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HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration

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Purpose: Two similarly designed phase 3 trials (HAWK and HARRIER) compared brolucizumab, a single-chain antibody fragment that inhibits vascular endothelial growth factor-A, with aflibercept to treat neovascular age-related macular degeneration (nAMD).

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

Participants: Patients (N = 1817) with untreated, active choroidal neovascularization due to age-related macular degeneration in the study eye.

Intervention: Patients were randomized to intravitreal brolucizumab 3 mg (HAWK only) or 6 mg or aflibercept 2 mg. After loading with 3 monthly injections, brolucizumab-treated eyes received an injection every 12 weeks (q12w) and were interval adjusted to every 8 weeks (q8w) if disease activity was present; aflibercept-treated eyes received q8w dosing.

Main Outcome Measures: The primary hypothesis was noninferiority in mean best-corrected visual acuity (BCVA) change from baseline to Week 48 (margin: 4 letters). Other key end points included the percentage of patients who maintained q12w dosing through Week 48 and anatomic outcomes.

Results: At Week 48, each brolucizumab arm demonstrated noninferiority to aflibercept in BCVA change from baseline (least squares [LS] mean, +6.6 [6 mg] and +6.1 [3 mg] letters with brolucizumab vs. +6.8 letters with aflibercept [HAWK]; +6.9 [brolucizumab 6 mg] vs. +7.6 [aflibercept] letters [HARRIER]; $P < 0.001$ for each comparison). Greater than 50% of brolucizumab 6 mg–treated eyes were maintained on q12w dosing through Week 48 (56% [HAWK] and 51% [HARRIER]). At Week 16, after identical treatment exposure, fewer brolucizumab 6 mg–treated eyes had disease activity versus aflibercept in HAWK (24.0% vs. 34.5%; $P = 0.001$) and HARRIER (22.7% vs. 32.2%; $P = 0.002$). Greater central subfield thickness reductions from baseline to Week 48 were observed with brolucizumab 6 mg versus aflibercept in HAWK (LS mean −172.8 μm vs. −143.7 μm; $P = 0.001$) and HARRIER (LS mean −193.8 μm vs. −143.9 μm; $P < 0.001$). Anatomic retinal fluid outcomes favored brolucizumab over aflibercept. Overall, adverse event rates were generally similar with brolucizumab and aflibercept.

Conclusions: Brolucizumab was noninferior to aflibercept in visual function at Week 48, and >50% of brolucizumab 6 mg–treated eyes were maintained on q12w dosing interval through Week 48. Anatomic outcomes favored brolucizumab over aflibercept. Overall safety with brolucizumab was similar to aflibercept (ClinicalTrials.gov; NCT02307682, NCT02434328). *Ophthalmology 2019;■:1–13 © 2019 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/).*

Supplemental material available at www.aaojournal.org.

Age-related macular degeneration (AMD) is a chronic, progressive disease and a leading cause of vision loss.[1–3] Pivotal trials validated intravitreally administered anti–vascular endothelial growth factor A (VEGF-A) therapy for neovascular AMD (nAMD) treatment, which has greatly improved patient outcomes.[4–6] However, the need for frequent clinic and injection visits coupled with the anticipated increased prevalence of patients with AMD portend a scenario that is not sustainable.[1,2,7] Factors leading to treatment nonadherence include travel to appointments, patient dissatisfaction, and the burden of numerous visits, which may contribute to suboptimal vision outcomes.[8–10] Real-world studies across several countries reveal lower treatment frequencies and poorer vision

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outcomes versus phase 3 trials.[11] An ongoing challenge is to maintain nAMD treatment efficacy while reducing clinic visits.[7,12,13]

Single-chain antibody fragments (scFv) are the smallest functional unit of an antibody, allowing delivery of a greater molar dose compared with larger molecules and the potential for more effective tissue penetration,[14–16] attributes designed to increase duration.[17] Brolucizumab (formerly ESBA1008 and RTH258) was developed by grafting complementarity-determining regions of a novel anti−VEGF-A antibody to a human scFv scaffold, thus circumventing the production, solubility, stability, and in vivo activity issues encountered over the last quarter century of scFv development.[16–21] Preclinical data demonstrated a 2.2- and 1.7-fold higher exposure in the retina and retinal pigment epithelium (RPE)/choroid, respectively, with brolucizumab compared with ranibizumab,[16] suggesting the potential for better intraretinal fluid (IRF), subretinal fluid (SRF), and sub-RPE fluid control across retinal layers.

HAWK and HARRIER are 2 similarly designed phase 3 trials comparing brolucizumab with aflibercept to treat nAMD. The design of these studies was informed by exploratory analyses of previous studies with other anti-VEGF agents, as well as the results of the phase 2 brolucizumab OSPREY study. Analyses from the PIER and EXCITE studies have shown that visual and anatomic response during and for the 12 weeks after the loading phase are associated with visual acuity outcomes over the remainder of the first year of treatment.[22–25] In addition, recent analyses from the EXCITE study have shown that patients who lose vision during the initial loading phase will have better visual outcomes with more frequent treatment versus patients who follow an every 12 weeks (q12w) treatment regimen.[26] Analyses from CATT and EXCITE have shown that new IRF/intraretinal cysts, and to a lesser degree central subfield thickness (CST) increase, are associated with later visual acuity decline.[27–29] Finally, the selection of q12w and every 8 weeks (q8w) dosing was based on results of the OSPREY study, in which a head-to-head comparison of the q8w treatment regimen between brolucizumab 6 mg and aflibercept 2 mg showed anatomic advantages with brolucizumab while reaching noninferiority in best-corrected visual acuity (BCVA).[14] In the same study, brolucizumab-treated patients were subsequently challenged with a q12w dosing interval, with an outcome suggesting that approximately 50% of patients were adequately treated.

The primary objective of both HAWK and HARRIER was to demonstrate that brolucizumab (q12w/q8w) is noninferior to fixed-dose aflibercept with respect to the change in BCVA from baseline to Week 48. In these studies, a q12w/q8w regimen allows for treatment interval assignment guided by assessment of individual disease activity using functional and anatomic parameters.

Methods

Trial Description and Oversight

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. The trials were designed by a committee of investigators and the sponsor. All investigators collected data, and the sponsor analyzed data. All authors had full 1-year data access. An independent data monitoring committee was established to monitor the safety of the trial participants, ensure that the trials were conducted with the highest scientific and ethical standards, and make appropriate recommendations based on the safety data reviewed. Specifically, the data monitoring committee was tasked to make recommendations to amend treatment rules, inclusion and exclusion criteria, and adverse event definitions and grading scales based on planned and unplanned safety data reviews. Medical writers (paid by the sponsor) provided editorial assistance, including first draft development with input from all authors. All authors contributed to data interpretation and manuscript writing, reviewed and provided feedback on all drafts, and collectively decided to publish the results; the sponsor reviewed and approved the manuscript. All authors vouch for the completeness and accuracy of the data and analyses and affirm the trial was conducted and reported in agreement with the protocol.

