

# EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT AND RANIBIZUMAB IN ASIAN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

## Subgroup Analyses From the VIEW Trials

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**Purpose:** To assess the treatment effect of intravitreal aflibercept and ranibizumab in Asian patients with neovascular age-related macular degeneration.

**Methods:** We evaluated data from VIEW 1 and VIEW 2, comparing functional and morphologic outcomes at Week 96 between intravitreal aflibercept 2 mg monthly (2q4) or 2 mg bimonthly after 3 initial monthly doses (2q8) versus ranibizumab 0.5 mg monthly among Asian patients (n = 269) and between Asian and white patients (n = 2044).

**Results:** In Asian patients, there were no significant differences between intravitreal aflibercept 2q4 and 2q8 compared with ranibizumab in mean gain in best-corrected visual acuity (10.23 and 8.35 vs. 8.51 letters). Reduction in central retinal thickness was greater for intravitreal aflibercept 2q4 (150.43  $\mu\text{m}$ ,  $P = 0.0075$ ) and 2q8 (148.15  $\mu\text{m}$ ,  $P = 0.0126$ ) than ranibizumab (119.46  $\mu\text{m}$ ). The proportion of dry retinas was greater for intravitreal aflibercept 2q4 (65.7%,  $P < 0.01$ ) than ranibizumab (41.7%). There were no differences in outcomes between Asian and white patients. Serious treatment-emergent ocular adverse events occurred in <8% of treated eyes, evenly distributed across subgroups.

**Conclusion:** In Asian patients with neovascular age-related macular degeneration, functional and morphologic outcomes were largely similar between intravitreal aflibercept and ranibizumab groups, and to results seen in white patients.

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Age-related macular degeneration (AMD) is one of the leading causes of blindness in elderly populations worldwide.<sup>1,2</sup> Results from recent epidemiologic studies indicate a similar prevalence of AMD among Asian and white populations: a systematic review and meta-analysis found pooled prevalence estimates of early and late AMD in Asian people of 6.8% and 0.56%, respectively, similar to the corresponding prevalence estimates in white people of 8.8% and 0.59%.<sup>3</sup> However, because of rapidly aging populations in Asia, it has been estimated that more than half of all AMD cases are expected to be among Asians by 2040.<sup>4</sup>

There are a number of characteristics that distinguish Asian patients with neovascular AMD (nAMD)

from white patients with nAMD, including a higher proportion of the polypoidal choroidal vasculopathy subtype of nAMD and a lower prevalence of retinal angiomatous proliferation.<sup>5–12</sup> Differences in the occurrence of disease-susceptible genes have also been suggested.<sup>13,14</sup> However, other studies have suggested that the incidence, natural history, and risk factors of nAMD are similar between Asian and white people.<sup>15–19</sup> Importantly, it is unclear whether ethnicity impacts treatment outcomes because no studies have directly compared treatment outcomes between these two groups.

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents, such as ranibizumab

and aflibercept, are now the standard of care for patients with nAMD.<sup>2,20</sup> However, most trials on nAMD have been conducted in white populations, and the efficacy and safety of anti-VEGF therapy in Asian patients with nAMD are less well investigated.<sup>21</sup> Furthermore, there are currently no data on the relative efficacy and safety of ranibizumab versus intravitreal aflibercept in Asian patients presenting with nAMD.

The VIEW trials present a unique opportunity to evaluate the efficacy and safety of anti-VEGF therapy in Asian people, as these trials included a large number of patients recruited from Asian countries. In a subgroup analysis of Japanese patients in the VIEW trials, intravitreal aflibercept was found to be effective and well tolerated in Japanese patients, with 52-week outcomes similar to those in the overall VIEW 2 population.<sup>22</sup> In this article, we report on a new post hoc subgroup analysis to evaluate, first, the longer-term efficacy and safety of intravitreal aflibercept compared with ranibizumab at 2 years (96 weeks) in all Asian patients with nAMD who were enrolled in the VIEW trials, and second, whether the treatment response for these agents is similar in Asian patients compared with that of white patients.

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## Methods

### Study Design

The details of the VIEW trials (clinicaltrials.gov NCT00509795 and NCT00637377) have been published previously.<sup>23,24</sup> In the Asia-Pacific region, sites were located in Japan (n = 15), South Korea (n = 6), Singapore (n = 3), India (n = 15), and Australia (n = 7). The studies were conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation. Protocols for the VIEW trials were prospectively approved by institutional review boards or ethics committees at each clinical site.

### Participants and Treatments

The Asian subpopulation analyzed here comprises all patients in Japan, South Korea, Singapore, India, and the subgroup of Asian patients in the United Kingdom and the United States. Race was defined based on participants' and investigators' declaration of listing race/ethnicity as "Asian" in the data collection form.

Patients with nAMD were randomized 1:1:1:1 to treatment with ranibizumab 0.5 mg monthly (Rq4) or intravitreal aflibercept 2 mg monthly (2q4), 0.5 mg monthly (0.5q4), or 2 mg every 2 months after 3 initial monthly doses (2q8). From Week 52 through Week 96, patients received their original dosing assignment using a capped pro re nata regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks.

### Outcome Measures

The primary endpoint analysis of the VIEW trials was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at Week 52 (defined in the VIEW trials as losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters). Prespecified secondary efficacy outcomes compared visual and anatomical changes from baseline to Week 52 among treatment groups. Efficacy endpoints evaluated after Week 52 were exploratory.

In this article, we evaluate functional and morphologic outcomes between treatment groups after 96 weeks, first in the Asian subpopulation and then between Asian and white patients enrolled in the VIEW trials.

