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Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial

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Purpose: To compare the efficacy and safety of brolucizumab with aflibercept to treat neovascular age-related macular degeneration (AMD).

Design: Prospective, randomized, double-masked, multicenter, 2-arm, phase 2 study.

Participants: Eighty-nine treatment-naïve participants, aged ≥50 years, with active choroidal neovascularization secondary to AMD.

Methods: Eligible participants were randomized 1:1 to intravitreal brolucizumab (6 mg/50 μl) or aflibercept (2 mg/50 μl). Both groups received 3 monthly loading doses and were then treated every 8 weeks (q8) with assessment up to week 40. In the brolucizumab group, the final q8 cycle was extended to enable 2 cycles of treatment every 12 weeks (q12; to week 56); participants on aflibercept continued on q8. Unscheduled treatments were allowed at the investigator's discretion.

Main Outcome Measures: The primary and secondary hypotheses were noninferiority (margin: 5 letters at a 1-sided alpha level 0.1) in best-corrected visual acuity (BCVA) change from baseline of brolucizumab versus aflibercept at weeks 12 and 16, respectively. BCVA, central subfield thickness (CSFT), and morphologic features were assessed throughout the study.

Results: The mean BCVA change from baseline (letters) with brolucizumab was noninferior to aflibercept at week 12 (5.75 and 6.89, respectively [80% confidence interval for treatment difference, −4.19 to 1.93]) and week 16 (6.04 and 6.62 [−3.72 to 2.56]), with no notable differences up to week 40. Outcomes exploring disease activity during the q8 treatment cycles suggest greater stability of the brolucizumab participants, supported by receipt of fewer unscheduled treatments versus aflibercept (6 vs. 15) and more stable CSFT reductions. In addition, from post hoc analysis, a greater proportion of brolucizumab-treated eyes had resolved intraretinal and subretinal fluid compared with aflibercept-treated eyes. Approximately 50% of brolucizumab-treated eyes had stable BCVA during the q12 cycles. Brolucizumab and aflibercept adverse events were comparable.

Conclusions: During the matched q8 phase, the BCVA in brolucizumab-treated eyes appeared comparable to aflibercept-treated eyes, with more stable CSFT reductions, receipt of fewer unscheduled treatments, and higher rates of fluid resolution. The brolucizumab safety profile was similar to aflibercept over 56 weeks of treatment. A 12-week treatment cycle for brolucizumab may be viable in a relevant proportion of eyes. *Ophthalmology 2017;■:1−9 © 2017 by the American Academy of Ophthalmology*

Supplementary files is available at www.aaojournal.org.

Therapies targeting vascular endothelial growth factor (VEGF) have substantially improved visual outcomes for patients with neovascular age-related macular degeneration (nAMD).[1,2] Current treatment guidelines recommend anti-VEGF injection as first-line therapy for this disease.[3,4]

Anti-VEGF treatment has enhanced nAMD outcomes, with recommended treatment regimens often requiring frequent intravitreal (IVT) injections and frequent clinical assessment to track patients' response to therapy. The burden of these frequent visits represents a significant challenge for elderly patients, their caregivers, and the treating physicians, and may lead to undertreatment of nAMD.[5] Alternative treatment options, with prolonged intervals between injections, are needed to reduce the treatment burden.

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2) were 2 phase 3, double-masked, multinational, parallel-group, active-controlled clinical trials that were designed to assess the efficacy and safety of aflibercept versus ranibizumab to treat nAMD.[6] During the loading-dose phase (3 monthly injections), all the treatment arms achieved rapid mean improvements in best-corrected visual acuity (BCVA) that were sustained over 52 weeks. The mean visual acuity in the pooled aflibercept 2.0-mg groups (VIEW 1 and VIEW 2) that received maintenance treatment every 8

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weeks (q8) was within 0.3 letters of the ranibizumab group that received dosing every 4 weeks (q4). The VIEW studies supported the regulatory approval of a q8 dosing regimen for aflibercept 2.0 mg for the treatment of nAMD.[6]

Brolucizumab (RTH258, formerly ESBA1008) is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A. It is the smallest of the anti-VEGF antibodies, with a molecular weight of 26 kDa, compared with 115 kDa for aflibercept and 48 kDa for ranibizumab.[7,8] By virtue of its design, it is possible to concentrate brolucizumab up to 120 mg/mL, allowing the administration of 6 mg in a single 50-μL IVT injection. On a molar basis, 6 mg of brolucizumab equals approximately 12 times the 2.0-mg dose of aflibercept and 22 times the 0.5-mg dose of ranibizumab.[8] These attributes may confer potential advantages in the treatment of nAMD. A small molecular weight and high drug concentration gradient between the vitreous and retina may support drug distribution into the retina. Assuming comparable half-life, higher molar doses of drug may be cleared more slowly from the eye, thus prolonging duration of action.

In a first-in-human study of participants with nAMD, the 1-month change in central subfield thickness (CSFT) in eyes treated with a single IVT injection of brolucizumab at 4.5- and 6.0-mg doses was noninferior to a single IVT injection of 0.5 mg ranibizumab (noninferiority margin: 40 μm, 1-sided alpha 0.05), and, numerically, the results supported the same conclusion for the 3.0-mg dose. Notably, the median time until another injection was required was 30 days longer for brolucizumab at the 3-mg and 6-mg doses and 15 days longer at the 4.5-mg dose compared with ranibizumab, providing support for a more durable treatment response.[9]

The primary and key secondary objectives of this study were to compare the change in BCVA after 3 monthly injections of brolucizumab treatment (6 mg/50 μl) with that of aflibercept (2 mg/50 μl) at 12 and 16 weeks, respectively. Other secondary objectives were to compare the functional and anatomic outcomes in eyes receiving maintenance treatment with brolucizumab and aflibercept q8 up to week 40, to assess the potential of treatment every 12 weeks (q12) with brolucizumab based on 2 q12 cycles, and to evaluate the relative safety of brolucizumab and aflibercept.

