

HAWK and HARRIER

Ninety-Six-Week Outcomes from the Phase 3 Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration

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Purpose: To report the 96-week outcomes from HAWK and HARRIER.

Design: Phase 3, prospective, randomized, double-masked, multicenter studies comparing efficacy and safety of brolucizumab 3 mg (HAWK only) and 6 mg with aflibercept 2 mg in eyes with neovascular age-related macular degeneration (nAMD).

Participants: Treatment-naïve eyes with nAMD were randomized 1:1:1 to brolucizumab 3 mg (n = 358), brolucizumab 6 mg (n = 360), aflibercept 2 mg (n = 360; HAWK) or 1:1 to brolucizumab 6 mg (n = 370), aflibercept 2 mg (n = 369; HARRIER).

Methods: After 3 monthly loading doses, brolucizumab patients received every (q)-12-week (w) dosing, possibly adjusting to q8w dosing if disease activity was present at predefined disease activity assessment (DAA) visits. Aflibercept was dosed in a fixed q8w regimen. Visual and anatomic parameters were assessed throughout. Primary end point was at week 48 (48w), confirmed at 96w.

Main Outcome Measures: Mean best-corrected visual acuity (BCVA) change from baseline, proportion of patients on an q12w regimen, retinal thickness, retinal fluid changes, and safety, all to 96w.

Results: Mean change (least squares [LS] mean $\pm$ standard error) in BCVA from baseline to 96w in HAWK was 5.6 ± 0.79 Early Treatment Diabetic Retinopathy Study (ETDRS) letters for brolucizumab 3 mg, 5.90 ± 0.78 letters for brolucizumab 6 mg, and 5.3 ± 0.78 letters for aflibercept and in HARRIER was 6.1 ± 0.73 letters for brolucizumab 6 mg and 6.6 ± 0.73 letters for aflibercept. Greater central subfield thickness reductions were observed with brolucizumab 6 mg versus aflibercept in HAWK (LS mean, $-174.8 \mu\text{m}$ vs. $-148.7 \mu\text{m}$; 95% confidence interval for treatment difference, -46.2 to $-5.9 \mu\text{m}$; $P = 0.0115$) and HARRIER (LS mean, $-197.7 \mu\text{m}$ vs. $-155.1 \mu\text{m}$; 95% confidence interval for treatment difference, -62.0 to $-23.3 \mu\text{m}$; $P < 0.0001$). The proportions of eyes with intraretinal fluid and/or subretinal fluid (IRF/SRF) at 96w in HAWK were 31% ($P = 0.0688$) and 24% ($P = 0.0002$) for brolucizumab 3 mg and 6 mg and 37% for aflibercept, whereas in HARRIER, they were 24% for brolucizumab 6 mg ($P < 0.0001$) and 39% for aflibercept. At 92w (last DAA), a 45.4% and 38.6% probability was observed for brolucizumab 6 mg patients of maintaining an q12w treatment regimen in HAWK and HARRIER, respectively. Brolucizumab exhibited an overall well-tolerated safety profile.

Conclusions: Visual outcomes from 48w to 96w confirm the efficacy achieved at 48w. Brolucizumab demonstrated greater fluid resolution compared with aflibercept. The q12w potential for brolucizumab observed at 48w was maintained to 96w. *Ophthalmology* 2021;128:89-99 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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The global burden of age-related macular degeneration is likely to reach 196 million affected individuals in 2020, with a projected increase to 288 million by 2040.¹ At a country level, similar trends are observed in the prevalence and incidence of the neovascular form of the disease, neovascular age-related macular degeneration (nAMD).^{2,3} Despite significant advances in therapeutic options,

clinicians struggle with the growing nAMD patient population and the associated monitoring and treatment demand.⁴

The current standard of care in nAMD is frequent intravitreal injections of an anti-vascular endothelial growth factor (VEGF) therapy, which have transformed patient outcomes within clinical trials.⁵⁻⁷ However, visual

outcomes in real-world settings remain well below those achieved with the fixed, frequent treatment regimens used in clinical trials.^{8,9} In real-world clinical practice, and despite widespread use of individualized treatment regimens,¹⁰ clinicians must monitor patients' disease activity regularly (functional assessment and anatomic assessment such as OCT) to determine treatment requirements.^{4,11,12} For this reason, the burden of multiple clinic visits associated with current anti-VEGF therapies remains high.

Innovative therapies are needed to lessen the treatment and monitoring-visit burden while maintaining treatment efficacy and safety.^{4,11} Brolicizumab is a novel anti-VEGF therapy comprising a humanized single-chain antibody fragment with a molecular weight of 26 kDa, allowing for higher molar dosing than previous anti-VEGF therapies.^{13,14} Its potential for a more sustained duration of action, greater tissue penetration, or both in the treatment of nAMD is supported by preclinical data of a 2.2- and 1.7-fold higher exposure in the neurosensory retina and the retinal pigment epithelium (RPE)—choroid, respectively, compared with ranibizumab (D. Escher. Single-chain antibody fragments in ophthalmology. Abstract: 15th EURETINA Congress, Nice, 2015). Additionally, a clinical phase 1/2 study reported an increase of 30 days in the median time to treatment after a single baseline dose compared with ranibizumab.¹⁴ During the matched every (q) 8 weeks (w) phase (up to week 40) of the phase 2 OSPREY study (3 loading doses followed by q8w injections given at weeks 16, 24, and 32), brolicizumab 6 mg (n = 44) demonstrated comparable visual gains to aflibercept 2 mg (n = 45), with higher rates of fluid resolution. Approximately 50% of brolicizumab-treated eyes showed stable BCVA during the 2 q12w cycles (weeks 32–44 and weeks 44–56, applied to the brolicizumab arm only, with an injection at week 44).¹³

In the phase 3 HAWK and HARRIER trials, brolicizumab 6 mg (administered in a q12w or q8w regimen) demonstrated noninferior best-corrected visual acuity (BCVA) gains and superior anatomic outcomes versus aflibercept (administered in a fixed q8w regimen), and more than 50% of brolicizumab patients were maintained on a q12w treatment interval until the primary end point at week 48.¹⁵ Of note, in the matched head-to-head phase of HAWK and HARRIER up to week 16, significantly fewer brolicizumab patients showed intraretinal fluid and/or subretinal fluid (IRF/SRF), compared with aflibercept (HAWK, 33.9% vs. 52.2% [$P < 0.0001$]; HARRIER, 29.4% vs. 45.1% [$P < 0.0001$]). The 96-week efficacy and safety outcomes from the phase 3 prospective HAWK and HARRIER studies are presented here.

Methods

HAWK and HARRIER are phase 3, prospective, randomized, double-masked, multicenter studies designed to compare the efficacy and safety of brolicizumab 3 mg (HAWK only) and 6 mg with aflibercept 2 mg in patients with nAMD. The studies were conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonization E6 Good Clinical Practice Consolidated Guidelines, and other regulations as applicable and complied with the Health Insurance Portability and

Accountability Act of 1996. HAWK (NCT02307682) and HARRIER (NCT02434328) were 2-year, randomized, double-masked, multicenter trials conducted in 408 sites in North, Central, and South America; Europe; Asia; Australia; and Japan. All patients provided written informed consent before screening or initiation of any study-related procedures. Protocols were approved by an Independent Ethics Committee/Institutional Review Board. Trials were conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonization E6 Good Clinical Practice Consolidated Guideline, and other regulations as applicable and were compliant with the Health Insurance Portability and Accountability Act of 1996. Full details of the trial oversight, randomization, sample size calculations, and inclusion and exclusion criteria have been published previously.¹⁵

Patients were randomized 1:1:1 to receive brolicizumab 3 mg or 6 mg or aflibercept 2 mg (HAWK) or 1:1 to receive brolicizumab 6 mg or aflibercept 2 mg (HARRIER). After the loading phase, brolicizumab was administered q12w with the possibility of adjusting to q8w if disease activity was present at predefined disease activity assessment (DAA) visits, as described previously.¹⁵ Starting at week 16 (the first DAA), and up to week 92 (the last DAA), HAWK had 8 DAAs and HARRIER had 14 DAAs at which patients could only be adjusted from q12w to q8w therapy. Brolicizumab patients adjusted to q8w therapy based on DAA results at any point remained on q8w therapy for the remainder of the study. No opportunity was provided to return to a q12w interval. After the loading phase, aflibercept was administered q8w throughout, as per the label at the time of study initiation.