### Statistical Analyses

The analyses reported here are based on pooled 2-year data of the VIEW 1 and VIEW 2 trials. All

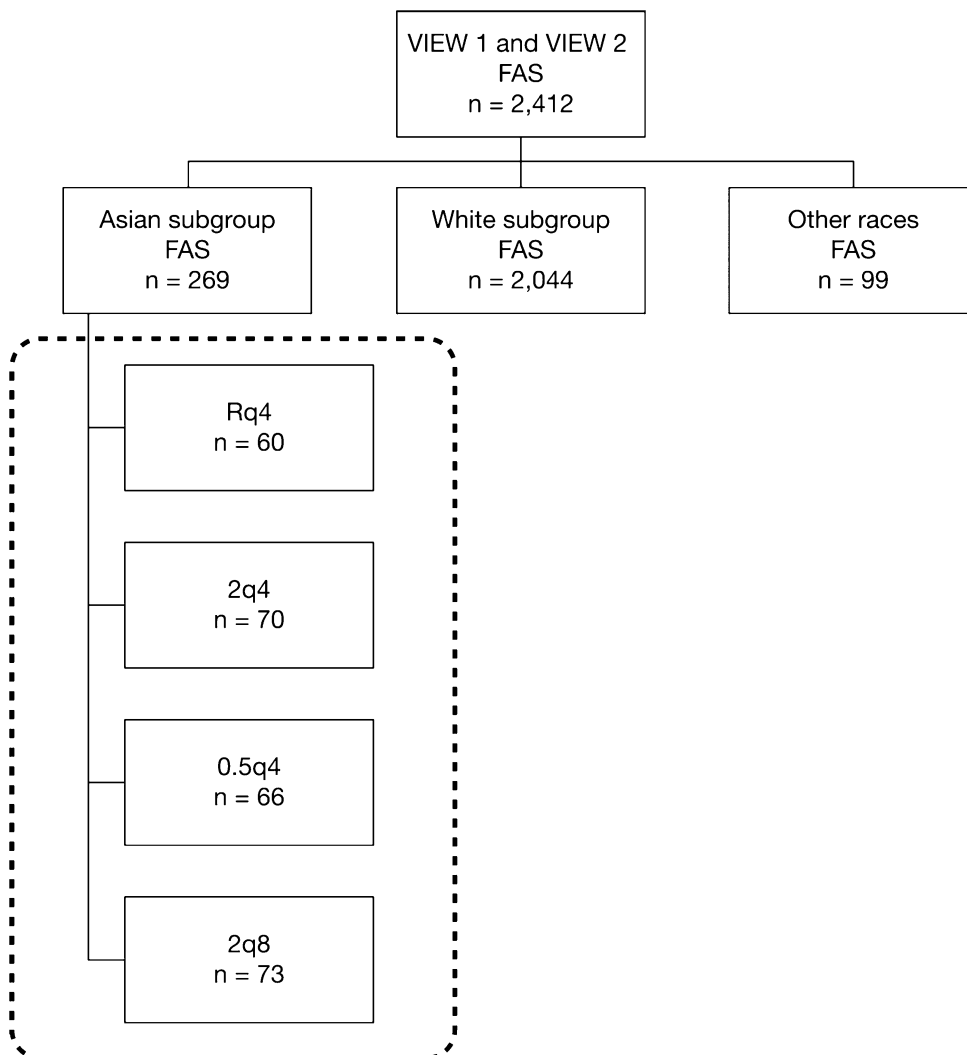
efficacy analyses were conducted in the full analysis set, which included all randomized patients who received any study drug and had a baseline and at least one postbaseline best-corrected visual acuity (BCVA) assessment, and all safety analyses were conducted in the safety analysis set, which included all patients who received any study medication. The last observation carried forward approach was used to impute missing values. All statistical tests are exploratory and were performed 2-sided with a Type I error rate of 5%. Cochran–Mantel–Haenszel tests and analyses of covariance were used to compare frequencies and continuous variables, respectively. Given the post hoc nature of these analyses, all *P* values are nonconfirmatory. All analyses were adjusted by study. Comparisons between Asian and white patients were also adjusted by age to address baseline differences. Given the small and underpowered sample, the results of these post hoc analyses should be considered hypothesis generating.

**Results**

*Patient Demographics, Disease Characteristics, and Disposition*

A total of 2,457 patients were randomized to treatment in the VIEW trials. Of the 2,412 patients who comprised the full analysis set, 2,044 (84.7%) were white and 269 (11.2%) were Asian (Rq4, *n* = 60; 2q4, *n* = 70; 0.5q4, *n* = 66; 2q8, *n* = 73) (Figure 1). The number of patients in other racial groups was too small for subgroup analysis.

Baseline demographics and disease characteristics were largely balanced across treatment groups within the Asian subpopulation, although the distribution of lesion types varied (Table 1). The differences in baseline demographics between Asian and white patients were in age, sex, and lens status. The mean age in Asian patients was 69.4 years, whereas the mean age in white patients was 76.9 years. In addition, among



**Fig. 1.** Patient disposition by race and treatment group in the VIEW trials. 0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2 mg every 4 weeks; 2q8, intravitreal aflibercept 2 mg every 8 weeks after 3 initial monthly doses; FAS, full analysis set; Rq4, ranibizumab 0.5 mg every 4 weeks.