Methods

Study Design

This was a prospective, randomized, double-masked, multicenter, 2-arm, phase 2 study comparing the efficacy and safety of brolucizumab with that of aflibercept in participants with nAMD (ClinicalTrials.gov identifier NCT01796964). The study protocol was approved by all institutional review boards and complied with the ethical standards defined by the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent before participating in the study. Forty-one investigational centers in the United States participated in the study, and the work is compliant with the Health Insurance Portability and Accountability Act of 1996.

Enrolled participants were randomized 1:1 using a web-based interactive response technology system to receive either brolucizumab (Alcon Laboratories Inc., Fort Worth, TX; 6.0 mg/50 μl IVT) or aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY; 2.0 mg/50 μl IVT) treatment. For masking purposes, sham treatment was administered when necessary, as described below.

There were 3 treatment periods over the course of the study (Fig 1). In the first period, loading doses of the study drug were administered at baseline and at weeks 4 and 8, with a corresponding efficacy assessment at week 12. The second period included 4 matching q8 dosing cycles (active treatments, besides week 8, at weeks 16, 24, and 32) for both treatment groups, with a corresponding assessment period up to week 40 (8 weeks after the last q8 dose administration in both treatment arms). During the third period up to week 56, participants in the brolucizumab group received only 1 additional treatment at week 44, extending the final q8 dosing cycle to a q12 dosing cycle, and a second q12 cycle was completed at week 56; participants on aflibercept continued on a q8 cycle, with treatments at weeks 40 and 48. To preserve masking during weeks 40 through 48, both groups had appropriately timed sham injections. The dosing schedule is shown schematically in Figure 1. At study visits when no active treatment was scheduled, the masked investigator could provide an unscheduled treatment with the participant's assigned treatment if the investigator determined it was medically necessary and after confirmation with the sponsor. At visits with potential sham injections, the investigator also had the option to apply an active treatment instead of a scheduled sham treatment based on medical need.

Efficacy assessors (BCVA technicians and photographers), the sponsor, and the monitors who reported, obtained, and reviewed the clinical evaluations were masked. Although the treating physician was masked through the week 36 injection, the application of sham injections could have unmasked the physician who administered injections and who conducted postinjection safety assessments from week 40 onward.

At screening, all participants underwent measurement of BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale in both eyes, as well as a complete bilateral ophthalmic examination that included slit-lamp examination, intraocular pressure (IOP) measurements, and a dilated fundus examination. In addition, color fundus photography (CF), fluorescein angiography (FA), and spectral-domain optical coherence tomography (SD OCT) imaging were obtained for both eyes of all participants (Appendix 1, available at www.aaojournal.org, for details regarding the protocols for ETDRS, IOP, CF, FA, and SD OCT data collection). The SD OCT, CF, and FA images were transferred to the Duke Reading Center for evaluation of study eligibility and analysis of relevant endpoints.

Participants

To be eligible for the study, participants had to be aged ≥50 years or older with untreated active choroidal neovascularization due to age-related macular degeneration in the study eye, with a BCVA between 73 and 23 letters, inclusive. The study eye had to have leakage on FA and subretinal fluid (SRF), intraretinal fluid (IRF), or sub−retinal pigment epithelium fluid on SD OCT, as confirmed by the Duke Reading Center. Exclusion criteria included any active intraocular or periocular infection or inflammation in either eye and previous treatment with an approved or investigational therapy for nAMD other than vitamin supplements in the study eye. The fellow eye could not be treated as a study eye. A detailed description of the inclusion and exclusion criteria is provided in Appendix 2 (available at www.aaojournal.org).

Outcomes

The primary efficacy parameter was BCVA. A certified visual acuity examiner evaluated BCVA in the study eye at all visits and

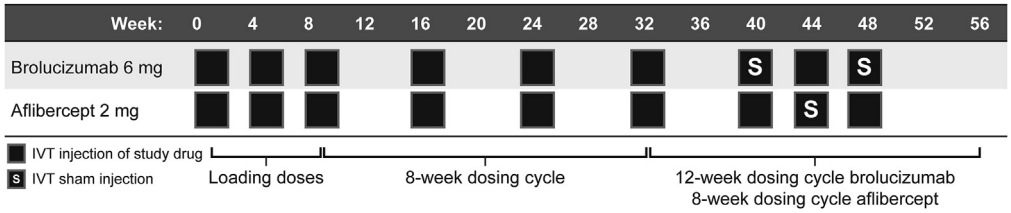

Figure 1. Schematic representation of study drug dosing regimens: loading, 8-week, and 12-week dosing cycles. IVT = intravitreal.

in both eyes at screening and at week 56. All evaluations were conducted according to ETDRS visual acuity protocol, and the results were reported as letters read correctly. The key secondary efficacy parameter was SD OCT–determined CSFT measured in the study eye at all visits and in both eyes at screening and at week 56. In addition, the presence or absence of IRF and SRF was assessed at each study visit. To ensure standardization, the same SD OCT imaging system was used at each investigational center throughout the study for each participant. The primary safety evaluation in this study was the incidence of ocular (separate for study eye and fellow eye) and nonocular adverse events (AEs) during treatment. Safety assessments also included vital signs and general physical examination, slit-lamp examination, IOP, dilated fundus examinations, postinjection assessments, and clinical laboratory results.