The primary objective of both HAWK and HARRIER was to demonstrate that brolicizumab (q12w/q8w) is noninferior to fixed-dose aflibercept with respect to the change in BCVA from baseline to week 48. The 96-week outcomes presented herein are as follows: mean change in BCVA from baseline at week 96; average change in BCVA from baseline from weeks 84 through 96; mean change in central subfield thickness (CST) from baseline at week 96; average change in CST from baseline from weeks 84 through 96; percentages of eyes with the presence of IRF/SRF in the central subfield at week 96; percentages of eyes with the presence of sub-RPE fluid at week 96; and proportion of eyes that lost 15 letters or more. The probability of maintaining an q12w interval up to the DAA at week 92 also is presented (week 92 was the last DAA visit), in addition to key safety outcomes. Full details of the statistical methods used have been published previously.¹⁵ For comparisons between groups at week 96, 2-sided P values are presented.

Results

Patient Baseline Characteristics

Patient baseline characteristics have been presented previously¹⁵ and also are included here as supplementary tables (Table S1 and Table S2, available at www.aaojournal.org).

Best-Corrected Visual Acuity

The mean change in BCVA from baseline at week 48 (primary end point) in brolicizumab-treated eyes was noninferior to that in aflibercept-treated eyes, and these visual gains were maintained to week 96. In HAWK, the least squares (LS) mean change $\pm$ standard error in BCVA (measured in Early Treatment Diabetic Retinopathy Study scale [ETDRS] letters) from baseline to week 96 was 5.6 ± 0.79 letters for brolicizumab 3 mg, 5.9 ± 0.78 letters for brolicizumab 6 mg, and 5.3 ± 0.78 letters for aflibercept (Fig 1A), whereas in HARRIER, it was 6.1 ± 0.73 letters for brolicizumab 6 mg and 6.6 ± 0.73 letters for aflibercept (Fig 1B). The average

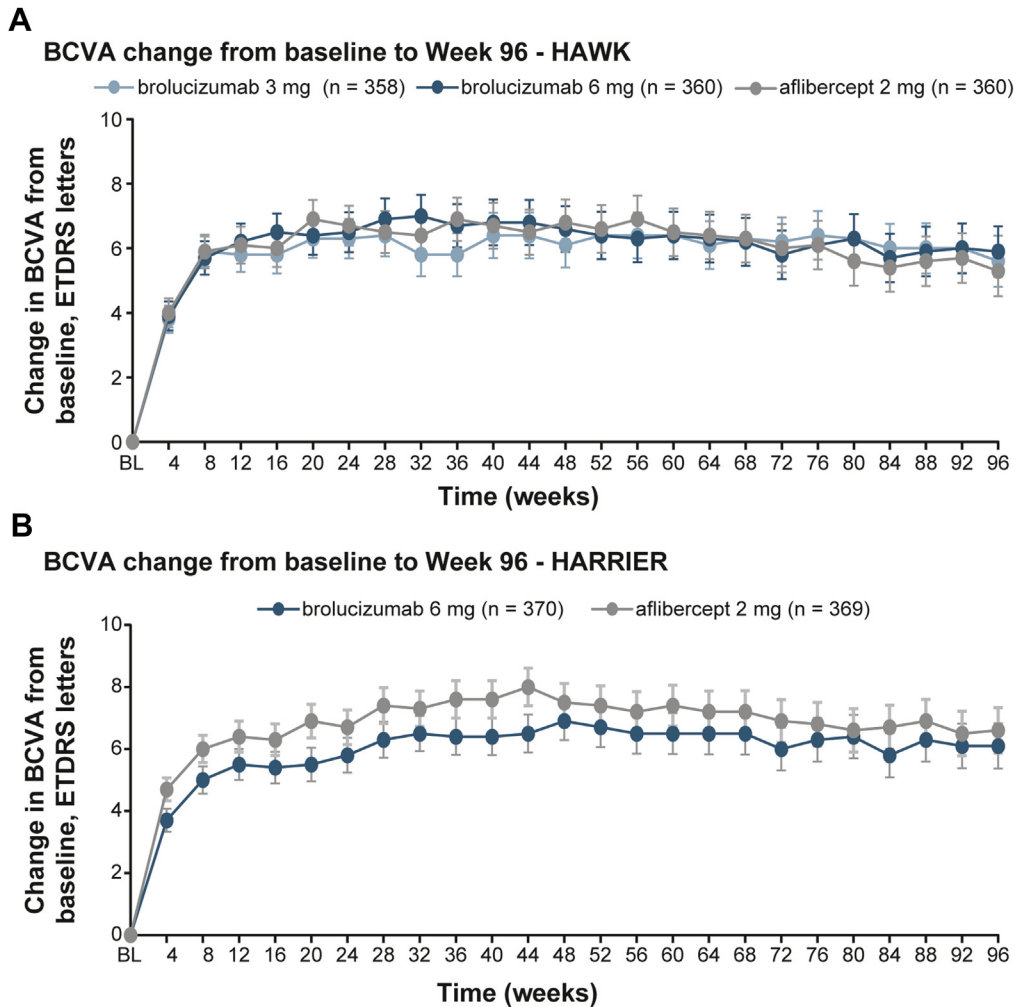


Figure 1. Graphs showing the least squares mean best-corrected visual acuity (BCVA) change from baseline to week 96 in the brolucizumab and aflibercept treatment groups in the (A) HAWK and (B) HARRIER studies. BL = baseline; ETDRS = Early Treatment Diabetic Retinopathy Study.

change in BCVA from baseline from weeks 84 through 96 was 5.9, 5.9, and 5.5 ETDRS letters for brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept, respectively, in HAWK and 6.1 and 6.7 ETDRS letters for brolucizumab 6 mg and aflibercept, respectively, in HARRIER.

Central Subfield Thickness

At week 96, greater CST reductions were observed with brolucizumab 3 mg and 6 mg versus aflibercept in HAWK (LS mean [brolucizumab 3 mg]: $-179.7 \mu\text{m}$ vs. $-148.8 \mu\text{m}$; 95% confidence interval for treatment difference, -50.6 to $-11.3 \mu\text{m}$; $P = 0.0021$; LS mean [brolucizumab 6 mg]: $-174.8 \mu\text{m}$ vs. $-148.7 \mu\text{m}$; 95% confidence interval for treatment difference, -46.2 to $-5.9 \mu\text{m}$; $P = 0.0115$; Fig 2A) and with brolucizumab 6 mg versus aflibercept in HARRIER (LS mean: $-197.7 \mu\text{m}$ vs. $-155.1 \mu\text{m}$; 95% confidence interval for treatment difference, -62.0 to $-23.3 \mu\text{m}$; $P < 0.0001$; Fig 2B). The average change in CST from baseline from weeks 84 through 96 was $-179.7 \mu\text{m}$, $-175.0 \mu\text{m}$, and $-156.4 \mu\text{m}$ for brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept, respectively, in HAWK (brolucizumab 3 mg vs. aflibercept, $P = 0.0176$; brolucizumab 6 mg vs. aflibercept, $P = 0.0629$) and $-198.5 \mu\text{m}$ and $-162.1 \mu\text{m}$ for

brolucizumab 6 mg and aflibercept, respectively, in HARRIER ($P = 0.0002$).

Intraretinal Fluid and/or Subretinal Fluid

In both HAWK and HARRIER, significantly fewer eyes treated with brolucizumab showed IRF or SRF at weeks 16 and 48, and this difference was maintained to week 96. The proportion of eyes with IRF or SRF at week 96 in HAWK was 31% for brolucizumab 3 mg ($P = 0.03$), 24% for brolucizumab 6 mg ($P = 0.0001$), and 37% for aflibercept (Fig 3A), whereas in HARRIER, it was 24% for brolucizumab 6 mg ($P < 0.0001$) and 39% for aflibercept (Fig 3B).