Table 1. Baseline Demographics and Disease Characteristics

	All Patients		Rq4		2q4		0.5q4		2q8	
	Asian	White	Asian	White	Asian	White	Asian	White	Asian	White
N (full analysis set)	269	2,044	60	508	70	521	66	511	73	504
Age, years*	69.4 (8.9)	76.9 (8.2)	67.6 (8.6)	76.5 (8.2)	68.9 (8.3)	76.9 (8.1)	71.9 (10.0)	77.3 (8.1)	68.9 (8.4)	76.8 (8.4)
Male, n (%)	190 (70.6)	805 (39.4)	45 (75)	201 (39.6)	51 (72.9)	184 (35.3)	47 (71.2)	226 (44.2)	47 (64.4)	194 (38.5)
Baseline VA, ETDRS letters*	51.8 (13.9)	54.0 (13.5)	53.0 (13.7)	54.1 (13.4)	52.6 (14.3)	54.2 (13.5)	48.5 (13.5)	54.1 (13.8)	52.9 (13.9)	53.8 (13.2)
Baseline CRT, $\mu\text{m}^*$			344 (147)	317 (104)	329 (120)	322 (111)	327 (138)	321 (109)	318 (142)	338 (115)
Baseline area of CNV, $\text{mm}^2*$	7.5 (5.8)	7.2 (5.2)	7.3 (6.0)	7.1 (5.3)	7.8 (6.3)	7.3 (5.2)	6.8 (4.7)	7.2 (5.0)	8.1 (6.1)	7.0 (5.2)
Baseline total NEI VFQ-25 score*	72.8 (18.4)	71.3 (18.0)	76.1 (17.6)	72.0 (18.2)	69.9 (19.1)	70.5 (17.8)	71.5 (19.2)	72.6 (18.0)	74.1 (17.6)	70.2 (18.0)
Pseudophakia, n (%)	59 (21.9)	715 (35.0)	9 (15.0)	184 (36.2)	14 (20.0)	171 (32.8)	18 (27.3)	181 (35.4)	18 (24.7)	179 (35.5)
Lesion type, n (%)										
Minimally classic	89 (33.1)	712 (34.8)	24 (40.0)	174 (34.7)	24 (34.4)	181 (35.0)	22 (33.3)	171 (33.5)	19 (26.0)	186 (37.1)
Occult	114 (42.4)	786 (38.5)	24 (40.0)	201 (40.0)	30 (42.9)	198 (38.3)	24 (36.4)	207 (40.6)	36 (49.3)	181 (36.1)
Predominantly classic	66 (24.5)	532 (26.0)	12 (20.0)	127 (25.3)	16 (22.9)	138 (26.7)	20 (30.3)	132 (25.9)	18 (24.7)	135 (26.9)

\*Mean (standard deviation).

0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2.0 mg every 4 weeks; 2q8, intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial monthly doses; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; Rq4, ranibizumab 0.5 mg every 4 weeks; VA, visual acuity.

Asian patients, the majority were male in all treatment groups, whereas among white patients, the majority were female in all treatment groups. Finally, the proportion of Asian patients with pseudophakia at baseline was 21.9% and in white patients it was 35.0%.

#### Treatment Experience

Within the Asian subgroup, patients received, on average, 17.1, 15.5, 15.9, and 11.0 injections over 96 weeks and 4.8, 3.7, 4.0, and 3.8 injections during Weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. Among white patients, mean injection frequencies were 16.5, 16.0, 16.3, and 11.2 injections over 96 weeks and 4.6, 4.0, 4.6, and 4.2 injections during Weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively.

#### Efficacy of Intravitreal Aflibercept and Ranibizumab in Asian Patients

At Week 96, a comparable proportion of Asian patients treated with intravitreal aflibercept achieved the primary endpoint of maintaining vision (i.e., loss of <15 letters from baseline) compared with those treated with ranibizumab (Table 2).

Mean BCVA increased across all treatment groups in the Asian subpopulation (Figure 2). There were no significant differences between treatment groups. At Week 96, the proportions of patients gaining  $\geq 15$  letters of vision were comparable across all treatment groups.

Central retinal thickness (CRT) on optical coherence tomography decreased from baseline across all treatment groups in the Asian subpopulation (Figure 2). The differences in decrease were nominally significant in favor of intravitreal aflibercept for 2q4 versus Rq4 and 2q8 versus Rq4 ( $P = 0.0075$  and  $P = 0.0126$ , respectively).

A total of 166 (61.7%) Asian patients achieved a dry retina at Week 12 (i.e., after 3 initial monthly doses). The difference in the proportion of patients achieving a dry retina at Week 12 was nominally significant for 2q4 versus Rq4 ( $P < 0.01$ ). At Week 96, 149 (55.4%) Asian patients achieved dry retina. The difference in proportion of patients achieving dry retina at Week 96 was nominally significant for 2q4 versus Rq4 ( $P < 0.01$ ).

Mean choroidal neovascularization area also decreased across all treatment groups in the Asian subpopulation. There were no significant differences between treatment groups.