Endpoints and Statistical Analyses

The primary and the key secondary efficacy endpoints were the change in BCVA from baseline at weeks 12 and 16 to assess the outcome at the end of the loading phase and after the first q8 cycle, respectively.

Additional secondary endpoints based on BCVA included the change from baseline at week 40 and the average changes from week 12 in BCVA for the period of week 16 to week 40, with week 40 representing the end of the matched q8 treatment phase. To assess stability regarding the efficacy outcome during the q8 treatment cycles, the average 1-month response after a visit with no injection (the average of the changes from weeks 12 to 16, 20 to 24, 28 to 32, and 36 to 40) was evaluated. Corresponding endpoints were also assessed for retinal thickness as post hoc analysis. Exploratory endpoints assessing the presence of SRF and IRF using SD OCT were performed at each follow-up visit as hypothesis-generating, post hoc analyses.

For the assessment of brolucizumab q12 treatment potential, the study-eye BCVA between week 36 (1 month after the first q12 treatment) and week 56 was evaluated. Eyes were considered to have "stable visual acuity under q12 treatment" if there were no unscheduled treatments and BCVA was stable (defined as a loss of <5 letters during weeks 40–56 compared with week 36). As the aflibercept arm remained on q8 treatment after the loading phase, no comparative assessments of q12 treatment potential between brolucizumab and aflibercept can be made.

The efficacy analysis was primarily based on the full-analysis set (FAS), which included all participants who were randomized, received ≥1 treatment, had a baseline value, and had ≥1 post-baseline measurement of the primary efficacy variable (BCVA). Missing data were imputed using the last-observation-carried-forward method.

One participant did not receive the study treatment according to randomization; however, in the absence of an intent (with a potential of introducing a bias), the primary efficacy analysis was conducted using the treatment allocation according to actual treatment received ("as treated").

For the assessment of the efficacy of brolucizumab given q12, participants were included only if they had completed the study visits at weeks 32, 44, and 56.

An analysis of variance (ANOVA) model with treatment and baseline BCVA categories (<55 and ≥55 letters) as class variables was used to estimate treatment group differences (i.e., brolucizumab − aflibercept) regarding the primary and key secondary efficacy endpoints. Noninferiority of brolucizumab to aflibercept at weeks 12 and 16 was concluded at a 1-sided alpha level of 0.1 if the lower limit of the corresponding 2-sided 80% confidence interval (CI) for this treatment group difference was greater than −5 letters. For this phase 2 study no formal alpha adjustment was specified related to testing multiple hypotheses.

Treatment differences related to the other secondary endpoints were assessed using 80% CIs derived from similar ANOVA models; for CSFT, this model included treatment and baseline CSFT categories (<400 and ≥400 μm) as class variables.

A sample size of 40 patients per treatment group gave an 80% power to demonstrate the noninferiority of brolucizumab compared with aflibercept at weeks 12 and 16 using a noninferiority margin of 5 letters at a 1-sided alpha level of 0.1 and assuming equal efficacy on BCVA. Approximately 84 participants were planned for randomization to account for an up to 5% dropout rate up to week 16.

Results

Participants

Ninety participants were randomized to either brolucizumab or aflibercept treatment (45 eyes per group; Fig 2). The study was conducted from March 2013 to August 2014. Of the 90 participants who were randomized, 7 discontinued early from the study (3 in the brolucizumab group and 4 in the aflibercept group). The reasons for discontinuation were AEs (1 participant in each treatment group), withdrawal by participant (1 participant in each treatment group), protocol violation (2 participants in the aflibercept group, including 1 participant who received no treatment), and death (1 participant in the brolucizumab group). Of the 89 randomized participants who received treatment, 1 participant who should have received brolucizumab received aflibercept at baseline and continued on aflibercept throughout the study. Thus, the as-treated FAS population included 44 participants in the brolucizumab group and 45 participants in the aflibercept group.

Demographic and baseline characteristics are summarized in Tables 1 and 2 for the as-treated FAS (identical to the safety-analysis set). The percentage of participants aged ≥75 years was higher in the brolucizumab group than in the aflibercept group (72.7% vs. 64.4%) and the percentage of female participants was higher in the brolucizumab group than in the aflibercept group (63.6% vs. 55.6%). The baseline BCVA was 54.1 and 55.6 letters in the brolucizumab and aflibercept groups, respectively. CSFT and