Sub-Retinal Pigment Epithelium Fluid

At week 96, the proportions of eyes with sub-RPE fluid in HAWK were 14% ($P = 0.9554$) and 11% ($P = 0.1213$) for brolucizumab 3 mg and 6 mg, respectively, compared with 15% for aflibercept (Fig 4A). In HARRIER, the proportion of eyes with sub-RPE fluid was 17% ($P = 0.0371$) for brolucizumab 6 mg compared with 22% for aflibercept (Fig 4B).

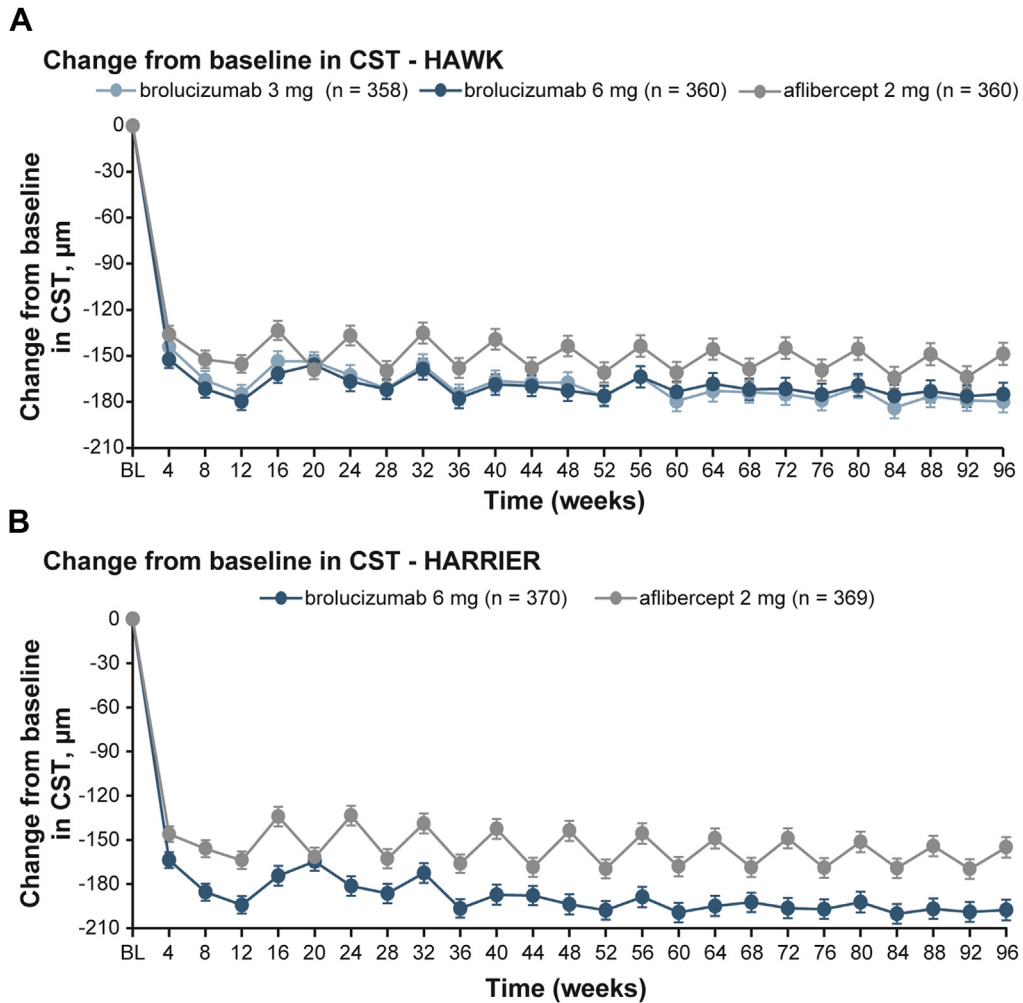


Figure 2. Graphs showing the central subfield thickness (CST) change from baseline to week 96 in the brolucizumab and aflibercept treatment groups in the (A) HAWK and (B) HARRIER studies. BL = baseline.

Every-12-Week Treatment Status

The probability that an eye could be maintained on an q12w interval after loading to the DAA at week 92 was 39.7% and 45.4% for the brolucizumab 3 mg and 6 mg treatment groups in HAWK, respectively, and 38.6% for the brolucizumab 6 mg group in HARRIER. In those eyes receiving treatment q12w at the week 44 DAA in HAWK, an 80.5% (brolucizumab 3 mg) and 81.5% (brolucizumab 6 mg) probability of remaining on an q12w interval until the final DAA at week 92 was found, whereas the probability was 75.4% for the brolucizumab 6 mg group in HARRIER.

Safety

Brolucizumab exhibited an overall well-tolerated safety profile. The incidence of ocular adverse events (AEs) was similar across all treatment groups in both HAWK and HARRIER up to week 96 (Table 1), with the exception of combined intraocular inflammation (IOI) (iritis and uveitis), which was higher in the brolucizumab 6 mg group of HAWK compared with the aflibercept group (4.7% vs. 0.6%). Conjunctival hemorrhage was the most frequently reported ocular AE across all treatment groups in HAWK, occurring in 39 (10.9%), 29 (8.1%), and 32 (8.9%) patients in the

brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg groups, respectively. In HARRIER, the most frequently reported ocular AEs were reduced visual acuity in the brolucizumab 6 mg group (32 patients [8.6%]) and cataract in the aflibercept 2 mg group (43 patients [11.7%]).

The AEs related to IOI reported in both studies were iritis, uveitis, anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorioretinitis, eye inflammation, iridocyclitis, keratic precipitates, retinal vasculitis, vitreous haze, and vitreitis; among these, the most frequently reported were iritis and uveitis. For the brolucizumab 3 mg and 6 mg groups in HAWK, iritis occurred with an incidence of 0.8% (n = 3) and 2.5% (n = 9) and uveitis occurred with an incidence of 1.7% (n = 6) and 2.2% (n = 8), respectively; for the aflibercept 2 mg group, the incidence was 0.3% (n = 1) for both iritis and uveitis. The corresponding incidences of iritis and uveitis in HARRIER were less than 1% for both brolucizumab 6 mg group and aflibercept 2 mg group. For those patients who experienced an IOI event in the study eye in the pooled HAWK and HARRIER studies (n = 17 patients in the brolucizumab 3 mg group, n = 32 patients in the brolucizumab 6 mg group, and n = 7 patients in aflibercept 2 mg group), up to one half of the total IOI events reported (10 of 26 in the brolucizumab 3 mg group, 27 of 44 in the brolucizumab 6 mg group, and 5 of 11 in