Table 2. Differences in Efficacy Endpoints Between Intravitreal Aflibercept and Ranibizumab in Asian Patients With nAMD

Endpoint	Rq4 (n = 60)	2q4 (n = 70)	0.5q4 (n = 66)	2q8 (n = 73)	Estimated Difference (95% CI)		
					2q4 vs. Rq4	0.5q4 vs. Rq4	2q8 vs. Rq4
Maintenance of vision (loss <15 letters)*	56 (93.3)	67 (95.7)	63 (95.5)	71 (97.3)	2.2 (−5.9 to 10.3)	1.7 (−6.6 to 10.1)	3.8 (−3.7 to 11.3)
Mean change, BCVA, ETDRS letters	8.51	10.23	9.04	8.35	1.71 (−3.81 to 7.24)	0.53 (−5.05 to 6.11)	−0.17 (−5.64 to 5.31)
Gain ≥15 letters*	24 (40.0)	24 (34.3)	25 (37.9)	28 (38.4)	−7.2 (−24.0 to 9.7)	−2.3 (−19.8 to 15.2)	−2.3 (−19.3 to 14.7)
Mean change, CRT, μm	−119.46	−150.43	−129.16	−148.15	−30.97 (−53.64 to −8.29)	−9.70 (−32.95 to 13.55)	−28.69 (−51.22 to −6.15)
Dry retina after 3, monthly injections*	32 (53.3)	53 (75.7)	33 (50.0)	48 (65.8)	22.8 (6.4 to 39.2)	−0.9 (−18.8 to 17.1)	13.3 (−3.6 to 30.3)
Dry retina at Week 96*	25 (41.7)	46 (65.7)	35 (53.0)	43 (58.9)	25.5 (8.6 to 42.4)	10.8 (−7.0 to 28.6)	14.9 (−2.4 to 32.1)
No dry retina in Year 1*	12 (20.0)	3 (4.3)	5 (7.6)	7 (9.6)	−15.6 (−27.2 to −4.1)	−11.8 (−25.0 to 1.3)	−9.9 (−22.6 to 2.8)
Time to first dry retina, days†	57	31	56	55	n/a	n/a	n/a
Mean change, CNV area, mm <sup>2</sup>	−4.23	−4.01	−5.02	−4.47	0.22 (−1.51 to 1.95)	−0.78 (−2.51 to 0.941)	−0.23 (−1.94 to 1.47)
Mean change, total NEI VFQ-25 score	8.27	4.07	7.71	6.10	−4.20 (−8.95 to 0.55)	−0.56 (−5.43 to 4.31)	−2.16 (−6.89 to 2.57)

Mean change in BCVA, CRT, CNV area, and NEI VFQ-25: least square mean values from analysis of covariance models adjusted by study are presented.

\*n (%).

†Median.

0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2.0 mg every 4 weeks; 2q8, intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial monthly doses; CI, confidence interval; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; Rq4, ranibizumab 0.5 mg every 4 weeks.

All treatment groups within the Asian subpopulation experienced improvements from baseline in mean total 25-item National Eye Institute Visual Function Questionnaire score. There were no significant differences between treatment groups.

*Efficacy in Asian Patients Versus White Patients*

Mean BCVA increased across all treatment groups in the white subpopulation (Figure 2). The mean gain in BCVA was numerically greater in white patients treated with intravitreal aflibercept 2q4 and 2q8 than in white patients treated with ranibizumab (Table 3).

Although there were a few numerical differences seen in descriptive results comparing Asian and white patients (Figure 2), there were no differences when results were adjusted for age, except for a greater decrease in CRT among Asian patients in the intravitreal aflibercept groups (Table 3).

When baseline lesion subtype was taken into account, some differences between Asian and white patients were observed (Figure 3), possibly because of fewer patients in the Asian subgroup. Specifically, among those with occult lesions in the 2q4 treatment group, a greater proportion of Asian patients main-

tained vision compared with white patients. Likewise, in those with minimally classic lesions in the 2q8 group, a greater proportion of Asian patients maintained vision compared with white patients. Finally, among patients with occult lesions in the 2q8 treatment group, decreases in CRT were greater in Asian patients compared with white patients.