Trial Participants

Eligible patients were aged ≥50 years and had untreated, active choroidal neovascularization lesions secondary to AMD affecting the central subfield (the circular area within 1 mm diameter around the foveal center on imaging); choroidal neovascularization lesions (including classic and occult), as assessed by fluorescein angiography, comprising >50% of total lesion area; IRF and/or SRF affecting the central subfield as assessed on spectral-domain OCT; BCVA between 78 and 23 Early Treatment Diabetic Retinopathy Study letters (inclusive; Snellen equivalents, approximately 20/32 to 20/400); and no fibrosis or geographic atrophy affecting the central subfield. Patients could not have received any approved or investigational nAMD treatment at any time (study eye). Full inclusion/exclusion criteria are provided in Supplemental Materials (available at www.aaojournal.org). Final anatomic eligibility determination was made by a central reading center (Duke Reading Center for HAWK and Vienna Reading Center for HARRIER).

Randomization and Treatment

Eyes were randomized (Interactive Response Technology [IRT]) 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg (HAWK) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg (HARRIER). The unmasked injecting investigator or his/her unmasked delegate contacted the IRT after confirming that the patient met all the inclusion and none of the exclusion criteria. The IRT assigned a randomization number to the patient that was used to link the patient to a treatment arm and specified a unique medication number for the first package of study treatment to be administered to the patient. The randomization number was not communicated to unmasked staff. The randomization numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and masked study center personnel. A member of the Statistical Programming group who was not part of the study team generated

the randomized allocation for the study treatment assignment based on a randomization plan that provided study-specific criteria for randomization, including block size and randomization ratio. Treatment was assigned to patients through the IRT. Each patient number was associated with a treatment arm, according to the randomized allocation generated using the computer software SAS version 9.2 (PROC PLAN; SAS Institute Inc, Cary, NC). Patients were assigned numbers sequentially according to the time of randomization.

After injections at Weeks 0, 4, and 8 (loading phase), brolucizumab was injected q12w unless disease activity was identified, resulting in permanent adjustment to q8w (collectively reported as a q12w/q8w regimen); aflibercept was injected q8w, per label at the time of study initiation[30] (Fig S1, available at www.aaojournal.org). On the basis of the assumption of stable treatment need,[31] subsequent monitoring of the adequacy of the brolucizumab q12w treatment interval was assessed by masked investigators at Week 16 and at scheduled q12w treatment visits (disease activity assessments at Weeks 20, 32, and 44). In HARRIER, additional assessments were performed 8 weeks after every scheduled q12w brolucizumab injection (Weeks 28 and 40) based on health authority feedback. Briefly, in addition to BCVA testing, the masked investigator assessed nAMD disease activity to identify eyes that required more frequent treatment at a q8w interval. To rapidly identify those patients with a higher anti-VEGF treatment need after loading, the protocol guidance at Week 16 provided specific criteria for CST and IRF status assessed by spectral domain OCT (Table S1; available at www.aaojournal.org). Thereafter, guidance was based on BCVA decline due to nAMD activity compared with Week 12. Ultimately, the masked investigator made the final treatment decisions based on clinical judgment. To maintain masking, aflibercept-treated eyes underwent the same disease activity assessments as brolucizumab-treated eyes. Treatment exposure was identical up to Week 16, allowing a matched comparison of brolucizumab and aflibercept up to 8 weeks after loading. In both studies, patients received a complete ophthalmic exam (including BCVA and anatomic assessments [IRF/SRF/sub-RPE fluid and CST]) and were evaluated for adverse events every 4 weeks (Table S2, available at www.aaojournal.org).

End Points, Statistical Analyses, and Sample Size Determination

Primary and key secondary end point analyses of BCVA change and noninferiority margins were established in discussion with the US Food and Drug Administration, European Medicines Agency, and Pharmaceutical and Medical Device Agency. The primary end point was mean BCVA change from baseline to Week 48. Key secondary end points were BCVA change from baseline averaged over the period of Week 36 through Week 48 (to account for differences in timing of treatment), q12w treatment status at Week 48 (brolucizumab only), and q12w treatment status at Week 48 among eyes with no q8w need during the first q12w cycle (to evaluate the predictive value of the first q12w cycle; brolucizumab only). Additional secondary efficacy end points included, for each post-baseline visit, changes from baseline in BCVA (including BCVA gain/loss of $\geq$15 letters) and CST, status of SRF/IRF and sub-RPE fluid, and presence of disease activity at Week 16. Safety end points included incidence and characteristics of treatment-emergent adverse events and treatment-emergent changes in ocular and nonocular parameters.

Primary and key secondary end points were analyzed on the basis of the full analysis set with last observation carried forward (LOCF) imputation of missing values. Supportive analyses of the primary end point were conducted using the per-protocol set with LOCF imputation as well as observed data for the full analysis set and per-protocol analysis set. A 2-sided 95% confidence interval (CI) for the treatment difference was derived from an analysis of variance model with treatment, baseline BCVA categories ($\leq$55, 56−70, and $\geq$71 letters), and age categories (<75 and $\geq$75 years) as fixed effects. To demonstrate noninferiority, the lower limit of the 95% CI was required to be greater than −4 letters. Supportive analyses were based on mixed-model repeated measures analysis models using observed data.

If each BCVA-related noninferiority hypothesis (Supplemental Materials, available at www.aaojournal.org), tested hierarchically by dose (6 mg before 3 mg) and end point (primary before secondary), reached statistical significance, additional confirmatory superiority testing of brolucizumab versus aflibercept was prespecified in HAWK (based on HARRIER learnings) with parallel testing in the categories of CST reductions, presence of IRF and/or SRF, and disease activity at Week 16 using a global 1-sided alpha of 0.025, which was split into local 1-sided significance levels of 0.005, 0.01, and 0.01, respectively. Within each end point category, multiplicity was controlled by hierarchical testing according to a prespecified order of doses and time points. The probabilities for maintaining q12w status were derived from time-to-event analyses (first disease activity/q8w need). In case of informative censoring (lack of efficacy or safety), q8w need was imputed.

A sample size of 297 eyes per arm allowed noninferiority determination of brolucizumab versus aflibercept regarding BCVA change from baseline to Week 48 at a 1-sided alpha level of 0.025 with a power of approximately 90%, assuming equal efficacy and an SD of 15 letters. To account for a 10% dropout rate, 330 eyes were planned to be randomized to each arm.

Results

Study Patients

Overall, 1082 patients were randomized in HAWK between December 2014 and May 2016, and 743 patients were randomized in HARRIER between June 2015 and April 2016 (Fig S2, available at www.aaojournal.org). No clinically meaningful differences in demographics and baseline ocular characteristics were observed in either trial (Tables S3 and S4, available at www.aaojournal.org). Mean baseline BCVA was 60.6 (HAWK) and 61.2 (HARRIER) letters, and approximately 25% of study eyes had BCVA $\geq$71 letters at baseline, which is reflective of current clinical practice and in line with BCVA inclusion criteria. In HAWK, 91.4%, 89.8%, and 87.3% of patients treated with brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept, respectively, completed study treatment up to Week 48. In HARRIER, 93.3% and 93.5% of brolucizumab 6 mg− and aflibercept-treated patients, respectively, completed study treatment up to Week 48. In both trials, the primary reasons for discontinuation of study treatments were withdrawal by patient and adverse events. In HAWK, zero patients treated with brolucizumab (both doses) and 3 patients (0.8%) treated with aflibercept discontinued the study treatment before Week 48 because of lack of efficacy. In HARRIER, 1 (0.3%) brolucizumab 6 mg−treated patient and 2 (0.5%) aflibercept-treated patients discontinued the study treatment before Week 48 because of lack of efficacy.

