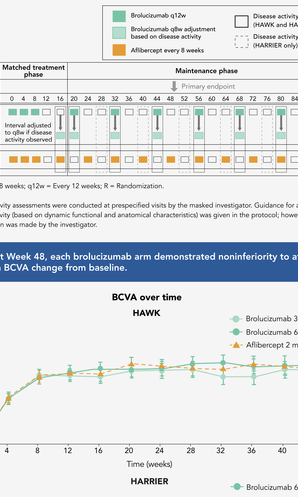
# HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration

Dugel PU, Koh A, Ogura Y, et al. *Ophthalmology*. 2020;127(1):72-84.
doi: 10.1016/j.ophtha.2019.04.017

The primary objective of both HAWK and HARRIER was to compare brolucizumab, a single-chain antibody fragment that inhibits vascular endothelial growth factor-A, with aflibercept to treat neovascular age-related macular degeneration (nAMD). Both phase 3 trials were similarly designed, with the primary hypothesis of noninferiority in mean best-corrected visual acuity (BCVA) change from baseline to Week 48 (margin: 4 letters).

## Patients were randomized to intravitreal brolucizumab 3 mg (HAWK only) or brolucizumab 6 mg or aflibercept 2 mg.

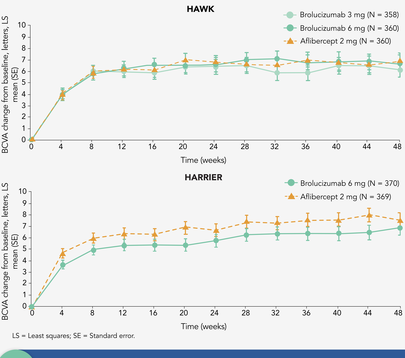
### Double-masked, multicenter, active-controlled, randomized trials

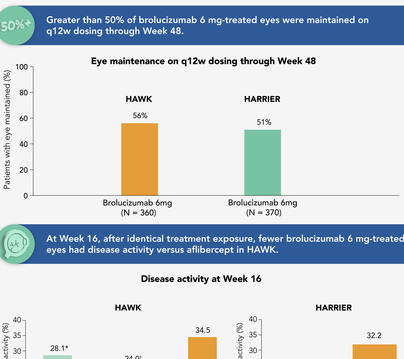



q8w = Every 8 weeks; q12w = Every 12 weeks; R = Randomization.
[a] HAWK only.
[b] Disease activity assessments were conducted at prespecified visits by the masked investigator. Guidance for assessing disease activity (based on dynamic functional and anatomical characteristics) was given in the protocol; however, the final decision was made by the investigator.

## At Week 48, each brolucizumab arm demonstrated noninferiority to aflibercept in BCVA change from baseline.

### BCVA over time

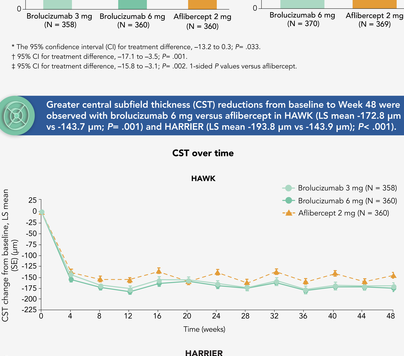



LS = Least squares; SE = Standard error.

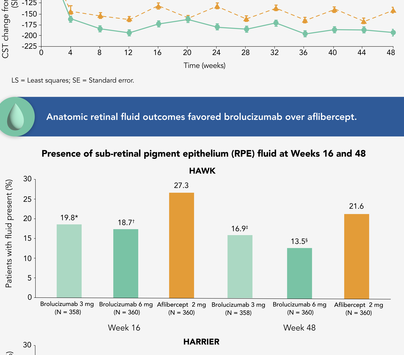
## Greater than 50% of brolucizumab 6 mg-treated eyes were maintained on q12w dosing through Week 48.

### Eye maintenance on q12w dosing through Week 48




## At Week 16, after identical treatment exposure, fewer brolucizumab 6 mg-treated eyes had disease activity versus aflibercept in HAWK.

### Disease activity at Week 16




* The 95% confidence interval (CI) for treatment difference, −13.2 to 0.3; *P*= .033.
† 95% CI for treatment difference, −17.1 to −3.5; *P*= .001.
‡ 95% CI for treatment difference, −15.8 to −3.1; *P*= .002. 1-sided *P* values versus aflibercept.

## Greater central subfield thickness (CST) 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*= .001) and HARRIER (LS mean -193.8 µm vs -143.9 µm; *P*< .001).

### CST over time







LS = Least squares; SE = Standard error.

## Anatomic retinal fluid outcomes favored brolucizumab over aflibercept.

### Presence of sub-retinal pigment epithelium (RPE) fluid at Weeks 16 and 48







* 95% CI for treatment difference, −11.8 to −1.1; *P*= .027.
† 95% CI for treatment difference, −14.4 to −2.9; *P*= .003.
‡ 95% CI for treatment difference, −9.4 to 1.4; *P*= .15.
§ 95% CI for treatment difference, −13.6 to −2.7; *P*= .004.
‖ 95% CI for treatment difference, −13.0 to −2.7; *P*= .004.
¶ 95% CI for treatment difference, −13.8 to −3.9; *P*< .001. 2-sided *P* values vs 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, although an imbalance of serious adverse events of uveitis (both trials) and endophthalmitis (HAWK) for brolucizumab was observed. The incidence of serious ocular adverse events was low in both trials, with no event occurring in >1% of eyes.**