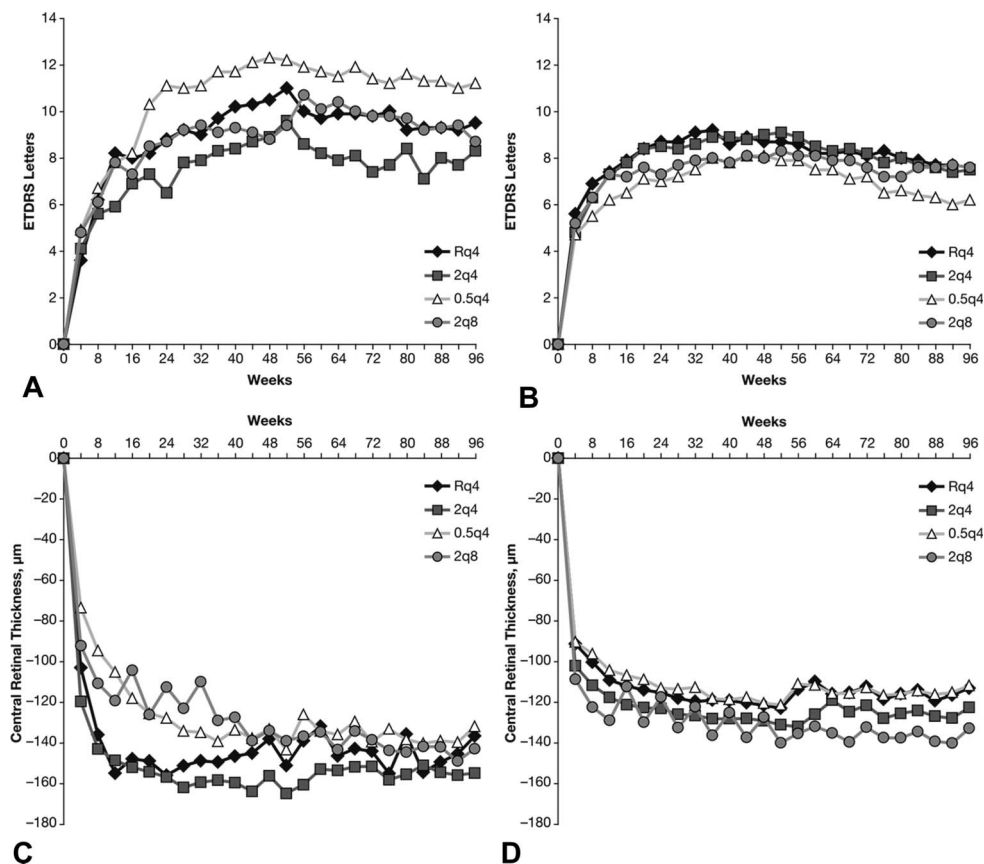
*Safety*

The overall number of ocular serious adverse events (SAEs) was low in the VIEW trials. The most common SAEs among Asian patients were cataract and visual acuity reduced (n = 4 for both) and the most common SAEs among white patients were retinal hemorrhage and visual acuity reduced (n = 14 for both) (Table 4).

The overall proportion of patients with ocular SAEs and the proportion of patients with Antiplatelet Trialists' Collaboration–defined arterial thromboembolic events were numerically higher in the white population versus the Asian population (Table 4).

Safety analyses for the Asian subpopulation of the VIEW trials should be interpreted with caution, given fewer patients in each treatment group.

**Fig. 2.** Mean changes over 96 weeks in the VIEW trials. **A.** Best-corrected visual acuity in Asian patients. **B.** Best-corrected visual acuity in white patients. **C.** Central retinal thickness in Asian patients. **D.** Central retinal thickness in white patients. 0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2 mg every 4 weeks; 2q8, intravitreal aflibercept 2 mg every 8 weeks after 3 initial monthly doses; ETDRS, early treatment diabetic retinopathy study; Rq4, ranibizumab 0.5 mg every 4 weeks.



## Discussion

We evaluated the long-term efficacy and safety of intravitreal aflibercept and ranibizumab for the treatment of nAMD in 269 Asian patients enrolled in the VIEW trials, and compared the outcomes in these Asian patients with those of white patients. In general, among the Asian population from the VIEW trials, patients in all treatment groups experienced visual and anatomical improvements after treatment with anti-VEGF therapy, with no differences between intravitreal aflibercept and ranibizumab. Furthermore, the outcomes in Asian patients were largely similar to those experienced by white patients. The frequencies of adverse events, including vascular events, were low among Asian patients and distributed evenly across treatment groups. These data emphasize two important findings: first, that the two anti-VEGF agents have long-term clinical effectiveness, safety, and value for Asian patients with nAMD, and second, that there are no appreciable differences in treatment response for Asian patients compared with white patients.

Our study included the largest group of Asian patients with nAMD enrolled in a clinical trial. Previous studies, including the Comparison of Age-related macular degeneration Treatment Trials

(CATT)<sup>25</sup> and a subgroup analysis of 84 Japanese patients in the VIEW trials,<sup>22</sup> reported that mean BCVA at baseline has an impact on mean change in BCVA over the study period, with better baseline visual acuity associated with lesser gains in visual acuity. The results of the current analysis are consistent with those of the previous studies. In this study, Asian patients in the 0.5q4 treatment group of the VIEW trials had the lowest baseline BCVA (48.5 ETDRS letters) and the greatest unadjusted gains in visual acuity at Week 52 (12.2 ETDRS letters) and Week 96 (11.2 ETDRS letters) compared with the other treatment groups. This high improvement in BCVA may be explained by the relatively small sample size and imbalances in baseline characteristics (e.g., age, sex, and lens status), or because these patients had more room to gain in BCVA. In the 2q4 and 2q8 groups, trends in BCVA scores over 96 weeks were similar between Asian and white patients. Asian and white patients in the 2q4 group experienced a mean change of approximately 9 letters at Week 52 and approximately 8 letters at Week 96. Asian patients in the 2q8 group experienced unadjusted mean changes approximately 1 letter greater than white patients in the 2q8 group at both Weeks 52 and 96 (Figure 2).

Table 3. Differences in Efficacy Endpoints Between Asian and White Patients

Endpoint	Rq4			2q4		
	Asian (n = 60)	White (n = 509)	Estimated Difference (95% CI)	Asian (n = 70)	White (n = 521)	Estimated Difference (95% CI)
Maintenance of vision*	56 (93.3)	466 (91.6)	-0.05 (-7.6 to 6.7)	67 (95.7)	477 (91.6)	-4.3 (-10.8 to 2.3)
Mean change, BCVA, ETDRS letters	8.3	8.4	0.09 (-4.76 to 4.93)	10.9	10.3	-6.0 (-4.94 to 3.74)
Gain ≥15 letters*	24 (40.0)	159 (31.2)	-6.6 (-21.3 to 8.0)	24 (34.3)	158 (30.3)	-7.9 (-20.1 to 4.3)
Mean change, CRT, μm	-118	-110	7.59 (-13.35 to 28.53)	-144	-124	20.00 (2.40 to 37.59)
Dry retina after 3 monthly injections*	32 (53.3)	281 (55.3)	0.8 (-14.3 to 15.8)	53 (75.7)	331 (63.8)	-6.4 (-18.2 to 5.4)
Dry retina at Week 96*	25 (41.7)	238 (46.9)	1.8 (-13.2 to 16.8)	46 (65.7)	280 (53.8)	-9.2 (-22.1 to 3.7)
No dry retina in Year 1*	12 (20.0)	68 (13.4)	-4.0 (-16.1 to 8.1)	3 (4.3)	38 (7.3)	0.20 (-7.1 to 7.6)
Time to first dry retina, days†	57	55	n/a	31	30	n/a
Mean change, CNV area, mm <sup>2</sup>	-4.62	-4.22	0.40 (-1.04 to 1.84)	-4.45	-4.98	-0.53 (-1.77 to 0.71)
Mean change, total NEI VFQ-25 score	5.24	5.56	0.31 (-3.61 to 4.24)	5.81	7.41	1.60 (-2.31 to 5.51)