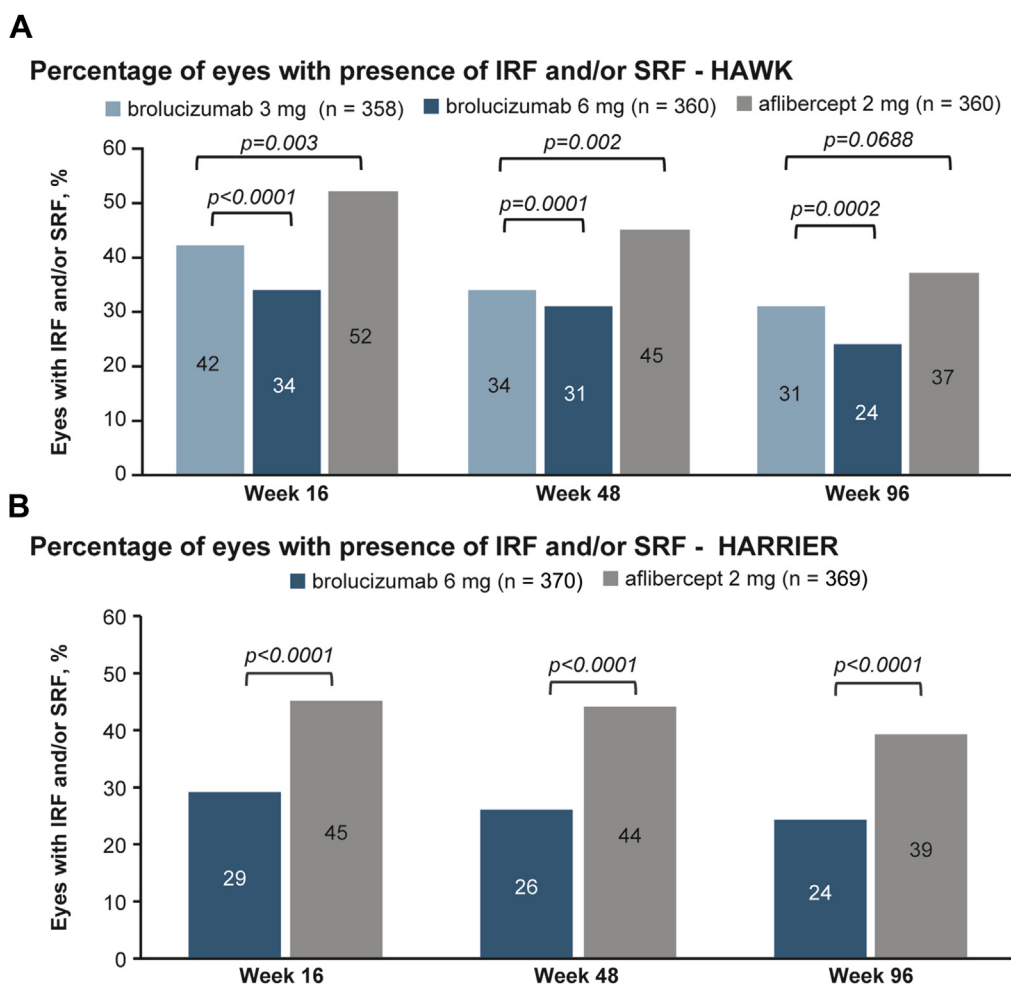


Figure 3. Bar graphs showing eyes with presence of intraretinal fluid and/or subretinal fluid (IRF/SRF) at weeks 16, 48, and 96 in the (A) HAWK and (B) HARRIER studies, full analysis set, last observation carried forward, with a prespecified secondary end point in both HAWK and HARRIER. Confirmatory superiority analysis was performed at week 16 and week 48 in HAWK only. One-sided *P* values for HAWK and HARRIER are shown. For confirmatory superiority testing in HAWK, 1-sided *P* values of less than the adjusted significance level (to account for multiplicity) of *P* < 0.01 (for IRF or SRF) are regarded as statistically significant. Two-sided *P* values for both HAWK and HARRIER at week 96 are shown; *P* values are descriptive.

the aflibercept 2 mg group) occurred in the first 12 weeks after commencing treatment. Of those patients who experienced an IOI, most continued treatment with study drug and completed the study, and the incidence of vision loss of more than 5 letters was 0.95% (*n* = 7, brolucizumab). Four of these 7 brolucizumab patients with IOI also demonstrated retinal artery occlusion (RAO), to be discussed in more detail below.

Up to week 96, a total of 24 patients in HAWK (*n* = 7 [2.0%] for brolucizumab 3 mg, *n* = 12 [3.3%] for brolucizumab 6 mg, and *n* = 5 [1.4%] for aflibercept 2 mg) and 19 patients in HARRIER (*n* = 13 [3.5%] for brolucizumab 6 mg and *n* = 6 [1.6%] for aflibercept 2 mg) experienced at least 1 ocular serious adverse event (SAE) in the study eye in HAWK and HARRIER, respectively (Table 2). In HAWK, the most frequently reported ocular SAE in the brolucizumab 3 mg and 6 mg groups was endophthalmitis, with 3 patients (0.8%) in each group. In HARRIER, 1 case of endophthalmitis was reported as an SAE in the brolucizumab 6 mg group and 1 was reported in the aflibercept group. For the 7 total endophthalmitis events reported as an SAE in HAWK and HARRIER for brolucizumab, 2 patients showed positive culture results, 1 patient showed negative culture results, culture

analysis was not performed in 3 patients, and culture analysis was carried out but the results were not interpretable in 1 patient. One patient treated with aflibercept demonstrated endophthalmitis that was found to show positive culture results. All but 1 of the brolucizumab endophthalmitis patients showed onset within 5 days from the last injection. In HAWK, the most frequently reported ocular SAE in the aflibercept 2 mg group was reduced visual acuity, reported by 2 patients (0.6%). In HARRIER, the most frequently reported ocular SAE in the brolucizumab 6 mg group was uveitis (*n* = 3 [0.8%]). None of the ocular SAEs in the study eye in the aflibercept 2 mg group were reported in more than 1 patient. Ocular AEs related to ocular arterial thromboembolic events (ATEs) in the study eye occurred in 4 patients (1.1%) in the brolucizumab 3 mg group (3 of which were reported as serious), 5 patients (1.4%) in the brolucizumab 6 mg group (1 of which was reported as serious), and 1 patient (0.3%) in the aflibercept 2 mg group of HAWK. In HARRIER, ocular AEs related to ocular ATEs in the study eye occurred in 6 patients (1.6%) in the brolucizumab 6 mg group (2 of which were reported as serious) and 2 patients (0.5%) in the aflibercept 2 mg group (1 of which was reported as serious).

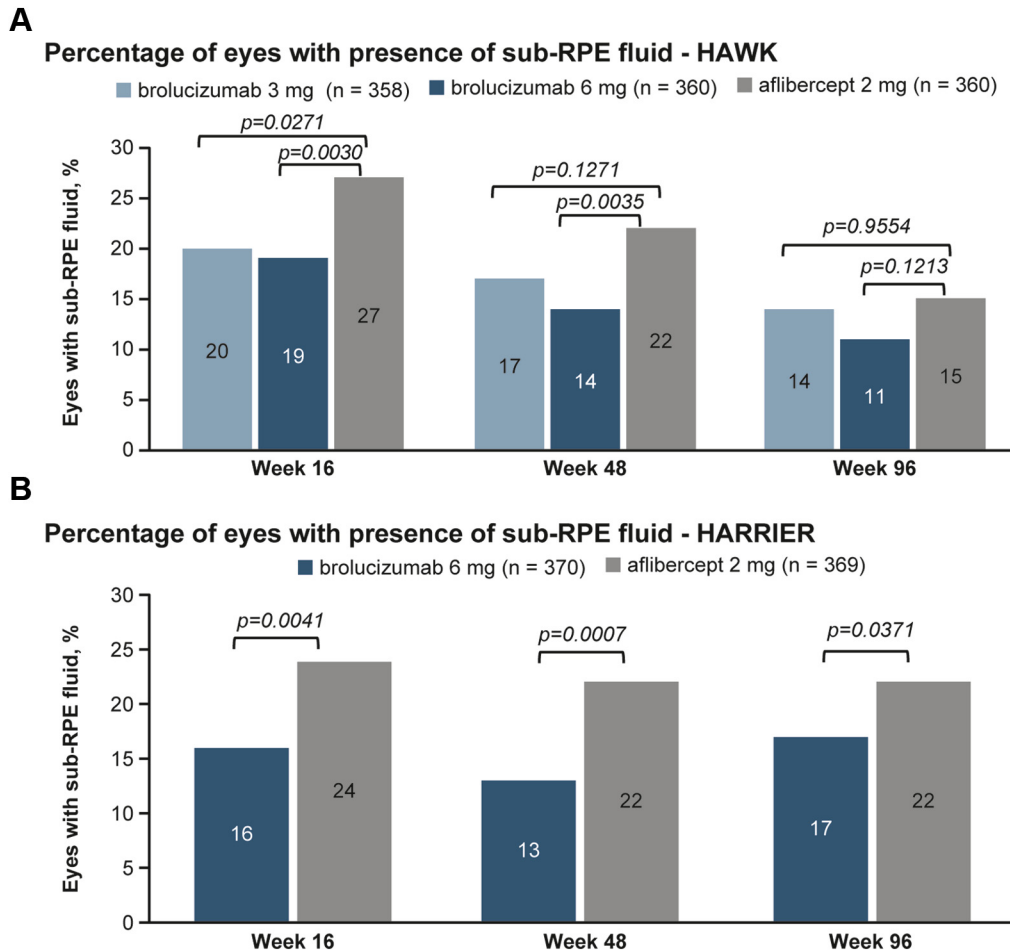


Figure 4. Bar graphs showing eyes with sub-retinal pigment epithelium (RPE) fluid at weeks 16, 48, and 96 for the (A) HAWK and (B) HARRIER studies, full analysis set, last observation carried forward. The prespecified secondary end point in both HAWK and HARRIER are shown, along with 2-sided *P* values for both HAWK and HARRIER. *P* values are descriptive.

