0	0	1 (<0.1%)
Musculoskeletal and connective tissue disorders	2 (0.7%)	3 (1.0%)	0	2 (0.7%)	5 (0.5%)	7 (0.6%)
Arthralgia	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Arthritis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Dupuytren's contracture	1 (0.3%)	0	0	0	0	1 (<0.1%)
Intervertebral disc protrusion	1 (0.3%)	0	0	0	0	1 (<0.1%)
Neck pain	0	1 (0.3%)	0	0	0	1 (<0.1%)
Rheumatoid arthritis	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Sjogren's syndrome	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Synovitis	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0%)	3 (1.0%)	9 (3.0%)	5 (1.6%)	17 (1.9%)	20 (1.7%)
Acute myeloid leukaemia	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Basal cell carcinoma	1 (0.3%)	0	2 (0.7%)	0	2 (0.2%)	3 (0.2%)
Bladder cancer	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Bladder cancer recurrent	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Breast cancer	1 (0.3%)	0	3 (1.0%)	1 (0.3%)	4 (0.4%)	5 (0.4%)
Colon cancer	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Colon cancer metastatic	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Lung cancer metastatic	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Lung carcinoma cell type unspecified stage IV	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Lung neoplasm malignant	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Oesophageal carcinoma	1 (0.3%)	0	0	0	0	1 (<0.1%)
Ovarian cancer	0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)
Prostate cancer metastatic	0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)
Squamous cell carcinoma	0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)

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Primary System Organ Class Preferred Term MedDRA Version 13.0	Ranibizumab		Intravitreal Aflibercept				Combined N = 913 (100%)	Total N = 1204 (100%)
	0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)				
Nervous system disorders	2 (0.7%)	8 (2.6%)	2 (0.7%)	3 (1.0%)			13 (1.4%)	15 (1.2%)
Brain oedema	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Cerebral infarction	0	0	1 (0.3%)	0			1 (0.1%)	1 (<0.1%)
Cerebral infarction	0	0	1 (0.3%)	0			1 (0.1%)	1 (<0.1%)
Cerebrovascular accident	1 (0.3%)	1 (0.3%)	0	2 (0.7%)			3 (0.3%)	4 (0.3%)
Epilepsy	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Headache	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Hypertensive encephalopathy	0	0	0	1 (0.3%)			1 (0.1%)	1 (<0.1%)
Lacunar infarction	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Nerve root compression	1 (0.3%)	0	0	0			0	1 (<0.1%)
Petit mal epilepsy	0	0	1 (0.3%)	0			1 (0.1%)	1 (<0.1%)
Syncope	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Transient ischaemic attack	0	2 (0.6%)	0	0			2 (0.2%)	2 (0.2%)
VIIIth nerve paralysis	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Renal and urinary disorders	0	1 (0.3%)	0	2 (0.7%)			3 (0.3%)	3 (0.2%)
Renal failure	0	1 (0.3%)	0	1 (0.3%)			2 (0.2%)	2 (0.2%)
Urinary tract obstruction	0	0	0	1 (0.3%)			1 (0.1%)	1 (<0.1%)
Reproductive system and breast disorders	0	1 (0.3%)	0	1 (0.3%)			2 (0.2%)	2 (0.2%)
Benign prostatic hyperplasia	0	0	0	1 (0.3%)			1 (0.1%)	1 (<0.1%)
Uterine haemorrhage	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	4 (1.3%)	1 (0.3%)	2 (0.7%)			7 (0.8%)	8 (0.7%)
Acute pulmonary oedema	1 (0.3%)	0	0	0			0	1 (<0.1%)
Chronic obstructive pulmonary disease	0	1 (0.3%)	0	1 (0.3%)			2 (0.2%)	2 (0.2%)
Cough	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Dyspnoea	0	0	0	1 (0.3%)			1 (0.1%)	1 (<0.1%)
Pleurisy	0	0	1 (0.3%)	0			1 (0.1%)	1 (<0.1%)
Pneumothorax	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)
Sleep apnoea syndrome	0	1 (0.3%)	0	0			1 (0.1%)	1 (<0.1%)

Primary System Organ Class Preferred Term MedDRA Version 13.0		Ranibizumab		Intravitreal Aflibercept				Total	
		0.5q4 N = 291 (100%)	2q4 N = 309 (100%)	0.5q4 N = 297 (100%)	2q8 N = 307 (100%)	Combined N = 913 (100%)	N = 1204 (100%)		
Skin and subcutaneous tissue disorders		2 (0.7%)	1 (0.3%)	2 (0.7%)	1 (0.3%)	4 (0.4%)	6 (0.5%)		
Dermal cyst		0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Dermatitis allergic		0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Erythema multiforme		0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Rash		0	1 (0.3%)	0	0	1 (0.1%)	1 (<0.1%)		
Skin necrosis		1 (0.3%)	0	0	0	0	1 (<0.1%)		
Skin ulcer		1 (0.3%)	0	0	0	0	1 (<0.1%)		
Surgical and medical procedures		2 (0.7%)	0	1 (0.3%)	1 (0.3%)	2 (0.2%)	4 (0.3%)		
Haematoma evacuation		1 (0.3%)	0	0	0	0	1 (<0.1%)		
Hip surgery		0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Strangulated hernia repair		0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Vaginal operation		1 (0.3%)	0	0	0	0	1 (<0.1%)		
Vascular disorders		2 (0.7%)	2 (0.6%)	2 (0.7%)	2 (0.7%)	6 (0.7%)	8 (0.7%)		
Circulatory collapse		0	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	2 (0.2%)		
Haematoma		1 (0.3%)	0	0	0	0	1 (<0.1%)		
Hypertension		0	0	1 (0.3%)	0	1 (0.1%)	1 (<0.1%)		
Hypertensive crisis		0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)		
Peripheral artery aneurysm		0	0	0	1 (0.3%)	1 (0.1%)	1 (<0.1%)		
Varicose vein		1 (0.3%)	0	0	0	0	1 (<0.1%)		

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks. At each level of subject summarization, a patientwas counted once if the subject reported one or more events.

Note: Aflibercept 2q4, aflibercept 0.5q4, aflibercept 2q8 administered at 2 mg every 4 weeks, 0.5 mg every 4 weeks, and 2 mg every 8 week, respectively. Ranibizumab administered at 0.5 mg every 4 weeks. At each level of subject summarization, a patient was counted once if the subject reported one or more events.

MedDRA = Medical Dictionary for Regulatory Activities .

APPENDIX 8. Immunogenicity to Intravitreal Aflibercept

As with all therapeutic proteins, there is a potential for immunoreactivity to intravitreal aflibercept in the VIEW studies. To determine this possibility, serum samples were analyzed with anti-drug antibody assays to evaluate the number of patients developing antibodies to aflibercept as well as the numbers developing neutralizing antibodies to aflibercept.

In the two studies, the pre-treatment incidence of immunoreactivity to intravitreal aflibercept was 1% to 3% across treatment groups. After dosing with intravitreal aflibercept for 52 weeks, antibodies to intravitreal aflibercept were detected in a similar 1% to 3% range in all treatment groups, including the ranibizumab group. Furthermore, only 1 sample from 1 patient demonstrated any neutralizing activity in these studies. There were no differences in efficacy or safety between patients with or without anti-drug reactivity results.

The results suggest that the majority of the positive responses in the assays were due to pre-existing immunoreactivity which was not drug induced and therefore were not due to an immune response to intravitreal aflibercept.