Endpoint	0.5q4			2q8		
	Asian (n = 66)	White (n = 510)	Estimated Difference (95% CI)	Asian (n = 73)	White (n = 504)	Estimated Difference (95% CI)
Maintenance of vision*	63 (95.5)	466 (91.4)	-1.9 (-8.0 to 4.2)	71 (97.3)	463 (91.9)	-3.0 (-7.9 to 1.9)
Mean change, BCVA, ETDRS letters	8.5	7.2	-1.3 (-5.61 to 3.01)	7.6	9.9	2.28 (-2.06 to 6.63)
Gain ≥15 letters*	25 (37.9)	138 (27.1)	-2.1 (-15.0 to 10.7)	28 (38.4)	165 (32.7)	1.5 (-11.9 to 15.0)
Mean change, CRT, μm	-131	-109	22.43 (2.75 to 42.11)	-157	-127	29.78 (12.05 to 47.51)
Dry retina after 3 monthly injections*	33 (50.0)	238 (46.9)	-0.8 (-14.2 to 12.5)	48 (65.8)	309 (61.3)	2.8 (-10.4 to 16.0)
Dry retina at Week 96*	35 (53.0)	215 (42.3)	-5.3 (-18.9 to 8.3)	43 (58.9)	243 (48.2)	-9.3 (-22.1 to 3.5)
No dry retina in Year 1*	5 (7.6)	84 (16.5)	10.6 (2.1 to 19.1)	7 (9.6)	51 (10.1)	0.10 (-7.6 to 7.9)
Time to first dry retina, days†	56	57	n/a	55	31	n/a
Mean change, CNV area, mm <sup>2</sup>	-5.14	-3.69	1.45 (-0.08 to 2.99)	-3.89	-4.27	-0.38 (-1.77 to 1.01)
Mean change, total NEI VFQ-25 score	7.40	4.79	-2.61 (-6.36 to 1.15)	6.27	5.67	-0.60 (-4.73 to 3.53)

Mean change in BCVA, CRT, CNV area, and NEI VFQ-25: least square mean values from analysis of covariance models adjusted by study and age are presented.

\*n (%).

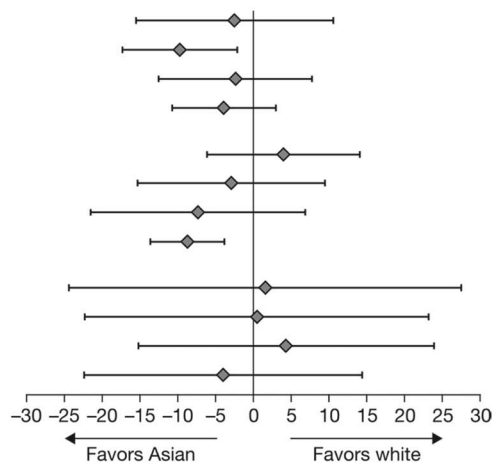
†Median.

0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2.0 mg every 4 weeks; 2q8, intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial monthly doses; CI, confidence interval; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; Rq4, ranibizumab 0.5 mg every 4 weeks.

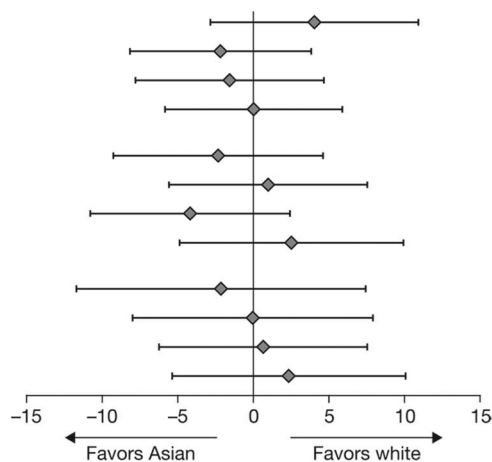
Taking into account the difference in age distribution between the two patient subgroups, our analysis also suggests that the overall benefit of treatments of both intravitreal aflibercept and ranibizumab was similar between Asian and white patients in the VIEW trials. Several interesting differences between white

and Asian patients were noted when lesion type was taken into account, reflecting results of other studies that showed ethnic differences in clinical nAMD subtypes.<sup>26</sup> For example, in the subgroup of patients with minimally classic lesions treated with intravitreal aflibercept 2q8, a greater proportion of Asian patients