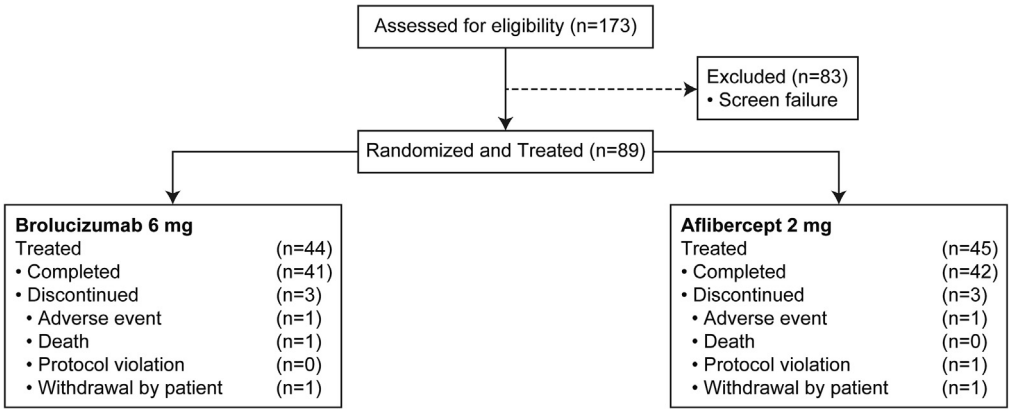

Figure 2. Participant disposition.

lesion type were balanced between groups. At baseline, SRF was present in 90.9% and 88.9% of the participants in the brolucizumab and aflibercept groups, respectively, and IRF was present in 86.4% and 84.4% of participants.

Efficacy

The least squares mean (LSM) BCVA change from baseline at week 12 was 5.75 letters in the brolucizumab group and 6.89 letters in the aflibercept group, with a difference between treatment groups of −1.13 letters (80% CI, −4.19 to 1.93 letters). At week 16, the BCVA change from baseline was 6.04 letters in the brolucizumab group and 6.62 letters in the aflibercept group, with a difference between treatment groups of −0.58 letters (80% CI, −3.72 to 2.56 letters). These results demonstrate the noninferiority of brolucizumab compared with aflibercept at weeks 12 and 16 at a 1-sided alpha level of 0.1 and a noninferiority margin of 5 letters. Subgroup analyses related to age and sex suggested that lower gains were achieved by older versus younger and female versus male participants in both treatment groups.

Table 1. Participant Demographics (As-Treated Full-Analysis Set)

Demographic	Brolucizumab (n = 44)	Aflibercept (n = 45)	Overall (N = 89)
Age, years			
Mean (SD)	78.8 (9.7)	77.3 (9.1)	78.0 (9.4)
Median	80	79	80
Min, max	58, 96	55, 92	55, 96
Age, n (%)			
<65 years	6 (13.6)	6 (13.3)	12 (13.5)
65–74 years	6 (13.6)	10 (22.2)	16 (18.0)
75–84 years	19 (43.2)	18 (40.0)	37 (41.6)
≥85 years	13 (29.5)	11 (24.4)	24 (27.0)
Sex, n (%)			
Female	28 (63.6)	25 (55.6)	53 (59.6)
Male	16 (36.4)	20 (44.4)	36 (40.4)
Race, n (%)			
White	42 (95.5)	44 (97.8)	86 (96.6)
Black or African American	1 (2.3)	0	1 (1.1)
Asian	1 (2.3)	1 (2.2)	2 (2.2)
Ethnicity, n (%)			
Not Hispanic or Latino	44 (100.0)	44 (97.8)	88 (98.9)
Hispanic or Latino	0	1 (2.2)	1 (1.1)

SD = standard deviation.

Figure 3A shows the LSM estimates for the BCVA change from baseline by visit from day 0 (baseline) through week 56. During the loading phase (up to week 12) and the period of matching q8 treatment cycles (weeks 12–40), there were no meaningful treatment group differences. At the end of the matching q8 treatment cycles (week 40), the LSM of the BCVA change from baseline was 6.25 letters for brolucizumab and 5.75 letters for aflibercept, a treatment difference of 0.50 letters (80% CI, −3.39 to 4.39). On average, for both treatment groups, the initial BCVA gains were maintained with q8 treatment cycles: the average change in BCVA from week 12 for the period of week 16 to week 40 (i.e., over the matched q8 treatment period relative to the BCVA at the end of the loading phase) was 1.08 letters for brolucizumab and −0.10 letters for aflibercept (difference, 1.18 [80% CI, −0.69 to 3.04]).

The LSM estimates for the CSFT change from baseline by visit from baseline through week 56 are shown in Figure 3B. For brolucizumab and aflibercept, the LSM change in CSFT from baseline at week 12 was −196.6 μm and −189.0 μm, respectively, and at week 40 was −197.5 μm and −178.3 μm. The average CSFT change from week 12 for the period of week 16 to week 40 was −3.1 μm for brolucizumab and 11.1 μm for aflibercept (difference, −14.21 μm [80% CI, −22.8 to −5.6]).

The post hoc analyses of SRF and IRF by study visit are presented in Figure 4A–C. The proportion of eyes with SRF for brolucizumab and aflibercept at week 12 was 9.3% and 20.9%, respectively (difference, −11.6% [80% CI, −21.4 to −1.9]) and at week 40 was 14.6% and 32.5% (difference, −17.9 [80% CI, −29.7 to −6.0]). The proportion of eyes with IRF at week 12 was 48.8% for both groups (difference: 0% [80% CI, −13.8 to 13.8]) and at week 40 was 36.6% and 40.0% for brolucizumab and aflibercept, respectively (difference, −3.4% [80% CI, −17.3 to 10.4]). The proportion of eyes simultaneously without SRF and IRF for brolucizumab and aflibercept at week 12 was 48.8% and 41.9%, respectively (difference, 7.0% [80% CI, −6.7 to 20.7]) and at week 40 was 61.0% and 35.0% (difference, 26.0% [80% CI, 12.2–39.7]).