More specifically in relation to ATEs, across both studies, 4 brolucizumab 3 mg patients and 6 brolucizumab 6 mg patients experienced a RAO event that was reported as a SAE in 3 patients in the brolucizumab 3 mg group and in 0 patients in the brolucizumab 6 mg group. All brolucizumab 6 mg patients and 1 of the brolucizumab 3 mg patients showed concomitant IOI either before or after the RAO event. All patients who experienced RAO demonstrated cardiovascular comorbidities such as hypertension or cardiac arrhythmias. Of patients with RAO and concomitant IOI, 6 patients lost letters (2, 15, 21, 55, 55, and 62 letters) and 1 patient gained 18 letters by the end of the study. Of the patients with RAO alone, 1 patient lost 57 letters and the 2 other patients gained 16 and 23 letters by the end of the study.

The incidence of nonocular AEs was similar across all treatment groups at week 96. Up to week 96, in HAWK, the most frequently reported nonocular SAE in every treatment group was pneumonia, reported by 7 patients (2.0%) in the brolucizumab 3 mg group, 10 patients (2.8%) in the brolucizumab 6 mg group, and 9 patients (2.5%) in the aflibercept 2 mg group. In HARRIER, the most frequently reported nonocular SAEs in the brolucizumab 6 mg group were lower limb fracture, reported in 3 patients (0.8%), and syncope, reported in 3 patients (0.8%). The most frequently reported nonocular SAE in the aflibercept 2 mg group was pneumonia (8 patients [2.2%]).

The proportion of eyes that lost 15 letters or more by week 96 in HAWK and HARRIER were comparable among the brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept groups (HAWK: 8.6% [brolucizumab 3 mg], 8.1% [brolucizumab 6 mg], and 7.4% [aflibercept 2 mg]; *P* = 0.5769 and *P* = 0.7210 for brolucizumab 3 mg vs. aflibercept and brolucizumab 6 mg vs. aflibercept, respectively; HARRIER: 7.1% [brolucizumab 6 mg] and 7.5% [aflibercept 2 mg]; *P* = 0.8377; Fig 5).

Discussion

In HAWK and HARRIER, brolucizumab was noninferior to aflibercept in BCVA gain (change from baseline) at week 48 (primary end point).¹⁵ These BCVA gains, comparable across treatment arms and studies, were maintained until week 96, with both the brolucizumab 6 mg group and the aflibercept group gaining between 5.3 and 6.6 ETDRS letters from baseline. These visual acuity gains may have been influenced by a ceiling effect resulting from a high mean baseline BCVA of 60 ETDRS letters (60.6 letters [HAWK] and 61.2 letters [HARRIER], resulting from the upper limit of 78 letters for the BCVA inclusion criterion). In earlier

Table 1. Ocular Adverse Events Reported by the Investigator up to Week 96 for the Study Eye (2% or More in Any Treatment Group)

Preferred Term	HAWK, No. (%)			HARRIER, No. (%)	
	Brolucizumab 3 mg (n = 358)	Brolucizumab 6 mg (n = 360)	Aflibercept 2 mg (n = 360)	Brolucizumab 6 mg (n = 370)	Aflibercept 2 mg (n = 369)
No. of patients with at least 1 event	218 (60.9)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)
Conjunctival hemorrhage	39 (10.9)	29 (8.1)	32 (8.9)	17 (4.6)	19 (5.1)
Visual acuity reduced	34 (9.5)	22 (6.1)	29 (8.1)	32 (8.6)	26 (7.0)
Vitreous floaters	26 (7.3)	22 (6.1)	16 (4.4)	15 (4.1)	5 (1.4)
Retinal hemorrhage	14 (3.9)	21 (5.8)	20 (5.6)	12 (3.2)	4 (1.1)
Cataract	18 (5.0)	20 (5.6)	13 (3.6)	11 (3.0)	43 (11.7)
Vitreous detachment	24 (6.7)	19 (5.3)	19 (5.3)	10 (2.7)	8 (2.2)
Dry eye	20 (5.6)	19 (5.3)	26 (7.2)	10 (2.7)	11 (3.0)
Eye pain	28 (7.8)	18 (5.0)	21 (5.8)	13 (3.5)	19 (5.1)
Posterior capsule opacification	16 (4.5)	14 (3.9)	11 (3.1)	7 (1.9)	5 (1.4)
Intraocular pressure increased	16 (4.5)	13 (3.6)	15 (4.2)	14 (3.8)	15 (4.1)
Blepharitis	8 (2.2)	13 (3.6)	12 (3.3)	13 (3.5)	5 (1.4)
Retinal pigment epithelial tear	5 (1.4)	12 (3.3)	4 (1.1)	8 (2.2)	5 (1.4)
Vision blurred	16 (4.5)	11 (3.1)	10 (2.8)	3 (0.8)	3 (0.8)
Visual impairment	15 (4.2)	10 (2.8)	14 (3.9)	1 (0.3)	3 (0.8)
Eye irritation	10 (2.8)	10 (2.8)	11 (3.1)	4 (1.1)	1 (0.3)
Punctate keratitis	11 (3.1)	9 (2.5)	10 (2.8)	1 (0.3)	7 (1.9)
Conjunctivitis	3 (0.8)	9 (2.5)	3 (0.8)	15 (4.1)	8 (2.2)
Iritis	3 (0.8)	9 (2.5)	1 (0.3)	0 (0.0)	1 (0.3)
Uveitis	6 (1.7)	8 (2.2)	1 (0.3)	3 (0.8)	0 (0.0)
Visual field defect	9 (2.5)	7 (1.9)	5 (1.4)	1 (0.3)	0 (0.0)
Corneal abrasion	6 (1.7)	7 (1.9)	10 (2.8)	1 (0.3)	1 (0.3)
Macular fibrosis	10 (2.8)	5 (1.4)	4 (1.1)	3 (0.8)	1 (0.3)
Dry age-related macular degeneration	7 (2.0)	5 (1.4)	3 (0.8)	7 (1.9)	4 (1.1)
Foreign body sensation in eyes	8 (2.2)	4 (1.1)	9 (2.5)	1 (0.3)	4 (1.1)
Lacrimation increased	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)	3 (0.8)
Lenticular opacities	7 (2.0)	1 (0.3)	4 (1.1)	13 (3.5)	12 (3.3)

anti-VEGF studies, nAMD patients showed a mean baseline BCVA of approximately 53 letters.^{7,16} Of note, at week 96, just less than 50% of patients across all HAWK and HARRIER treatment groups showed a mean BCVA of 73

letters or more (46.4%–48.6% in HAWK and 47.6%–49.6% in HARRIER).

The superior anatomic outcomes observed at weeks 16 and 48 with brolucizumab 6 mg versus aflibercept were

Table 2. Serious Ocular Adverse Events Reported by the Investigator up to Week 96 for the Study Eye

Preferred Term	HAWK, No. (%)			HARRIER, No. (%)	
	Brolucizumab 3 mg (n = 358)	Brolucizumab 6 mg (n = 360)	Aflibercept 2 mg (n = 360)	Brolucizumab 6 mg (n = 370)	Aflibercept 2 mg (n = 369)
No. of patients with at least 1 event	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)
Endophthalmitis	3 (0.8)	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)
Retinal detachment	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Visual acuity reduced	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Retinal artery thrombosis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Retinal artery occlusion	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Uveitis	1 (0.3)	2 (0.6)	0 (0.0)	3 (0.8)	0 (0.0)
RPE tear	—	—	—	2 (0.5)	0 (0.0)
Macular hole	0 (0.0)	1 (0.3)	1 (0.3)	—	—
Cataract	0 (0.0)	1 (0.3)	0 (0.0)	—	—
Retinal artery embolism	—	—	—	1 (0.3)	0 (0.0)
Retinal depigmentation	0 (0.0)	1 (0.3)	0 (0.0)	—	—
Proliferative retinopathy	0 (0.0)	1 (0.3)	0 (0.0)	—	—
Vitreitis	0 (0.0)	1 (0.3)	0 (0.0)	—	—
Anterior chamber inflammation	—	—	—	1 (0.3)	0 (0.0)
Dry age-related macular degeneration	—	—	—	0 (0.0)	1 (0.3)
Cataract traumatic	—	—	—	1 (0.3)	0 (0.0)

— = event not reported in the trial.