Best-Corrected Visual Acuity

In both trials, each brolucizumab arm demonstrated noninferiority versus aflibercept in least squares (LS) mean BCVA change from baseline to Week 48 (Table 1). In HAWK, brolucizumab 3 mg− and

Table 1. Primary End Point and Secondary End Points (Full Analysis Set, Last Observation Carried Forward)

Outcome	HAWK			HARRIER	
	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)
Primary end point					
Change in BCVA from baseline to Week 48					
Letters, LS mean (SE)	6.1 (0.69)	6.6 (0.71)	6.8 (0.71)	6.9 (0.61)	7.6 (0.61)
LS mean difference (brolucizumab − aflibercept)					
Difference (SE)	−0.6 (0.98)	−0.2 (1.00)	—	−0.7 (0.86)	—
95% CI for treatment difference	−2.5 to 1.3	−2.1 to 1.8	—	−2.4 to 1.0	—
P value for noninferiority (1-sided; margin: 4 letters)	<0.001	<0.001		<0.001	
Key secondary end point					
Average change in BCVA from baseline over the period of Weeks 36-48					
Letters, LS mean (SE)	6.2 (0.67)	6.7 (0.68)	6.7 (0.68)	6.5 (0.58)	7.7 (0.58)
LS mean difference (brolucizumab − aflibercept)					
Difference (SE)	−0.5 (0.95)	0.0 (0.96)	—	−1.2 (0.82)	—
95% CI for treatment difference	−2.4 to 1.3	−1.9 to 1.9	—	−2.8 to 0.5	—
P value for noninferiority (1-sided; margin: 4 letters)	<0.001	<0.001		<0.001	
Secondary end point					
Patients with ≥15 letter gain from baseline to Week 48, %	25.2	33.6	25.4	29.3	29.9

BCVA = best-corrected visual acuity; CI = confidence interval; LS = least squares; SE = standard error.

brolucizumab 6 mg–treated eyes gained +6.1 and +6.6 letters, respectively, versus +6.8 letters among aflibercept-treated eyes (LS mean; 95% CI for treatment difference, −2.5 to 1.3; *P* value for noninferiority <0.001 and 95% CI for treatment difference, −2.1 to 1.8; *P* value for noninferiority <0.001, respectively). In HARRIER, brolucizumab 6 mg–treated eyes gained +6.9 letters versus +7.6 letters among aflibercept-treated eyes (LS mean; 95% CI for treatment difference, −2.4 to 1.0; *P* value for noninferiority <0.001). In general, these outcomes were not affected by baseline BCVA or age (Fig S3, available at www.aaojournal.org). As an alternative to the LOCF approach, an analysis of the observed data (based on the mixed-model repeated-measures analysis) in HAWK revealed an LS mean BCVA change from baseline to Week 48 of +6.4 (3 mg) and +6.6 (6 mg) letters with brolucizumab compared with +7.3 letters with aflibercept (95% CI for treatment difference, −2.8 to 1.0; *P* value for noninferiority <0.001 and 95% CI for treatment difference, −2.7 to 1.3; *P* value for noninferiority <0.001, respectively); in HARRIER, LS mean BCVA change from baseline to Week 48 was +7.2 letters with brolucizumab (6 mg) versus +7.7 letters with aflibercept (95% CI for treatment difference, −2.1 to 1.2; *P* value for noninferiority <0.001; Table S5A, available at www.aaojournal.org). Brolucizumab was also noninferior to aflibercept in LS mean BCVA change from baseline averaged over the period of Week 36 through Week 48 in both trials (HAWK: brolucizumab 3 mg vs. aflibercept 2 mg, +6.2 vs. +6.7 letters; 95% CI for treatment difference, −2.4 to 1.3; *P* value for noninferiority <0.001 and brolucizumab 6 mg vs. aflibercept 2 mg, +6.7 vs. +6.7 letters; 95% CI for treatment difference, −1.9 to 1.9; *P* value for noninferiority <0.001; HARRIER: brolucizumab 6 mg vs. aflibercept 2 mg, +6.5 vs. +7.7 letters; 95% CI for treatment difference, −2.8 to 0.5; *P* value for noninferiority <0.001). Noninferiority of BCVA outcomes was confirmed on the basis of the per-protocol analysis (Table S5A and S5B, available at www.aaojournal.org). In all treatment arms, LS mean BCVA gains were observed during the loading phase and slightly increased further up to Week 48 (Fig 1A and B). The proportion of study eyes that gained ≥15 letters of vision from baseline to Week 48 was 25.2% (brolucizumab 3 mg), 33.6% (brolucizumab 6 mg), and 25.4% (aflibercept 2 mg) in HAWK and 29.3% and 29.9% (brolucizumab 6 mg and aflibercept 2 mg, respectively) in HARRIER.

Every 12-Week Dosing Maintenance Over 48 Weeks

For brolucizumab-treated eyes, the probabilities (Kaplan–Meier estimates) for exclusively maintaining q12w dosing after loading through Week 48 were 49.4% (3 mg; 95% CI for Kaplan–Meier estimate, 43.9% to 54.6%) and 55.6% (6 mg; 95% CI for Kaplan–Meier estimate, 50.2% to 60.8%) in HAWK, and 51.0% (6 mg; 95% CI for Kaplan–Meier estimate, 45.7% to 56.1%) in HARRIER (Fig 1C). Under the condition that a brolucizumab-treated eye did not show disease activity during the first q12w interval, the probabilities for remaining on q12w dosing up to Week 48 increased to 80.9% (3 mg; 95% CI for Kaplan–Meier estimate, 74.5% to 85.7%) and 85.4% (6 mg; 95% CI for Kaplan–Meier estimate, 79.9% to 89.5%) in HAWK and 81.7% (6 mg; 95% CI for Kaplan–Meier estimate, 75.8% to 86.3%) in HARRIER.

Disease Activity Assessment (Week 16, Matched) and Anatomic Outcomes

Each of the 4 BCVA-related noninferiority hypotheses of HAWK reached statistical significance (1-sided $P < 0.025$); therefore, additional confirmatory superiority testing was conducted in HAWK to assess the superiority of brolucizumab regarding CST reduction, presence of IRF and/or SRF, and presence of disease activity at Week 16 (Table S6, available at www.aaojournal.org).