The stability of functional and anatomic outcomes during the matched q8 treatment cycles was assessed based on the number of unscheduled treatments as well as possible fluctuations in BCVA, CSFT, SRF, and IRF.

Regarding the number of additional treatments received during the matched q8 treatment cycle phase of the study, a treatment difference was observed: 6 additional unscheduled treatments were received by 5 participants in the brolucizumab group versus 15 treatments in 10 participants in the aflibercept group.

Table 2. Participant Baseline Characteristics (As-Treated Full-Analysis Set)

Characteristics	Brolucizumab (n = 44)	Aflibercept (n = 45)	Overall (N = 89)
Presence of subfoveal choroidal neovascularization, n (%)	44 (100.0)	45 (100.0)	89 (100.0)
Unilateral age-related macular degeneration, n (%)	32 (72.7)	38 (84.4)	70 (78.7)
Time since diagnosis ≤30 days, n (%)	42 (95.5)	42 (93.3)	84 (94.4)
BCVA letters, n			
Mean (SD)	54.1 (13.9)	55.6 (12.3)	54.8 (13.0)
Min, max	25, 72	24, 72	24, 72
BCVA <55 letters, n (%)	16 (36.4)	15 (33.3)	31 (34.8)
CSFT, μm			
Mean (SD)	490.1 (149.2)	495.7 (144.6)	492.9 (146.1)
Min, max	241, 926	231, 907	231, 926
CSFT ≥400 μm, n (%)	32 (72.7)	31 (68.9)	63 (70.8)
Presence of intraocular hemorrhage, n (%)	14 (31.8)	18 (40.0)	32 (36.0)
Lesion type, n (%)			
Predominantly classic	21 (47.7)	23 (51.1)	44 (49.4)
Minimally classic	12 (27.3)	8 (17.8)	20 (22.5)
Occult	11 (25.0)	14 (31.1)	25 (28.1)
Presence of hyperreflective material, n (%)	37 (84.1)	38 (84.4)	75 (84.3)
Presence of subretinal fluid, n (%)	40 (90.9)	40 (88.9)	80 (89.9)
Presence of intraretinal fluid, n (%)	38 (86.4)	38 (84.4)	76 (85.4)

BCVA = best-corrected visual acuity; CSFT = central subfield thickness; SD = standard deviation.

Regarding BCVA, the stability assessment during the matched q8 treatment cycles was based on the LSM estimates for the average of the 4 1-month changes in BCVA after a visit with no injection (i.e., the average of the changes from weeks 12−16, 20−24, 28−32, and 36−40). This analysis revealed an LSM change of −0.43 letters for brolucizumab and −0.03 letters for aflibercept (difference, −0.40 [80% CI, −1.08 to 0.28]), thus indicating, on average, no relevant instability and no differences between treatments.

A similar analysis of stability was conducted post hoc for the CSFT. The CSFT fluctuated in both treatment arms and the fluctuation was numerically greater in aflibercept-treated eyes. The LSM change was 10.1 μm for brolucizumab and 18.4 μm for aflibercept (difference, −8.39 [80% CI, −15.9 to −0.9]). Increased CSFT after visits with no injection was not seen in all eyes and was driven by a subgroup in each treatment arm, with upper quartiles for this average change of 18.2 μm and 31.5 μm for brolucizumab and aflibercept, respectively.

Fluctuations in the proportions of eyes with IRF and SRF were observed in both treatment groups; peak values occurred 8 weeks after treatment and trough values occurred 4 weeks after treatment.

For the first q12 treatment cycle in the brolucizumab group, the mean change in BCVA from week 36 to week 44 (after injection at week 32) suggested, on average, BCVA stability (mean change, 0.8 letters; median change, 0 letters). For the second q12 treatment cycle, the corresponding BCVA declined an average of −1.3 letters (median change, 0 letters) from week 48 to week 56 (after injection at week 44). Out of 39 brolucizumab-treated eyes with data that allowed for a by-eye assessment of their q12 response (completed visits at weeks 32 and 44, both with the scheduled injection and the week 56 follow-up), 18 had stable BCVA and had not received unscheduled treatment during the period from week 36 to week 52. During this q12 phase, 14 brolucizumab-treated patients received unscheduled treatment at 4 potential visits (weeks 36, 40, 48, and 52), while during the same period 10 out of 39 corresponding aflibercept-treated patients received unscheduled treatment at 3 potential visits (weeks 36, 44, 52). Seven BCVA-unstable eyes that did not receive any unscheduled treatments during the q12 treatment period substantially contributed to the mean BCVA reduction during the second q12 cycle with brolucizumab. These eyes had poor initial BCVA response during the loading phase and had dynamic IRF activity during the q12 treatment cycles.

Safety

The safety-analysis set was identical to the as-treated FAS. Treatment-emergent AEs are summarized in Table 3. Overall, the most commonly occurring AE in the study eye was conjunctival hemorrhage, which was reported by 5 participants in the brolucizumab group and 7 participants in the aflibercept group. Other commonly reported study-eye ocular AEs included vitreous floaters, reduced visual acuity, and vitreous detachment. Commonly reported nonocular AEs were upper respiratory tract infection and urinary tract infection.

There was a single death after the third injection in the brolucizumab treatment arm due to myocardial ischemia in an 80-year-old male patient with a medical history of hypertension, polycythemia vera with hemachromatosis, splenomegaly, and thrombocytopenia as well as testicular, prostate, and kidney cancers. His concomitant medications included terazosin, hydrochlorothiazide, and aspirin. The participant's blood pressure remained stable at each study visit (131−138/79−84 mmHg). The principal investigator assessed the event as serious, severe, and related to brolucizumab because causality could not be ruled out.