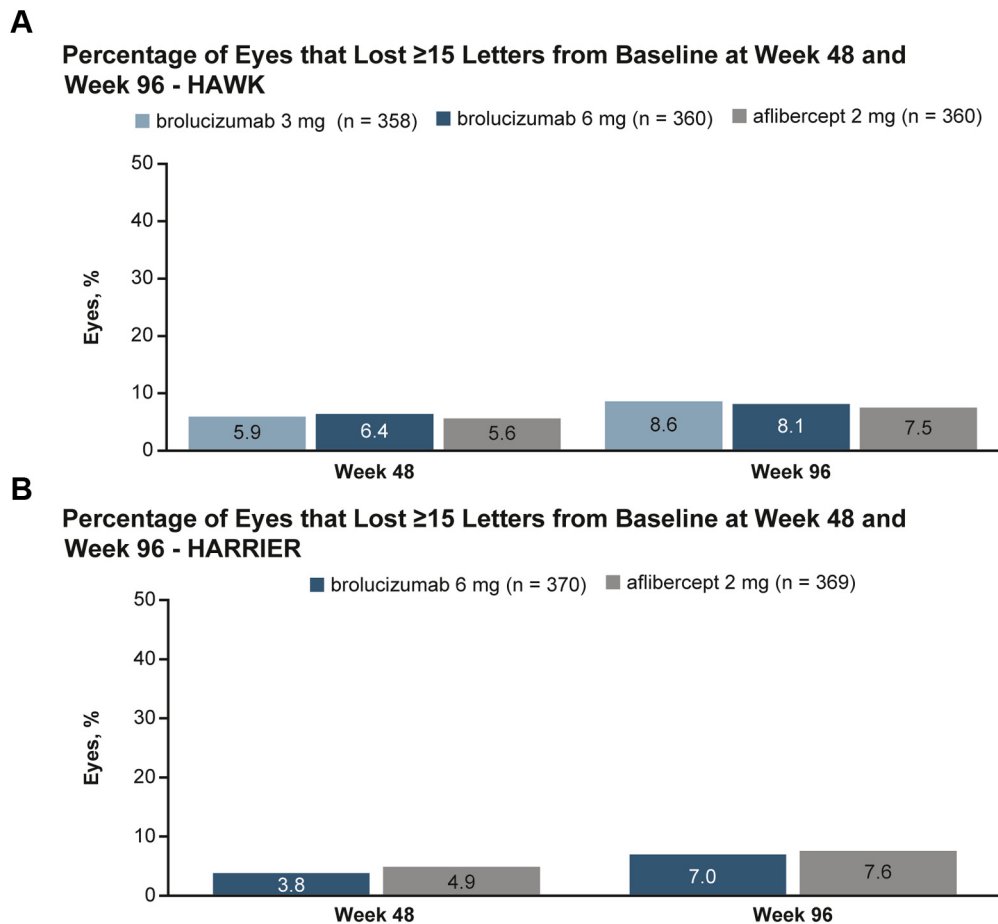


Figure 5. Bar graphs showing the proportion of eyes that lost 15 letters or more at weeks 48 and 96 for the (A) HAWK and (B) HARRIER studies.

maintained until week 96. In HAWK and HARRIER, fewer eyes showed fluid (IRF and/or SRF and sub-RPE fluid) at week 96 in the brolucizumab group versus the aflibercept group. The greater reductions in CST observed in HAWK and HARRIER are consistent with those observed in the phase 2 study OSPREY, in which brolucizumab demonstrated a numerical advantage in CST reduction versus aflibercept in a matched q8w regimen (weeks 8 to 40).¹³ Taken together with the CST outcomes, the fluid resolution data from HAWK and HARRIER suggest greater inhibition of vascular leakage with brolucizumab, a finding that may be attributable to the unique molecular characteristics of the drug, that is, smaller molecular weight allowing for higher molar dosing.¹³

Findings from OSPREY, HAWK, and HARRIER demonstrate that brolucizumab is more effective at reducing retinal thickness and resolving retinal fluid than aflibercept in nAMD.^{13,15} Although no studies have shown a direct relationship between OCT-derived CST reduction and vision gain,¹⁷⁻¹⁹ this is likely because of the multifactorial nature of nAMD. Furthermore, although CST is a good biomarker of permeability, it may not be reflective solely of underlying physiologic mechanisms.¹⁹ Nonetheless, it is widely accepted in clinical practice that reduction of retinal thickness and the resolution of retinal fluid are key parameters in effective

nAMD management, as reflected in current clinical practice guidelines.^{12,20,21} Furthermore, clinicians use CST and fluid status, as measured by OCT, as the best indicators of disease activity and for making treatment decisions.^{12,20,21}

In the interpretation of the visual and anatomic results from HAWK and HARRIER, it is important to remember the different treatment regimens used in the brolucizumab and aflibercept groups. After 3 loading doses (weeks 0, 4, and 8), brolucizumab-treated eyes were treated q12w, with the possibility of being adjusted to q8w dosing during the first q12w treatment interval and at each scheduled q12w treatment visit. Brolucizumab-treated eyes that were adjusted to an q8w treatment interval at any DAA visit did not have the opportunity to be extended back to q12w treatment interval for the remainder of the study. Aflibercept was dosed in a fixed q8w regimen after loading, as per label at the time of study initiation. More than 75% of brolucizumab 6 mg-treated eyes that completed week 48 on an q12w dosing interval successfully remained with an q12w dosing interval until week 96, that is, they showed no disease activity identified at week 92, the last DAA, and hence qualified for an eighth consecutive q12w treatment interval. In summary, brolucizumab, with an q12w or q8w regimen and a 40% to 45% probability to be maintained on an q12w dosing interval until the end of the second year, achieved

comparable visual acuity outcomes and superior anatomic outcomes versus aflibercept. A planned future study comparing brolucizumab and aflibercept in an identical treat-to-control regimen will provide further insight into how the observed durability of brolucizumab will impact nAMD management in real-world clinical practice ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier, NCT04005352).

Brolucizumab exhibited an overall well-tolerated safety profile. Among ocular AEs reported more frequently for brolucizumab, the incidences of iritis and uveitis were numerically higher in HAWK (brolucizumab 3 mg and 6 mg) as compared with HARRIER (brolucizumab 6 mg with an incidence <1%; [Table 1](#)). Compared with week 48, the incidence of these AEs from week 48 through week 96 was low, with additional cases in HAWK only (2 cases of iritis in the brolucizumab 3 mg group, 1 case in the brolucizumab 6 mg group, and 1 case in the aflibercept group and 1 case of uveitis in the brolucizumab 6 mg group). For ocular SAEs reported more frequently in the brolucizumab groups, the incidence of endophthalmitis was numerically higher in the brolucizumab groups versus aflibercept in HAWK and equal to aflibercept in HARRIER. No clear explanation exists for these differences between treatment groups and studies. All but 1 of the brolucizumab endophthalmitis patients experienced onset within 5 days from the last injection. The time to onset since the last active injection and the investigator assessments suggest that it is likely that these endophthalmitis cases were related to the injection procedure. In both studies, a difference was found between treatment groups in the incidence of ocular ATEs, with brolucizumab being numerically higher. The overall incidence was low, and all such patients had cardiovascular comorbidities. Rates of severe vision loss were comparable across all treatment arms. Although numerical differences were found in some AEs and SAEs,

primarily driven by HAWK, brolucizumab exhibited an overall well-tolerated safety profile.