The period up to Week 16 allowed for a masked, dosing frequency–matched (all treatment arms had 3 monthly loading

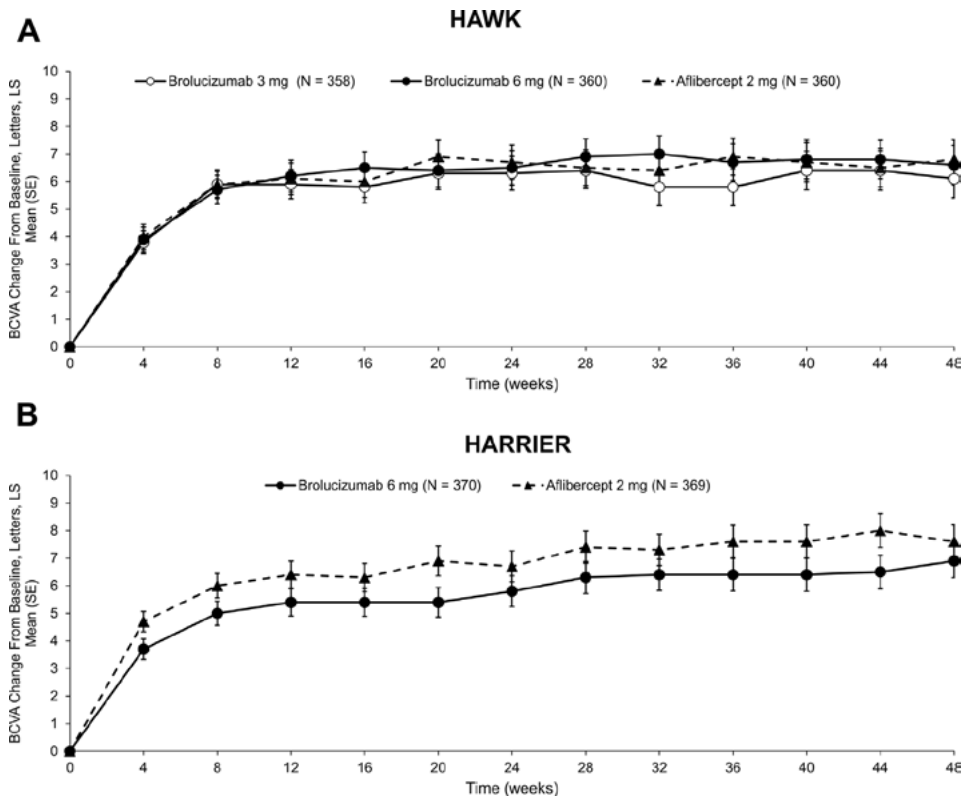


Figure 1. Best-corrected visual acuity (BCVA) over time in (**A**) HAWK and (**B**) HARRIER, and (**C**) Kaplan–Meier analysis of every 12 weeks (q12w) treatment status (time to first every 8 weeks [q8w] need). **A**, **B**, Full analysis set; last observation carried forward (LOCF). **C**, Full analysis set; efficacy/safety approach (for Kaplan–Meier curve). *In the case of informative censoring (lack of efficacy or safety), disease activity/q8w need was imputed (efficacy approach: in case of lack of efficacy; efficacy/safety approach: in case of lack of efficacy and/or safety). †Based on 220 patients. CI = confidence interval; LS = least squares; q8w = every 8 weeks; q12w = every 12 weeks.

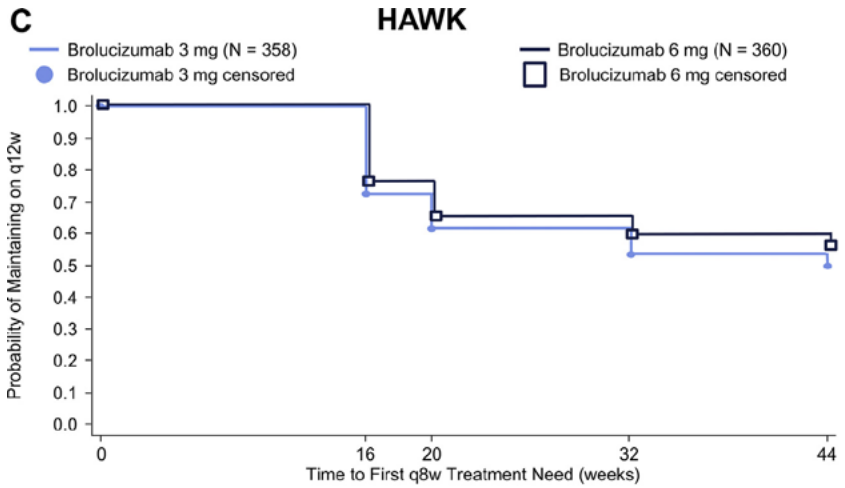
doses followed by 8 weeks before the next possible treatment) assessment. Fewer brolucizumab 6 mg–treated eyes had disease activity versus aflibercept in HAWK (24.0% vs. 34.5%; 95% CI for treatment difference, −17.1% to −3.5%; $P = 0.001$) and HARRIER (22.7% vs. 32.2%; 95% CI for treatment difference, −15.8% to −3.1%; $P = 0.002$; Fig 2A), thus revealing a formal demonstration of superiority versus aflibercept in HAWK regarding duration of effect.

Greater CST reductions from baseline to Week 16 were observed among eyes treated with brolucizumab 6 mg versus aflibercept in HAWK (LS mean; −161.4 vs. −133.6 μm; 95% CI for treatment difference, −45.1 to −10.5; $P < 0.001$) and HARRIER (LS mean; −174.4 vs. −134.2 μm; 95% CI for treatment difference, −58.9 to −21.6; $P < 0.001$); similar results were observed at Week 48 in HAWK (LS mean; −172.8 vs. −143.7 μm; 95% CI for treatment difference, −47.6 to −10.4; $P = 0.001$) and HARRIER (LS mean; −193.8 vs. −143.9 μm; 95% CI for treatment difference, −68.9 to −30.9; $P < 0.001$; Fig 3), with formal significance demonstrated versus aflibercept in HAWK. The CST reduction difference from baseline averaged over the period of Week 36 through Week 48 between brolucizumab 6 mg, and aflibercept was numerically higher for brolucizumab in both studies without formally reaching significance in HAWK (Table S7, available at www.aaojournal.org).