Nineteen participants (10 in the brolucizumab group and 9 in the aflibercept group) had nonfatal serious AEs (SAEs); only 1 of the nonfatal SAEs (transient ischemic attack in the aflibercept group) was considered by the investigator to be treatment related. One participant in the brolucizumab group discontinued treatment owing to an SAE of pancreatic carcinoma, and 1 participant in the aflibercept group discontinued treatment owing to an SAE of retinal detachment in the study eye; neither event was considered by the investigator to be treatment related. No other nonfatal events led to study discontinuation.

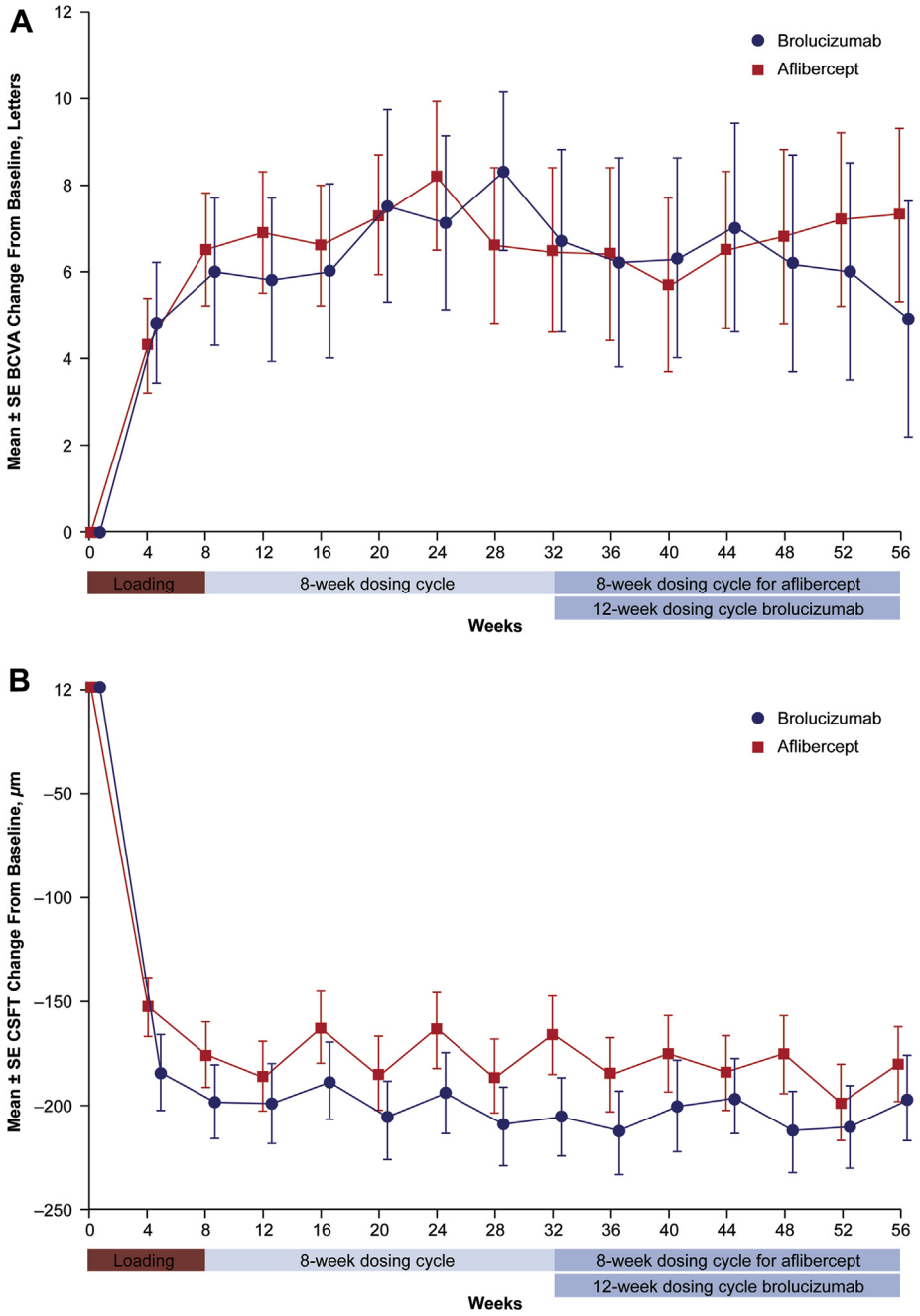

Figure 3. **A**, Least square mean best-corrected visual acuity (BCVA) change from baseline (number of letters) and **B**, central subfield thickness (CSFT) change from baseline (μm). Data in each graph are by visit for the as-treated full-analysis set, last observation carried forward. SE = standard error.

Discussion

In this phase 2 study, brolucizumab met the primary and secondary objectives to demonstrate noninferiority (margin: 5 letters at a 1-sided alpha level 0.1) to aflibercept in BCVA change from baseline at weeks 12 and 16.