Cases of IOI, vasculitis, and retinal occlusive vasculitis occurring after marketing in relation to the use of brolucizumab have been reported, as noted in reports issued by the American Society of Retina Specialists to its members.²² These AE reports are being investigated by Novartis, who have established an external safety review committee to complete an independent review. As the assessment is ongoing at this time, updated information is being provided to the medical community by Novartis regularly.²³

It is important to acknowledge the limitations of the HAWK and HARRIER study designs when interpreting the study data. Unlike real-world clinical practice, eyes in the brolucizumab treatment group that were switched from q12w to q8w therapy based on a DAA were not permitted to move back to q12w treatment. As a consequence, the probability for patients to remain on an q12w regimen at week 96 may be underestimated.

In conclusion, 96-week results from the phase 3 HAWK and HARRIER trials show that brolucizumab provides vision gains comparable with those of aflibercept, with greater fluid resolution and a high probability of remaining on an q12w regimen from weeks 48 through 96. These 2-year findings from HAWK and HARRIER demonstrate that brolucizumab may allow for better disease control and reduced treatment burden in nAMD, with an overall well-tolerated safety profile.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This multicenter trial was conducted in 408 sites in North, Central, and South America; Europe; Asia; Australia; and Japan. All patients provided written informed consent. Protocols were approved by an Independent Ethics Committee/Institutional Review Board. Trials were conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonization E6 Good Clinical Practice Consolidated Guideline, and other regulations as applicable and were compliant with the

Health Insurance Portability and Accountability Act of 1996. All patients provided written informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Weissgerber

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Obtained funding: N/A

Overall responsibility: Dugel, Singh, Koh, Ogura, Weissgerber, Gedif, Jaffe, Tadayoni, Schmidt-Erfurth, Holz

Abbreviations and Acronyms:

AE = adverse event; **ATE** = arterial thromboembolic event; **BCVA** = best-corrected visual acuity; **CST** = central subfield thickness; **DAA** = disease activity assessment; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IOI** = intraocular inflammation; **IRF** = intraretinal fluid; **LS** = least squares; **nAMD** = neovascular age-related macular degeneration; **RAO** = retinal artery occlusion; **RPE** = retinal pigment epithelium; **SAE** = serious adverse event; **SRF** = subretinal fluid; **VEGF** = vascular endothelial growth factor.

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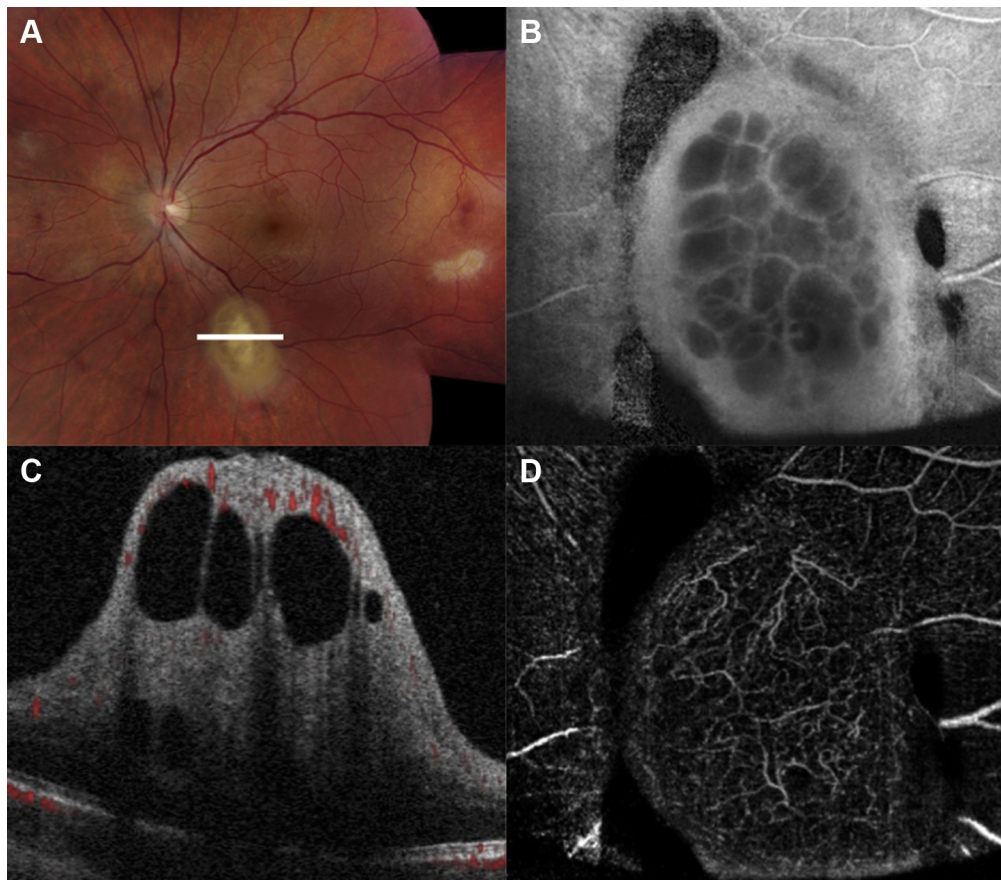
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Pictures & Perspectives



Multimodal Imaging Findings in a Retinal Astrocytic Hamartoma

A 23-year-old man with a history of tuberous sclerosis presented with multiple white globular elevated lesions bilaterally (Fig A). The most prominent of these astrocytic hamartomas in his left eye was raised, cystic, and calcific (Fig A, white line). En face OCT infrared scan (Fig B) highlights the clear cystic spaces. Angiographic flow (Fig C) and en face OCT angiography (Fig D) demonstrates a plexus of capillary vessels in the apex of the hamartoma. (Magnified version of Fig A–D is available online at www.aaojournal.org).

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In the article entitled, “Randomized controlled trial of a dichoptic digital therapeutic for amblyopia” (*Ophthalmology*. 2022;129:77-85) the correspondence address should have appeared as follows:

Correspondence: Scott Xiao, 955 Massachusetts Avenue, #335 Cambridge, MA 02139. E-mail: scott@luminopia.com.



The authors of “HAWK and HARRIER Ninety-Six-Week Outcomes from the Phase 3 Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration” (*Ophthalmology*. 2021;1:89-99) would like to make the following corrections to their article:

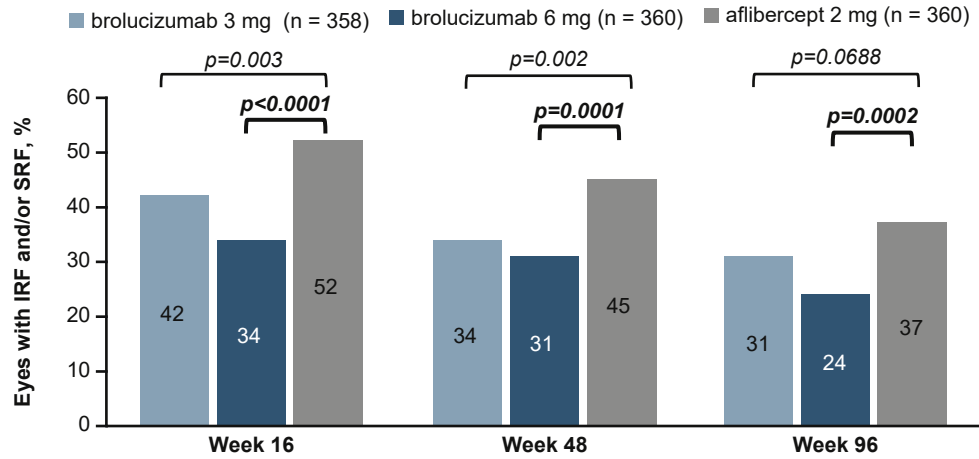
In the Results section, the second sentence under the subheading Intraretinal Fluid and/or Subretinal Fluid should read (changes in bold): The proportion of eyes with IRF or SRF at week 96 in HAWK was 31% for brolucizumab 3 mg ($P = \mathbf{0.0688}$), 24% for brolucizumab 6 mg ($P = \mathbf{0.0002}$), and 37% for aflibercept (Fig 3A), whereas in HARRIER, it was 24% for brolucizumab 6 mg ($P < 0.0001$) and 39% for aflibercept (Fig 3B).

[Supplemental Table 1](#) has been updated to correct an error in the alignment in the sixth row. There is no change to the data.