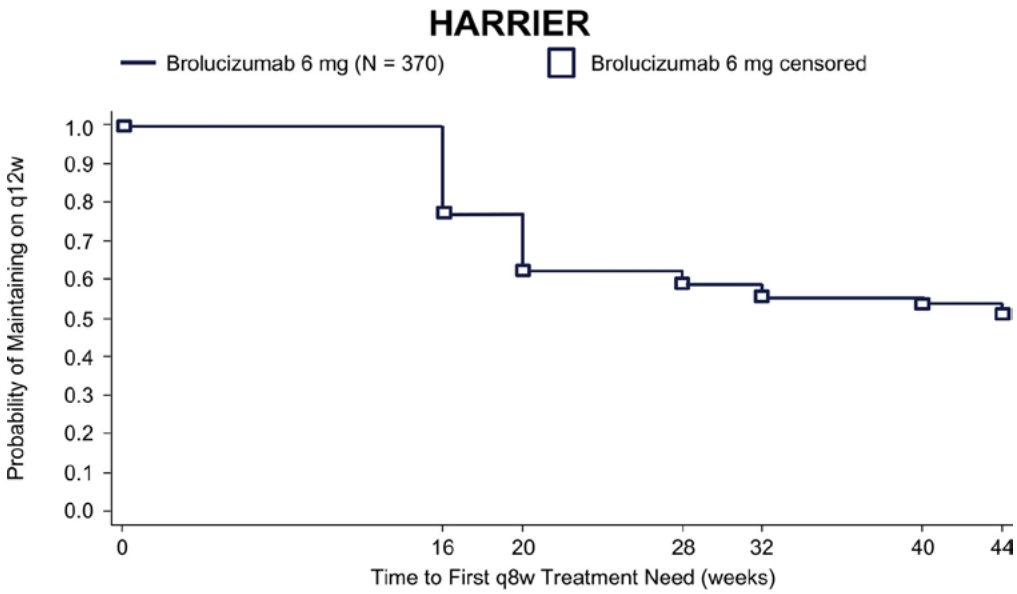
Intraretinal fluid/SRF was present in fewer brolucizumab-treated eyes versus aflibercept-treated eyes at Week 16 in HAWK (3 mg, 41.8% vs. 52.0%; 95% CI for treatment difference, −17.3% to −2.5%; $P = 0.003$ and 6 mg, 33.9% vs. 52.2%; 95% CI for treatment difference, −25.3% to −10.9%; $P < 0.001$) and HARRIER (29.4% vs. 45.1%; 95% CI for treatment difference, −22.9% to −9.0%; $P < 0.001$); similar results were observed at Week 48 in HAWK (3 mg, 34.1% vs. 44.7%; 95% CI for treatment difference, −17.4% to −3.3%; $P = 0.002$ and 6 mg, 31.2% vs. 44.6%; 95% CI for treatment difference, −20.7% to −6.1%; $P < 0.001$) and HARRIER (25.8% vs. 43.9%; 95% CI for treatment difference, −24.9% to −11.8%; $P < 0.001$; Fig 2B), with formal demonstration of statistical superiority versus aflibercept in HAWK. At Week 48, sub-RPE fluid was present in fewer brolucizumab 6 mg–treated eyes than aflibercept-treated eyes in HAWK (13.5% vs. 21.6%; 95% CI for treatment difference, −13.6% to −2.7%; $P = 0.004$) and HARRIER (12.9% vs. 22.0%; 95% CI for treatment difference, −13.8% to −3.9%; $P < 0.001$; Fig 2C). Analyses of IRF and/or SRF, as well as sub-RPE fluid presence between Weeks 36 and 48 also supported better fluid control with brolucizumab 6 mg (Tables S8 and S9, available at www.aaojournal.org).

Safety

Brolucizumab was generally well tolerated; overall ocular and nonocular adverse event rates were similar to those with aflibercept within each trial (Table 2). The most common ocular adverse events were conjunctival hemorrhage (brolucizumab 3 and 6 mg; HAWK) and reduced visual acuity (aflibercept; HAWK, both treatments; HARRIER; Table 3). Adverse events of interest included uveitis and iritis (2.2% for each) with brolucizumab 6



Parameter*	Brolucizumab 3 mg	Brolucizumab 6 mg
Positive q12w treatment status at Week 48 (95% CI for Kaplan-Meier estimate), %		
Patients, N	358	360
Efficacy-only approach	50.0 (44.5 to 55.3)	57.5 (52.0 to 62.6)
Efficacy/safety approach	49.4 (43.9 to 54.6)	55.6 (50.2 to 60.8)
Positive q12w treatment status at Week 48 among those with no q8w need during first q12w cycle (95% CI for Kaplan-Meier estimate), %		
Patients, n	208	222
Efficacy-only approach	80.8 (74.5 to 85.7)	87.1 (81.7 to 91.0)
Efficacy/safety approach	80.9 (74.5 to 85.7)	85.4 (79.9 to 89.5)



Parameter*	Brolucizumab 6 mg
Positive q12w treatment status at Week 48 (95% CI for Kaplan-Meier estimate), %	
Patients, N	370
Efficacy-only approach	52.2 (46.8 to 57.3)
Efficacy/safety approach	51.0 (45.7 to 56.1)
Positive q12w treatment status at Week 48 among those with no q8w need during first q12w cycle (95% CI for Kaplan-Meier estimate), %	
Patients, n	221
Efficacy-only approach	82.5 (76.7 to 87.0)
Efficacy/safety approach	81.7 (75.8 to 86.3)†

Figure 1. Continued

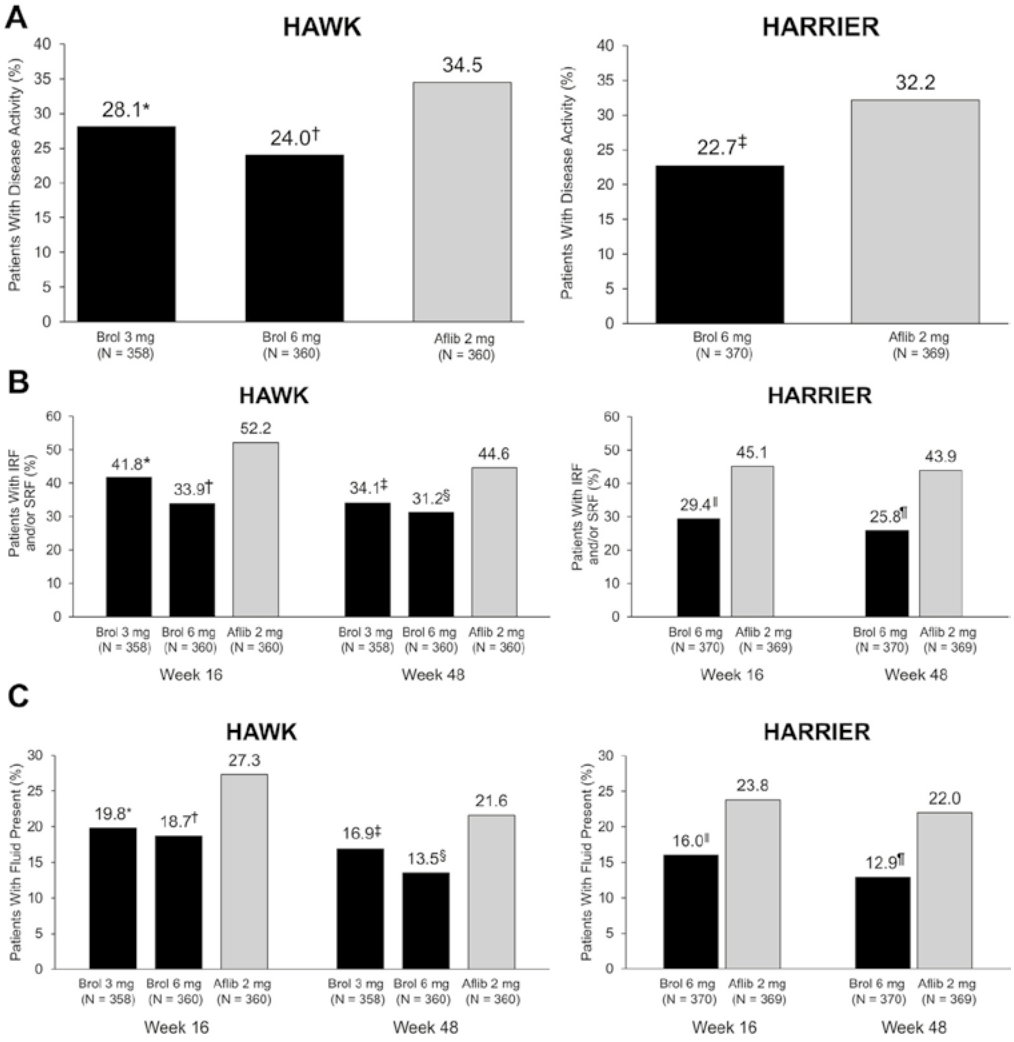
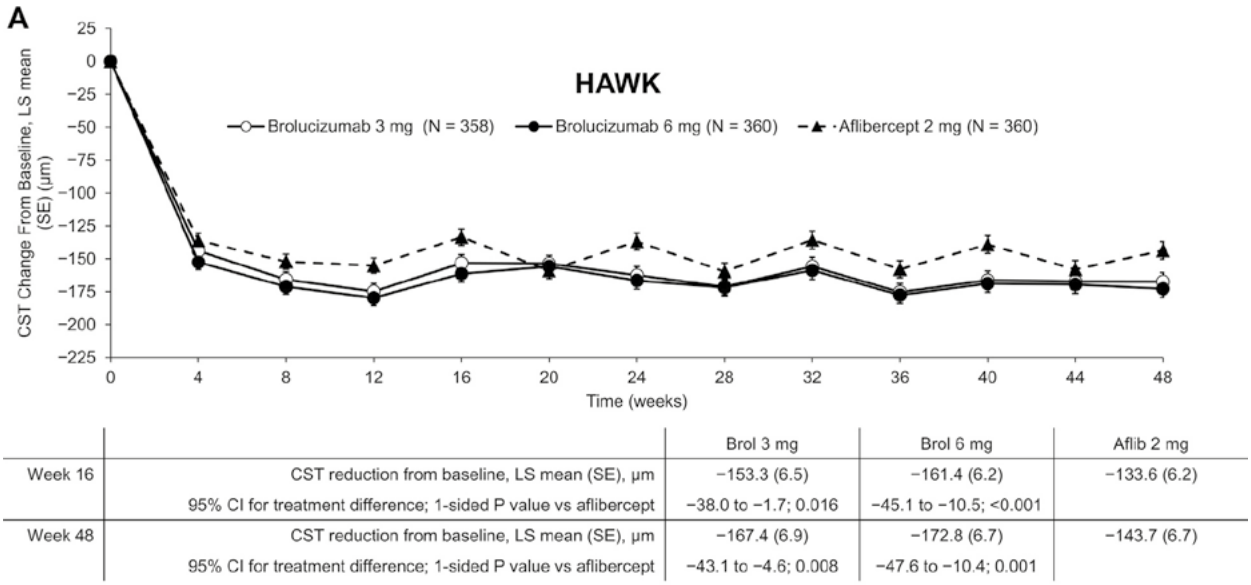