Over the q8 treatment cycles (weeks 12−40), the initial treatment effects were sustained, without indication of meaningful differences in BCVA response between the groups. For comparison, the change from baseline in mean BCVA for the q8 2.0-mg aflibercept dosing regimens in the VIEW 1 and 2 studies was 7.9±15.0 letters and 8.9±14.4 letters, respectively, at 52 weeks,[6] which was similar to the 52-week results for the aflibercept group in the present study (7.2±13.2 letters). Comparable results for BCVA efficacy between the VIEW studies and this study for the 2.0-mg q8 dosing of aflibercept help substantiate the noninferiority of brolucizumab for the maintenance of treatment effect with q8 dosing.

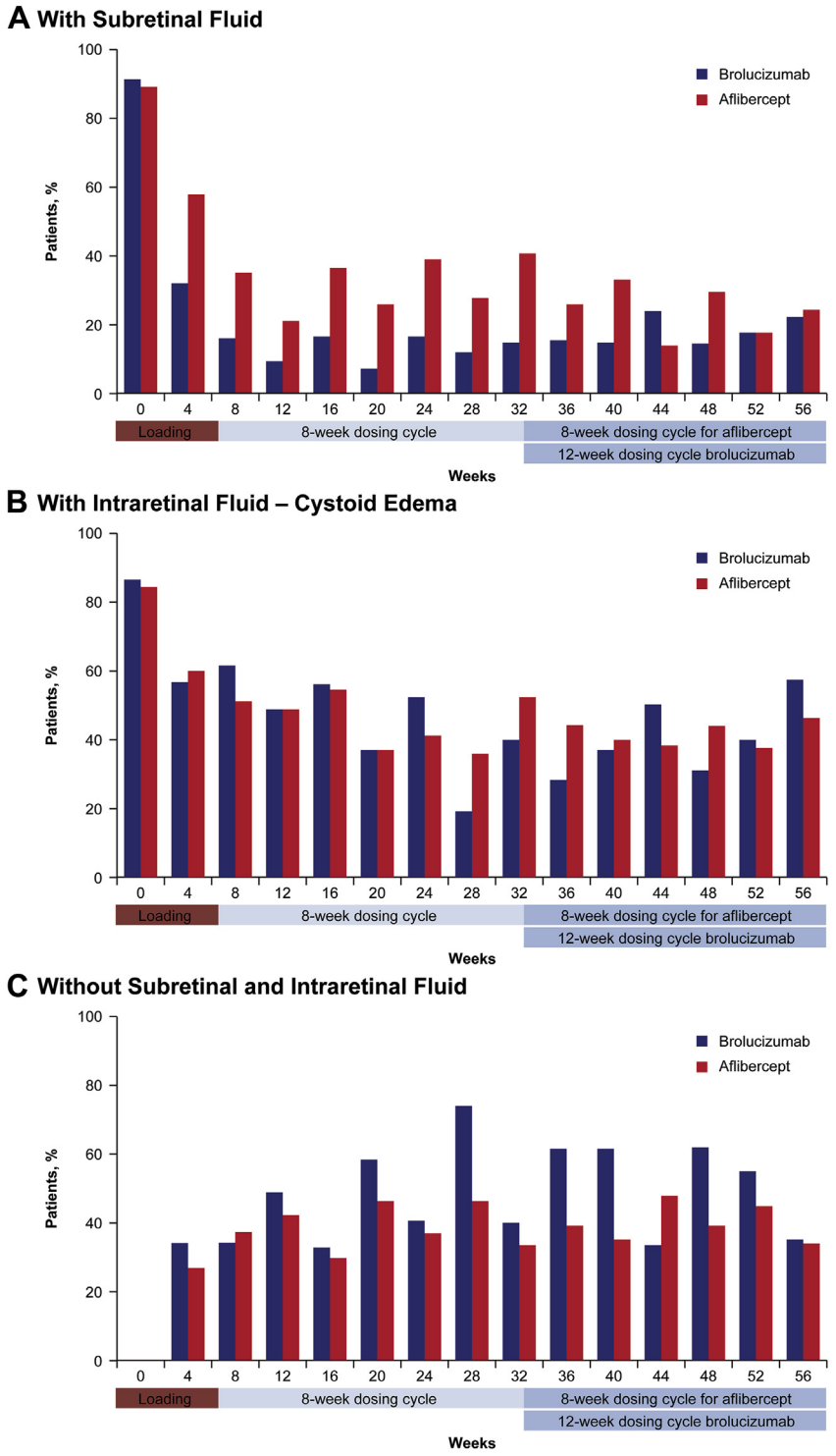

Figure 4. **A**, Percentage of eyes with subretinal fluid by visit, **B**, percentage of eyes with intraretinal fluid by visit, and **C**, percentage of eyes simultaneously without subretinal fluid and intraretinal fluid by visit. Data in each graph are for the as-treated full-analysis set, observed.

During the q8 treatment cycles (weeks 12–40), there were numerical advantages of brolucizumab compared with aflibercept, both to reduce CSFT from baseline and to maintain a stable treatment effect. A higher proportion of brolucizumab participants (61% vs. 35%) achieved simultaneous resolution of IRF and SRF by week 40, suggesting a greater brolucizumab anti-VEGF biological effect. Furthermore, twice as many aflibercept as brolucizumab

Table 3. Summary of Treatment-Emergent Adverse Events (Safety-Analysis Set)