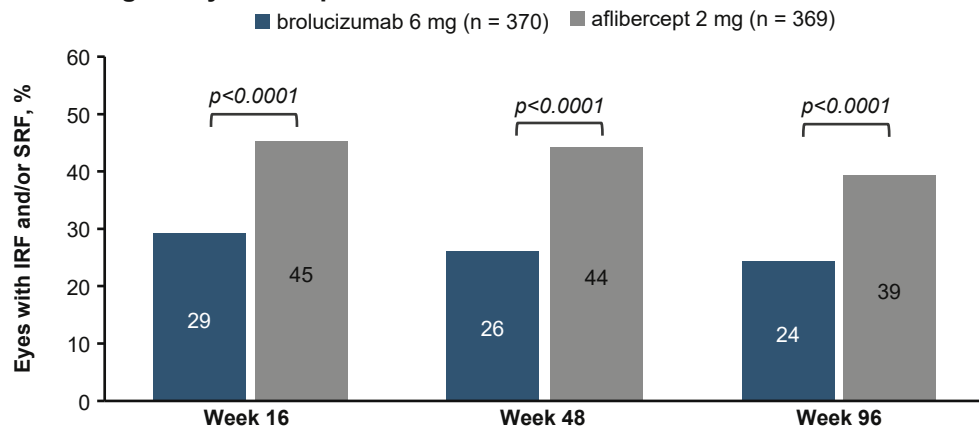
These changes do not affect the overall results of the article.



A Percentage of eyes with presence of IRF and/or SRF - HAWK

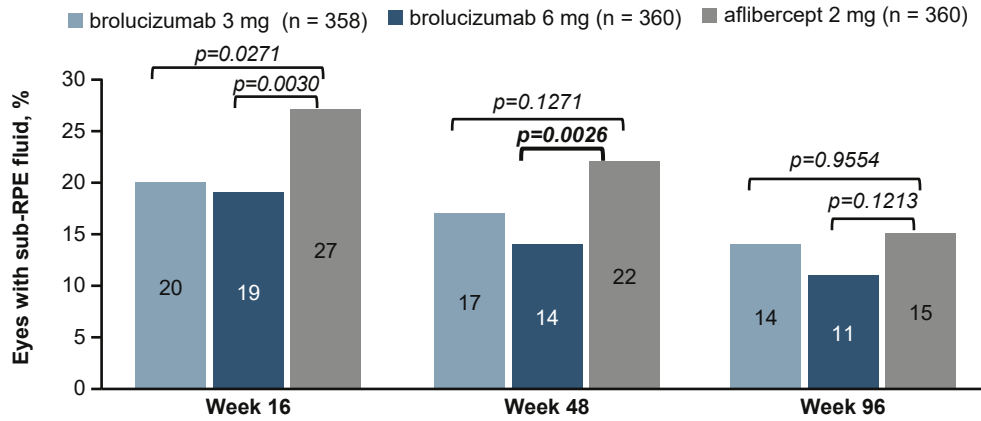


B Percentage of eyes with presence of IRF and/or SRF - HARRIER

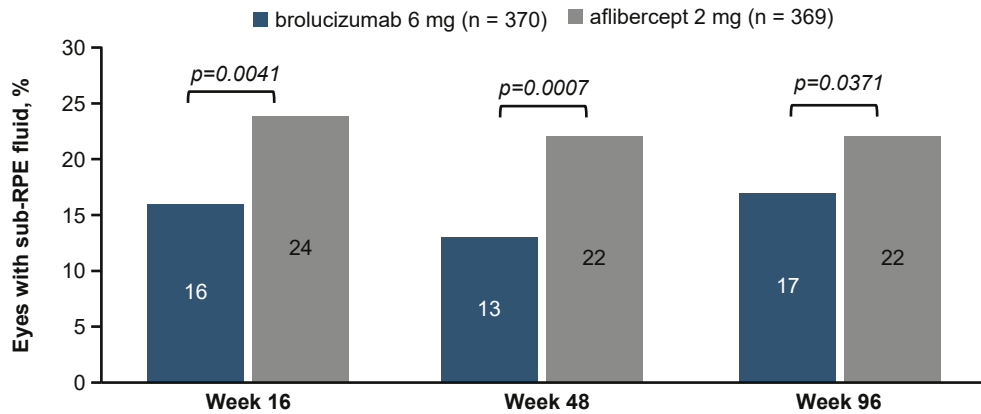


In Figure 3, the location of the lower P values and brackets in part A of the Figure have been moved for accuracy.

A Percentage of eyes with presence of sub-RPE fluid - HAWK

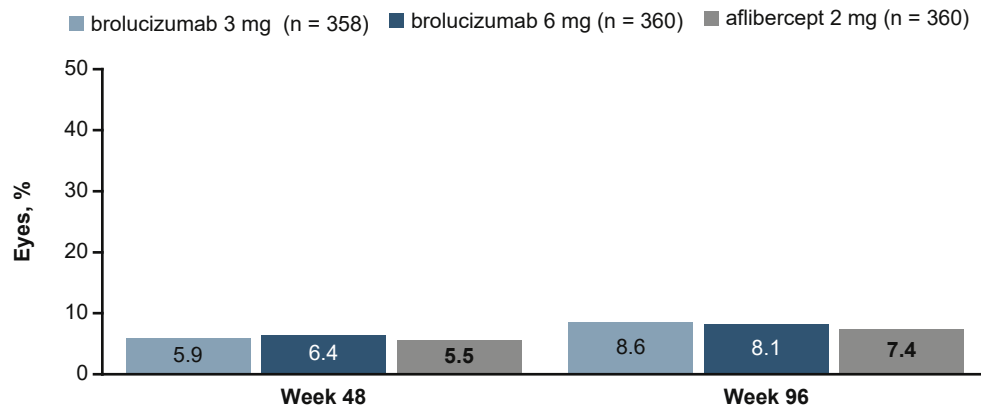


B Percentage of eyes with presence of sub-RPE fluid - HARRIER

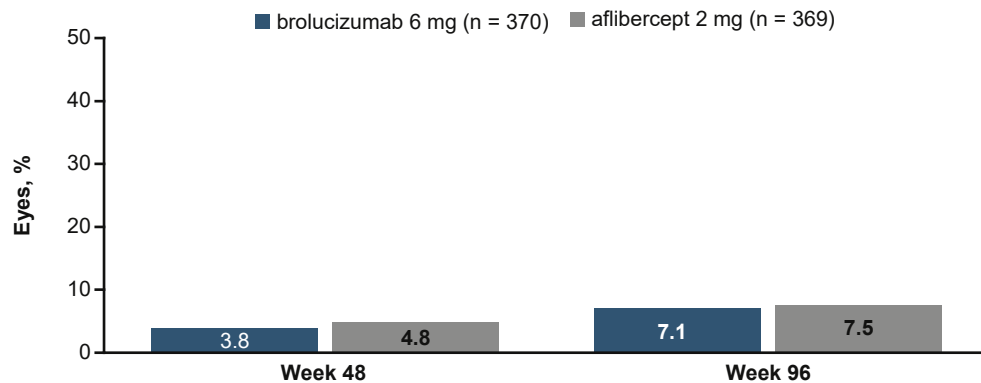


In Figure 4, the P value for brolucizumab 6 mg vs. aflibercept 2 mg at Week 48 for HAWK (part A) has been changed from $P = 0.0035$ to $P = 0.0026$.

A Percentage of Eyes that Lost ≥ 15 Letters from Baseline at Week 48 and Week 96 - HAWK



B Percentage of Eyes that Lost ≥ 15 Letters from Baseline at Week 48 and Week 96 - HARRIER



In Figure 5 in the HAWK graph (A), for the percentage of eyes that lost 15 or more letters, the 48-week value for aflibercept has been changed from 5.6 to 5.5, and the 96-week value for aflibercept has been changed from 7.5 to 7.4. In the HARRIER graph (B), the 48-week value for aflibercept has been changed from 4.9 to 4.8, the 96-week value for brolucizumab has been changed from 7.0 to 7.1 and the 96-week value for aflibercept has been changed from 7.6 to 7.5.