Figure 2. (**A**) Disease activity at Week 16. Full analysis set; analysis conducted based on the efficacy/safety approach. *The 95% confidence interval (CI) for treatment difference, −13.2 to 0.3; $P = 0.033$. †95% CI for treatment difference, −17.1 to −3.5; $P = 0.001$. ‡95% CI for treatment difference, −15.8 to −3.1; $P = 0.002$. 1-sided P values versus aflibercept. (**B**) Presence of intraretinal (IRF) and/or subretinal fluid (SRF) at Weeks 16 and 48. Full analysis set; LOCF. *95% CI for treatment difference, −17.3 to −2.5; $P = 0.003$. †95% CI for treatment difference, −25.3 to −10.9; $P < 0.001$. ‡95% CI for treatment difference, −17.4 to −3.3; $P = 0.002$. §95% CI for treatment difference, −20.7 to −6.1; $P < 0.001$. ‖95% CI for treatment difference, −22.9 to −9.0; $P < 0.001$. ¶95% CI for treatment difference, −24.9 to −11.8; $P < 0.001$. 1-sided P values versus aflibercept. (**C**) Presence of sub-RPE fluid at Weeks 16 and 48. Full analysis set; LOCF. * 95% CI for treatment difference, −11.8 to −1.1; $P = 0.027$. †95% CI for treatment difference, −14.4 to −2.9; $P = 0.003$. ‡95% CI for treatment difference, −9.4 to 1.4; $P = 0.15$. §95% CI for treatment difference, −13.6 to −2.7; $P = 0.004$. ‖95% CI for treatment difference, −13.0 to −2.7; $P = 0.004$. ¶95% CI for treatment difference, −13.8 to −3.9; $P < 0.001$. 2-sided P values vs aflibercept. Aflib = aflibercept; Brol = brolucizumab; LOCF = last observation carried forward; RPE = retinal pigment epithelium.

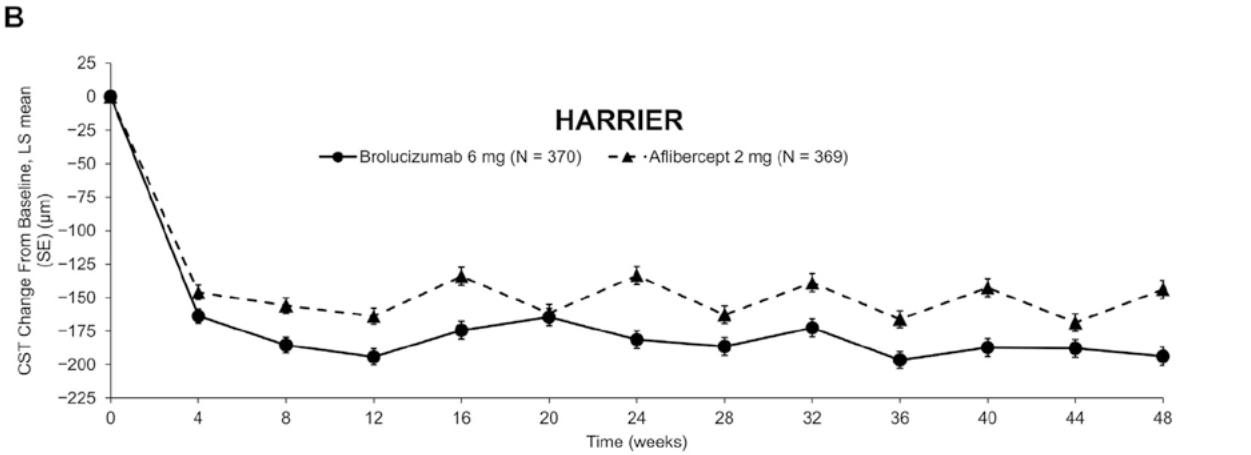
mg versus 0.3% and 0%, respectively, with aflibercept in HAWK; corresponding rates in HARRIER were <1% in both arms (Table 3). Approximately 90% of the uveitis and iritis cases were mild to moderate and treated with a course of topical corticosteroids/anti-infectives; most resolved with no sequelae. Incidence of increased intraocular pressure was similar with brolucizumab and aflibercept (2.5%−3.2% and 2.2%−2.4%, respectively; Table 3). The incidence of serious ocular adverse events was low in both trials; no event occurred in >1% of eyes (Table 4). An imbalance of uveitis serious adverse events between brolucizumab and aflibercept was observed in both trials, and an imbalance of endophthalmitis serious adverse events was observed in HAWK; however, there was a small number of reports (Table 4). The proportion of eyes with a ≥15-letter loss at Week 48 was balanced across all treatments (Table 2). The incidence of nonocular arterial thromboembolic events and death was consistent across treatment arms within each trial (Table 2). Nonocular adverse events and nonocular serious adverse events are summarized in Tables S10 and S11, respectively (available at www.aaojournal.org).