Participants with AE, n (%)	Brolucizumab 6 mg (n = 44)	Aflibercept 2 mg (n = 45)
Serious AEs	11 (25.0)	9 (20.0)
Deaths	1 (2.3)	0
Nonfatal serious AEs	10 (22.7)	9 (20.0)
Related to study drug	0	1 (2.2)
Related to IVT procedure	1 (2.3)	0
AEs leading to study discontinuation (participants)	2 (4.5)	1 (2.2)
Related to study drug	1 (2.3)	0
Related to IVT procedure	0	0
Most frequent treatment-emergent AEs*		
Ocular AEs in study eye		
Conjunctival hemorrhage	5 (11.4)	7 (15.6)
Vitreous floaters	5 (11.4)	4 (8.9)
Visual acuity reduced	4 (9.1)	4 (8.9)
Vitreous detachment	3 (6.8)	3 (6.7)
Age-related macular degeneration	3 (6.8)	1 (2.2)
Cataract	1 (2.3)	3 (6.7)
Macular fibrosis	3 (6.8)	1 (2.2)
Punctate keratitis	1 (2.3)	3 (6.7)
Vision blurred	1 (2.3)	3 (6.7)
Foreign body sensation in eyes	0	3 (6.7)
Nonocular AEs		
Upper respiratory tract infection	5 (11.4)	3 (6.7)
Nausea	3 (6.8)	1 (2.2)
Chronic obstructive pulmonary disease	3 (6.8)	0
Urinary tract infection	2 (4.5)	4 (8.9)
Adverse events related to study drug		
Vitreal cells	1 (2.3)	1 (2.2)
Eye inflammation	1 (2.3)	0
Iridocyclitis	1 (2.3)	0
Keratitis	1 (2.3)	0
Myocardial ischemia	1 (2.3)	0
Vision blurred	1 (2.3)	0
Visual acuity reduced	1 (2.3)	0
Vitreous floaters	1 (2.3)	0
Anterior chamber cell	0	1 (2.2)
Transient ischemic attack	0	1 (2.2)

AE = adverse event; IVT = intravitreal.
*Ocurring in ≥3 participants in any treatment group.

participants received unscheduled treatment up to week 40. This may indicate a more durable anti-VEGF treatment effect for brolucizumab.

During the q12 treatment cycle phase for brolucizumab, BCVA was maintained without additional treatments in approximately 50% of evaluable eyes. A decline in mean BCVA during the second q12 cycle could be attributed mainly to a subgroup of 7 eyes. Interestingly, this subset had poor initial responses to treatment, as evidenced by their BCVA outcomes during the loading dose phase and dynamic IRF activity during the q12 treatment cycles. These clinical parameters may well serve as indicators for more frequent treatment.

At sites where the assessing physicians also performed the injections, the assessing physicians were unmasked from week 40 onward because during that time active/sham injections with different schedules for the 2 treatment groups were applied. Masking before week 40 was complete, so the head-to-head q8 comparison between brolucizumab and ranibizumab was not affected. The likelihood of bias regarding the assessment of the q12 potential of brolucizumab was considered minimal because the BCVA and photographic technicians at each investigational site remained masked.

The most common ocular treatment-emergent AEs in the study eye recorded for the brolucizumab group (occurring in >10% of participants) were conjunctival hemorrhage, reduced visual acuity, vitreous floaters, and macular degeneration (11.4% for each AE). In comparison, the rates of conjunctival hemorrhage for ranibizumab and aflibercept were higher in VIEW 1 (47.4% for ranibizumab 0.5-mg q4 dosing; 43.2% for aflibercept 2.0-mg q8 dosing), lower in VIEW 2 (7.9% and 9.8%, respectively),[6] and comparable to the rates reported in this study (11.4% for brolucizumab; 15.6% for aflibercept). The rates of reduced visual acuity reported in the VIEW 1 and 2 trials ranged from 6.6% to 6.9% for ranibizumab and 6.6% to 10.7% for aflibercept at the 2.0-mg q8 dose interval (reduced visual acuity was reported by 8.9% of aflibercept participants in the present study). The incidence of vitreous floaters and of macular degeneration observed in the VIEW 1 and 2 studies were <11% in the ranibizumab and aflibercept (2.0-mg q8) groups,[6] and similar to the incidences for brolucizumab (11.4% and 11.4%, respectively) and aflibercept (8.9% and 4.4%) in this study. The safety profile of brolucizumab in this small phase 2 study was consistent with the safety profile of intravitreally injected anti-VEGF agents and did not show any unexpected events.

Based on its favorable stability data, brolucizumab appears to function at least as well as aflibercept in a q8 regimen in this phase 2 study. In addition, the data suggest that a relevant proportion of brolucizumab-treated eyes may be adequately treated on a q12 regimen. The selection of the optimal treatment regimen needs to be identified on an individualized basis, and dynamic parameters of disease activity, such as BCVA response during loading phase and IRF activity, may play a role. These results have informed the design of pivotal phase 3 studies that are currently underway (ClinicalTrials.gov Identifier numbers: NCT02307682 and NCT02434328).

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **ANOVA** = analysis of variance; **BCVA** = best-corrected visual acuity; **CF** = color fundus photography; **CI** = confidence interval; **CSFT** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FA** = fluorescein angiography; **FAS** = full-analysis set; **IOP** = intraocular pressure; **IRF** = intraretinal fluid; **IVT** = intravitreal; **LSM** = least squares mean; **nAMD** = neovascular age-related macular degeneration; **q4** = every 4 weeks; **q8** = every 8 weeks; **q12** = every 12 weeks; **SAE** = serious adverse event; **SD OCT** = spectral-domain optical coherence tomography; **SRF** = subretinal fluid; **VEGF** = vascular endothelial growth factor.

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