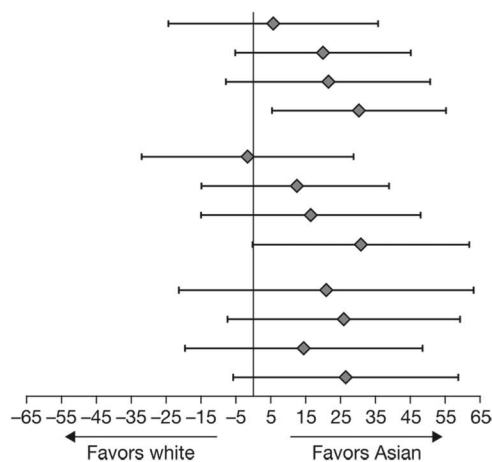
	Cluster	Asian n/N	White n/N	Estimated difference (95% CI)
Maintenance of vision – occult	Rq4	22/24	181/202	-2.5 (-15.5 to -10.6)
	2q4	30/30	186/198	-9.7 (-17.3 to -2.1)
	0.5q4	23/24	190/206	-2.3 (-12.5 to 7.8)
	2q8	35/36	166/181	-3.9 (-10.7 to 3.0)
Maintenance of vision – minimally classic	Rq4	23/24	161/174	4.0 (-6.1 to 14.1)
	2q4	22/24	160/181	-2.9 (-15.3 to 9.5)
	0.5q4	21/22	152/171	-7.3 (-21.5 to 6.9)
	2q8	19/19	172/186	-8.7 (-13.6 to -3.8)
Maintenance of vision – predominantly classic	Rq4	11/12	119/127	1.6 (-24.4 to 27.5)
	2q4	15/16	127/138	0.5 (-22.3 to 23.2)
	0.5q4	19/20	123/132	4.3 (-15.2 to 23.9)
	2q8	17/18	124/135	-4.0 (-22.4 to 14.4)



	Cluster	Asian N	White N	Estimated difference (95% CI)
Change in BCVA – occult	Rq4	24	202	4.04 (-2.84 to 10.91)
	2q4	30	198	-2.18 (-8.17 to 3.82)
	0.5q4	24	206	-1.57 (-7.8 to 4.66)
	2q8	36	181	0.02 (-5.84 to 5.88)
Change in BCVA – minimally classic	Rq4	24	174	-2.33 (-9.27 to 4.6)
	2q4	24	181	0.97 (-5.58 to 7.53)
	0.5q4	22	171	-4.19 (-10.79 to 2.41)
	2q8	19	186	2.5 (-4.95 to 9.94)
Change in BCVA – predominantly classic	Rq4	12	127	-2.15 (-11.72 to 7.42)
	2q4	16	138	-0.06 -8.00 to 7.89)
	0.5q4	20	132	0.64 (-6.25 to 7.52)
	2q8	18	135	2.33 (-5.39 to 10.06)



	Cluster	Asian N	White N	Estimated difference (95% CI)
Change in CRT – occult	Rq4	24	197	5.68 (-24.37 to 35.74)
	2q4	30	193	19.92 (-5.23 to 45.06)
	0.5q4	24	198	21.51 (-7.75 to 50.78)
	2q8	35	178	30.26 (5.32 to 55.19)
Change in CRT – minimally classic	Rq4	24	167	-1.67 (-32.06 to 28.72)
	2q4	24	173	12.48 (-14.92 to 39.89)
	0.5q4	22	166	16.43 (-15.04 to 47.89)
	2q8	19	176	30.79 (-0.27 to 61.85)
Change in CRT – predominantly classic	Rq4	12	120	20.87 (-21.39 to 63.13)
	2q4	16	131	25.90 (-7.42 to 59.22)
	0.5q4	20	124	14.41 (-19.64 to 48.46)
	2q8	18	131	26.47 (-5.77 to 58.70)



**Fig. 3.** Efficacy endpoints by lesion type, Asian versus white patients. CI, confidence interval; n, number of patients with this outcome; N, total number of patients; 0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2 mg every 4 weeks; 2q8, intravitreal aflibercept 2 mg every 8 weeks after three initial monthly doses; Rq4, ranibizumab 0.5 mg every 4 weeks.



maintained vision compared with white patients. Among patients with occult lesions in the same subgroup treated with intravitreal aflibercept 2q8, decreases in CRT were greater in Asian patients compared with white patients. These findings may indicate a potential role for lesion type as a predictor of treatment response to anti-VEGF therapy. However, these findings should be interpreted with caution. This is a subgroup analysis (lesion size) within a subgroup

analysis (Asian patients vs. white patients) of the VIEW trials, the number of patients is not balanced in the compared lesion subgroups, and the described findings do not follow a consistent pattern. It is therefore possible that these findings could be due to chance. Whether these interesting differences between Asian and white patients reflect true ethnic differences in response to anti-VEGF therapy or whether they result from the inherent imbalance of sample sizes in

Table 4. Serious Ocular Adverse Events in the Study Eye and Antiplatelet Trialists' Collaboration–Defined Arterial Thromboembolic Events in Asian and White Patients