Discussion

HAWK and HARRIER, the phase 3 trials evaluating brolucizumab on a q12w/q8w regimen versus q8w aflibercept, met the primary end point of noninferiority in BCVA of brolucizumab versus aflibercept, with >50% of brolucizumab 6 mg patients being maintained on a q12w interval



		Brol 3 mg	Brol 6 mg	Aflib 2 mg
Week 16	CST reduction from baseline, LS mean (SE), µm	−153.3 (6.5)	−161.4 (6.2)	−133.6 (6.2)
	95% CI for treatment difference; 1-sided P value vs aflibercept	−38.0 to −1.7; 0.016	−45.1 to −10.5; <0.001	
Week 48	CST reduction from baseline, LS mean (SE), µm	−167.4 (6.9)	−172.8 (6.7)	−143.7 (6.7)
	95% CI for treatment difference; 1-sided P value vs aflibercept	−43.1 to −4.6; 0.008	−47.6 to −10.4; 0.001	



		Brol 6 mg	Aflib 2 mg
Week 16	CST reduction from baseline, LS mean (SE), µm	−174.4 (6.7)	−134.2 (6.7)
	95% CI for treatment difference; 1-sided P value vs aflibercept	−58.9 to −21.6; <0.001	
Week 48	CST reduction from baseline, LS mean (SE), µm	−193.8 (6.8)	−143.9 (6.8)
	95% CI for treatment difference; 1-sided P value vs aflibercept	−68.9 to −30.9; <0.001	

Figure 3. Central subfield thickness (CST) over time in (**A**) HAWK and (**B**) HARRIER. Full analysis set; LOCF. Aflib = aflibercept; Brol = brolucizumab; CI = confidence interval; LOCF = last observation carried forward; LS = least squares.

through Week 48. Moreover, anatomic retinal fluid outcomes favored brolucizumab over aflibercept. Overall adverse event rates were generally similar with brolucizumab and aflibercept.

Neovascular AMD is a variable disease with regard to individual treatment needs; for example, patients with early persistent retinal fluid have better outcomes with more frequent treatment.[32] Therefore, a goal of nAMD management is to determine therapeutic needs on an individual basis and treat accordingly to achieve an optimal visual outcome with minimal clinic visits and intravitreal injection burden. The disease is characterized by exudation from abnormally growing blood vessels in the macula, resulting in progressive degeneration of the photoreceptors and RPE.[1,33] The course of the disease is that VEGF increases, causing increased retinal fluid accumulation, which then leads to edema and functional deterioration.[34,35] Thus, presence of retinal fluid and increased CST are indicators of disease activity, and disease activity can be identified more rapidly through analysis of fluid on OCT compared with BCVA-based indicators.[1,33,36] Clinical practice guidelines from the American Academy of Ophthalmology, The Royal College of Ophthalmology, and EURETINA state that fluid on OCT is an indication of

Table 2. Safety Summary (Safety Analysis Set)

Adverse Event	HAWK			HARRIER	
	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)
Patients with ≥1 adverse event, n (%)*					
Ocular	175 (48.9)	179 (49.7)	170 (47.2)	122 (33.0)	119 (32.2)
Nonocular	242 (67.6)	232 (64.4)	258 (71.7)	219 (59.2)	211 (57.2)
Patients with ≥1 serious adverse event, total, n (%)*					
Ocular	5 (1.4)	11 (3.1)	3 (0.8)	9 (2.4)	4 (1.1)
Nonocular	47 (13.1)	47 (13.1)	68 (18.9)	35 (9.5)	43 (11.7)
Patients with ≥15-letter loss from baseline at Week 48, %†	5.9	6.4	5.5	3.8	4.8
Death, n (%)	4 (1.1)	4 (1.1)	6 (1.7)	3 (0.8)	4 (1.1)
Patients with ≥1 nonocular arterial thromboembolic event, n (%)*	11 (3.1)	6 (1.7)	10 (2.8)	6 (1.6)	8 (2.2)

Medical Dictionary for Regulatory Activities version 20.1 has been used for the reporting of adverse events.
*Adverse events with a start date on or after the date of first study treatment administration were counted. A patient with multiple occurrences of an adverse event for a preferred term or system organ class was counted only once in each specific category.
†Last observation carried forward.

active disease and recommend retreatment when fluid is present.[1,34,37]

Previous investigations of fixed q12w ranibizumab dosing without interval adjustment for disease activity showed inferiority of visual acuity outcomes to monthly dosing.[25] The resulting need to provide individualized treatment has led to the emergence of pro re nata (PRN, or "as needed") regimens, whereby patients are monitored monthly and treated only if signs of active disease are present.[38,39] Clinical trial data in CATT and HARBOR demonstrated effective BCVA improvements with PRN treatment;[38,39] however, the monthly monitoring need does

Table 3. Ocular Adverse Events by Preferred Term in Study Eye (≥2% of Eyes in any Treatment Group of any Study; Safety Analysis Set)

Preferred Term, n (%)*	HAWK			HARRIER	
	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)
Patients with ≥1 event	175 (48.9)	179 (49.7)	170 (47.2)	122 (33.0)	119 (32.2)
Conjunctival hemorrhage	30 (8.4)	23 (6.4)	20 (5.6)	7 (1.9)	12 (3.3)
Visual acuity reduced	23 (6.4)	19 (5.3)	24 (6.7)	20 (5.4)	20 (5.4)
Vitreous floaters	24 (6.7)	18 (5.0)	11 (3.1)	11 (3.0)	3 (0.8)
Eye pain	21 (5.9)	16 (4.4)	15 (4.2)	10 (2.7)	12 (3.3)
Dry eye	11 (3.1)	14 (3.9)	15 (4.2)	8 (2.2)	6 (1.6)
Retinal hemorrhage	10 (2.8)	13 (3.6)	16 (4.4)	5 (1.4)	2 (0.5)
Retinal pigment epithelial tear	5 (1.4)	12 (3.3)	4 (1.1)	6 (1.6)	4 (1.1)
Vitreous detachment	16 (4.5)	10 (2.8)	13 (3.6)	7 (1.9)	5 (1.4)
Eye irritation	8 (2.2)	10 (2.8)	8 (2.2)	3 (0.8)	1 (0.3)
Intraocular pressure increased	11 (3.1)	9 (2.5)	8 (2.2)	12 (3.2)	9 (2.4)
Posterior capsule opacification	5 (1.4)	9 (2.5)	7 (1.9)	5 (1.4)	1 (0.3)
Uveitis	5 (1.4)	8 (2.2)	1 (0.3)	3 (0.8)	0
Blepharitis	4 (1.1)	8 (2.2)	7 (1.9)	8 (2.2)	3 (0.8)
Iritis	1 (0.3)	8 (2.2)	0	0	1 (0.3)
Cataract	10 (2.8)	7 (1.9)	8 (2.2)	4 (1.1)	12 (3.3)
Visual field defect	7 (2.0)	7 (1.9)	3 (0.8)	1 (0.3)	0
Conjunctivitis	2 (0.6)	7 (1.9)	3 (0.8)	10 (2.7)	3 (0.8)
Vision blurred	11 (3.1)	6 (1.7)	5 (1.4)	1 (0.3)	2 (0.5)
Visual impairment	10 (2.8)	6 (1.7)	10 (2.8)	0	2 (0.5)
Punctate keratitis	5 (1.4)	6 (1.7)	8 (2.2)	1 (0.3)	3 (0.8)
Corneal abrasion	5 (1.4)	5 (1.4)	8 (2.2)	0	1 (0.3)
Lenticular opacities	6 (1.7)	0	3 (0.8)	8 (2.2)	7 (1.9)

Medical Dictionary for Regulatory Activities version 20.1 has been used for the reporting of adverse events.
*Adverse events with a start date on or after the date of first study treatment administration were counted. A patient with multiple occurrences of an adverse event for a preferred term or system organ class was counted only once in each specific category.

Table 4. Ocular Serious Adverse Events by Preferred Term in Study Eye (Safety Analysis Set)

	HAWK			HARRIER	
Preferred Term, n (%)*	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)
Patients with ≥1 event	5 (1.4)	11 (3.1)	3 (0.8)	9 (2.4)	4 (1.1)
Uveitis	1 (0.3)	2 (0.6)	0	3 (0.8)	0
Retinal detachment	1 (0.3)	1 (0.3)	0	0	1 (0.3)
Retinal pigment epithelial tear	—	—	—	2 (0.5)	0
Visual acuity reduced	0	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Macular hole	0	1 (0.3)	1 (0.3)	—	—
Cataract	0	1 (0.3)	0	—	—
Retinal artery embolism	—	—	—	1 (0.3)	0
Retinal artery occlusion	2 (0.6)	0	0	0	1 (0.3)
Retinal artery thrombosis	0	1 (0.3)	0	1 (0.3)	0
Retinal depigmentation	0	1 (0.3)	0	—	—
Retinopathy proliferative	0	1 (0.3)	0	—	—
Vitritis	0	1 (0.3)	0	—	—
Anterior chamber inflammation	—	—	—	1 (0.3)	0
Dry age-related macular degeneration	—	—	—	0	1 (0.3)
Endophthalmitis	3 (0.8)	2 (0.6)	0	1 (0.3)	0
Cataract traumatic	—	—	—	1 (0.3)	0

Medical Dictionary for Regulatory Activities version 20.1 has been used for the reporting of adverse events.
*Serious adverse events with a start date on or after the date of first study treatment administration were counted. A patient with multiple occurrences of an adverse event for a preferred term or system organ class was counted only once in each specific category. A dash indicates the event was not reported in the trial.

not alleviate the overall burden to patients, clinics, and the healthcare system.

As an alternative to PRN, "treat-and-extend" regimens gradually extend treatment intervals in patients without active disease, and the approach has been investigated recently in randomized trials using ranibizumab.[40,41] Standard "treat-and-extend" regimens in these studies extend the treatment interval in 2-week increments, thereby requiring 36 weeks of successive extensions postloading to observe the initial q12w interval and, on average, result in 9 to 10 injections in the first year.[40,41] Thus, a treatment providing comparable efficacy to fixed dosing but in a regimen in which the monitoring and dosing interval is based on an individual's anti-VEGF need soon after loading may alleviate the treatment burden associated with nAMD.

HAWK and HARRIER are the first multinational nAMD registration trials to use masked investigator identification of disease activity after the loading phase to identify a suitable maintenance dose interval based on individual treatment need. This approach differs from previous studies evaluating q12w dosing intervals[24,25] by providing the opportunity for masked physicians to adjust to q8w dosing during the study, if needed. As a result, q8w allocation was not randomized but driven by disease activity, making comparative analyses of eyes treated exclusively with a q12w interval versus eyes adjusted to a q8w interval not valid. Time-to-event analyses revealed that most q8w treatment need was identified during the first q12w interval (Weeks 16 and 20). Thus, these data support the predictive value of dynamic changes early in the treatment course and may offer a novel and reliable paradigm for efficient and individualized long-term nAMD management.

On the basis of this treatment concept of assessment during the initial q12w cycle and potential adjustments at scheduled q12w injection visits, the probability for maintaining on q12w dosing throughout Year 1 was estimated to be >50% for eyes treated with brolucizumab 6 mg. Eyes treated with a maintenance regimen of q12w dosing corresponds to a reduction of 2 injections per year compared with a q8w maintenance regimen.

In both HAWK and HARRIER, disease activity was assessed at each disease activity assessment visit. At the matched Week 16 assessment, corresponding to 8 weeks after completion of the loading phase in all patients, fewer brolucizumab 6 mg–treated eyes had disease activity versus aflibercept in both studies, with formal demonstration of superiority in HAWK, suggesting a prolonged duration of effect. In both studies, this advantage of brolucizumab 6 mg versus aflibercept was also reflected in the anatomic assessments at Week 16, again with formal demonstration of superiority in HAWK, regarding reductions of CST and presence of IRF and/or SRF. These advantages in anatomic parameters support the underlying hypothesis that a lower molecular weight combined with a higher concentration gradient between the vitreous and retina increase the drug distribution to the target site, resulting in more effective control of anatomic disease activity. Collectively, the data suggest greater treatment duration and thus reduced treatment need with brolucizumab.

In previous nAMD registration trials, the mean visual acuity improvements after 1 year of treatment were 6.5−7.2 (ranibizumab, MARINA), 8.5−11.3 (ranibizumab, ANCHOR), and 6.9−10.9 (aflibercept, VIEW) letters compared with 6.1−6.9 letters with brolucizumab (current report).[4−6] The difference in the magnitude in BCVA change between the present trials and previous registration trials can be explained by differences in baseline BCVA. The higher baseline BCVA value (resulting from the upper limit of 78 letters for the BCVA inclusion criterion) compared with previous registrational trials (upper limit of 73 letters in the ANCHOR, MARINA, and VIEW 1/2 trials[4−6]) is in line with current disease management.

The 48-week results of the trials showed robust visual acuity gains with brolucizumab dosed with a q12w/q8w regimen that were noninferior to aflibercept dosed q8w, while >50% of brolucizumab 6 mg−treated eyes were estimated to maintain on q12w dosing immediately after the loading phase through Week 48. Superior anatomic outcomes regarding retinal fluid and retinal thickness with brolucizumab 6 mg versus aflibercept could be concluded from HAWK and HARRIER at Weeks 16 and 48 in both studies. The predictive value of the behavior during the first q12w interval allows physicians to confidently determine which patients are suitable to continue on q12w dosing. Overall safety of brolucizumab was similar to aflibercept and consistent with other anti−VEGF-A agents approved for nAMD treatment.[6,42−44] The 96-week results will provide additional insight into the safety and efficacy of q12w/q8w brolucizumab versus that of q8w aflibercept.

In conclusion, the HAWK and HARRIER studies successfully evaluated an alternative treatment option, combining the prolonged duration of effect of brolucizumab with an individualized treatment regimen, allowing for favorable efficacy, effective treatment scheduling, and minimal monitoring burden.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CST** = central subfield thickness; **IRF** = intraretinal fluid; **IRT** = Interactive Response Technology; **LOCF** = last observation carried forward; **LS** = least squares; **nAMD** = neovascular age-related macular degeneration; **PRN** = pro re nata; **q8w** = every 8 weeks; **q12w** = every 12 weeks; **RPE** = retinal pigment epithelium; **scFv** = single-chain antibody fragments; **SRF** = subretinal fluid; **VEGF-A** = vascular endothelial growth factor A.

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