	Rq4		2q4		0.5q4		2q8	
	Asian	White	Asian	White	Asian	White	Asian	White
N (safety analysis set)	60	509	70	521	67	513	73	507
Patients who died, n (%)	0	15 (2.9)	5 (7.1)	8 (1.5)	2 (3.0)	17 (3.3)	1 (1.4)	18 (3.6)
Patients with ≥1 ocular SAE, n (%)	2 (3.3)	24 (4.7)	5 (7.1)	15 (2.9)	2 (3.0)	16 (3.1)	4 (5.5)	16 (3.2)
AMD	0	0	0	1 (0.2)	0	0	0	0
Angle closure glaucoma	0	0	0	1 (0.2)	0	0	0	0
Blindness	0	0	0	0	0	0	0	1 (0.2)
Blindness transient	0	1 (0.2)	0	0	0	0	0	0
Cataract	0	1 (0.2)	2 (2.9)	2 (0.4)	0	3 (0.6)	2 (2.7)	2 (0.4)
Cataract cortical	1 (1.7)	0	0	0	0	0	0	0
Cataract nuclear	0	0	1 (1.4)	0	1 (1.5)	0	0	0
Cataract subcapsular	0	0	1 (1.4)	0	0	0	0	0
Choroidal detachment	0	0	0	0	0	0	0	1 (0.2)
Choroidal hemorrhage	0	1 (0.2)	0	0	0	0	0	0
Choroidal neovascularization	0	0	0	0	0	0	0	1 (0.2)
Conjunctivitis	0	0	0	0	0	0	0	1 (0.2)
Endophthalmitis	0	5 (1.0)	0	2 (0.4)	0	1 (0.2)	0	0
Herpes zoster ophthalmicus	0	0	0	0	0	0	0	1 (0.2)
Hyphemia	0	1 (0.2)	0	0	0	0	0	0
Incorrect dose administered	0	1 (0.2)	0	0	0	0	0	0
Intraocular pressure increased	0	1 (0.2)	0	0	0	1 (0.2)	0	1 (0.2)
Iridocyclitis	0	0	0	0	0	0	0	1 (0.2)
Keratitis	0	0	0	1 (0.2)	0	0	0	0
Macular cyst	0	0	0	0	0	0	1 (1.4)	0
Macular degeneration	0	0	0	0	0	0	1 (1.4)	1 (0.2)
Macular hole	0	0	0	0	0	2 (0.4)	0	0
Macular scar	0	0	0	1 (0.2)	0	0	0	0
Posterior capsule opacification	0	2 (0.4)	0	0	0	0	0	0
Pseudoendophthalmitis	0	1 (0.2)	0	0	0	0	0	0
Retinal degeneration	0	1 (0.2)	0	1 (0.2)	0	0	0	0
Retinal detachment	0	3 (0.6)	0	1 (0.2)	0	1 (0.2)	0	0
Retinal hemorrhage	0	4 (0.8)	1 (1.4)	2 (0.4)	0	4 (0.8)	0	4 (0.8)
Retinal edema	0	1 (0.2)	0	0	0	1 (0.2)	0	0
RPE tear	1 (1.7)	0	0	0	0	1 (0.2)	0	1 (0.2)
Retinal pigment epitheliopathy	0	0	0	1 (0.2)	0	0	0	0
Retinal tear	0	1 (0.2)	0	0	0	1 (0.2)	0	0
Visual acuity reduced	0	5 (1.0)	1 (1.4)	3 (0.6)	1 (1.5)	2 (0.4)	2 (2.7)	4 (0.8)
Vitreous detachment	0	0	0	0	0	0	1 (1.4)	0
Vitreous hemorrhage	0	1 (0.2)	1 (1.4)	0	0	0	0	0
Patients with any APTC-ATE, n (%)	0	17 (3.3)	1 (1.4)	13 (2.5)	2 (3.0)	21 (4.1)	3 (4.1)	18 (3.6)
Nonfatal myocardial infarction	0	11 (2.2)	0	5 (1.0)	0	12 (2.3)	1 (1.4)	6 (1.2)
Nonfatal stroke	0	4 (0.8)	0	5 (1.0)	1 (1.5)	2 (0.4)	1 (1.4)	4 (0.8)
Vascular death	0	3 (0.6)	1 (1.4)	4 (0.8)	1 (1.5)	7 (1.4)	1 (1.4)	9 (1.8)

0.5q4, intravitreal aflibercept 0.5 mg every 4 weeks; 2q4, intravitreal aflibercept 2.0 mg every 4 weeks; 2q8, intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial monthly doses; RPE, retinal pigment epithelium; Rq4, ranibizumab 0.5 mg every 4 weeks; APTC-ATE, antiplatelet trialists' collaboration–defined arterial thromboembolic events.

this post hoc analysis would need to be determined using prospective randomized studies. These findings are consistent with the guidance of the International Conference on Harmonisation E5 report titled Ethnic Factors in the Acceptability of Foreign Clinical Data, that intravitreal aflibercept is insensitive to ethnic factors.

Limitations of this analysis should be taken into account. This is a post hoc analysis, and not a pre-specified subgroup analysis, and these analyses were limited by smaller sample sizes in each subgroup, including lesion size subgroups. The effect of potential polypoidal choroidal vasculopathy subtype in some patients could not be analyzed. Nevertheless, results of two recent randomized trials of polypoidal choroidal vasculopathy (EVEREST II and PLANET) suggest that intravitreal aflibercept and ranibizumab monotherapy are safe and efficacious over 1 year (presented by Koh et al at the American Academy of Ophthalmology, November 2016 and by Lee et al at the Asia-Pacific Vitreoretinal Society, December 2016). Our subgroup analysis represents the largest Asian study of nAMD to date.

In conclusion, we conducted a post hoc analysis of the VIEW trials to address two clinically important questions: first, if anti-VEGF therapy with intravitreal aflibercept and ranibizumab is similarly efficacious and safe in Asian patients with nAMD, and second, if treatment outcomes are similar between Asian and white patients. We demonstrated that intravitreal aflibercept and ranibizumab are safe and effective in Asian patients with nAMD through 2 years (96 weeks). Despite differences in clinical disease presentation between Asian and white patients with nAMD, the magnitude of the benefits observed in both groups was comparable. The incidence of SAEs was consistent with the known safety profile of anti-VEGF therapy. This study clearly demonstrates the benefit of intravitreal anti-VEGF therapy for nAMD in Asian patients, with significant functional and morphologic benefits as seen in other pivotal trials.

**Key words:** aflibercept, age-related macular degeneration, anti-vascular endothelial growth factor, Asian patients.

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