VISUAL AND EXPANDED ANATOMICAL OUTCOMES FOR BROLUCIZUMAB VERSUS AFLIBERCEPT IN PATIENTS WITH NEOVASCULAR AMD: 96-WEEK DATA FROM HAWK AND HARRIER

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HAWK HARRIER

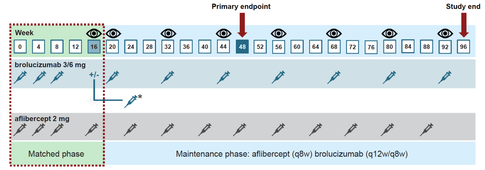
INTRODUCTION

- Neovascular age-related macular degeneration (nAMD) is a common cause of severe and irreversible vision loss and often results in blindness.[1]
- Anti-VEGF therapy has been demonstrated to be effective for patients with nAMD but can require frequent injections[1–3]
- Reducing the treatment burden while maintaining long-term treatment efficacy is a major challenge in the management of nAMD.[1]
- Brolucizumab is a novel single-chain antibody fragment with potent anti-vascular endothelial growth factor (anti-VEGF) attributes.[6]
- The innovative molecular structure and small size of brolucizumab enables concentrated molar dosing and may facilitate effective tissue penetration for a longer-lasting effect.[2,6]
- Retinal fluid and central subfield thickness (CST) values assessed by OCT are key anatomical markers used by physicians to determine injection frequency in clinical practice.[1]
- Here we report outcomes over 96 weeks in HAWK (NCT02307682) and HARRIER (NCT02434328), two Phase III, prospective studies that assessed the efficacy and safety of brolucizumab versus aflibercept in patients with nAMD.

METHODS

- Patients were randomised 1:1:1 to brolucizumab 3 mg (n=358), brolucizumab 6 mg (n=360) or aflibercept 2 mg (n=360) (HAWK), or 1:1 with brolucizumab 6 mg (n=370) or aflibercept 2 mg (n=369) (HARRIER), administered in one eye.
- After three monthly loading doses, brolucizumab patients were treated every 12 weeks (q12w), with an option to adjust to 8-week dosing (q8w) for the remainder of the study based on disease activity assessments; aflibercept was dosed in a fixed q8w regimen **(Figure 1).**
- Spectral domain optical coherence tomography (SD-OCT) assessments were conducted at every monthly visit and were analysed by independent central reading centres.

Figure 1. Study design of HAWK and HARRIER



*If disease activity was detected at any DAA visit, patients on brolucizumab q12w were adjusted to, and remained on, a q8w regimen

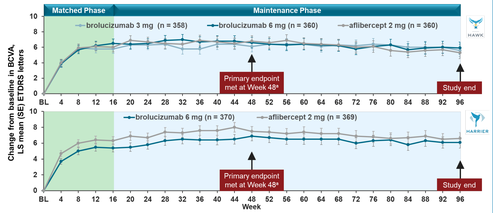
*Disease activity assessments were conducted at pre-specified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics. Additional assessments and potential dosing interval adjustments occurred at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only. Sham injections were administered to maintain masking. Visual and anatomic assessments were made prior to injections at Week 16 and 48.

RESULTS

BCVA change from baseline to Week 96

- Robust vision gains from baseline to Week 96 was observed in all study arms of HAWK and HARRIER (**Figure 2**).

Figure 2. BCVA change from baseline to Week 96 in HAWK and HARRIER

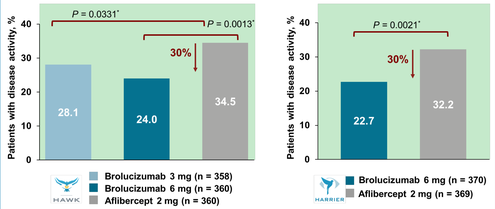


Full Analysis Set, LOCF. Mean differences in BCVA (brolucizumab–aflibercept, Δ). ᵃNon-inferiority (NI) margin = 4 letters. Analyzed using ANOVA model with baseline BCVA categories (<=55, 56–70, >=71 letters), age categories (<75,≥75 years) and treatment as fixed effect factors.
BCVA, best corrected visual acuity; BL, baseline; EDTRS, early treatment diabetic retinopathy study; LOCF, last observation carried forward; LS, least squares; SE, standard error.

Effect on nAMD disease activity

- Fewer patients on brolucizumab 6 mg than on aflibercept had disease activity at Week 16, as assessed by a masked investigator (**Figure 3**).

Figure 3. Proportion of patients with disease activity at Week 16

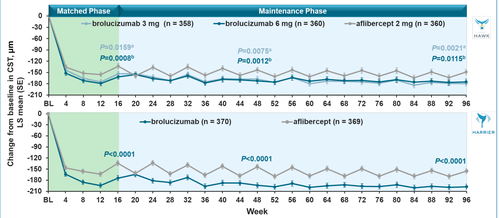


*Prespecified endpoint in both HAWK and HARRIER at Week 16, with confirmatory superiority analysis in HAWK only. 1-sided p values are presented. For superiority testing in HAWK, one-sided p values below the adjusted significance level (to account for multiplicity) of P<0.01 are regarded as statistically significant. Full analysis set, Efficacy/Safety approach: In case of missing / confounded data due to lack of efficacy and safety a 'q8-need' is allocated, otherwise censoring is applied.

Effect on fluid control

- Brolucizumab achieved superior reductions in CST from baseline to Week 16 and Week 48, and this difference was maintained at Week 96 compared to aflibercept (**Figure 4**).

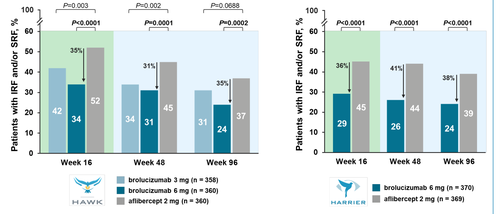
Figure 4. Change in CST from baseline to Week 96



Full analysis set, LOCF. Prespecified secondary endpoint in both HAWK and HARRIER at Week 16 and Week 48, with confirmatory superiority analysis in HAWK only. 1-sided p-values for HAWK; 1-sided p-values below the adjusted significance level (to account for multiplicity) of P<0.005 (for CST) are regarded as statistically significant. 1-sided p-values for HARRIER. P-values are descriptive. 2-sided P-values for both HAWK and HARRIER at week 96; P-values are descriptive. ᵃbrolucizumab 3 mg vs aflibercept 2 mg; brolucizumab 6 mg vs aflibercept 2 mg. BL, baseline; CST, central subfield thickness; LOCF, last observation carried forward; LS, least square; SE, standard deviation.

- In both HAWK and HARRIER, fewer patients on brolucizumab had IRF and/or SRF fluid at Weeks 16, 48 and 96 compared to aflibercept (**Figure 5**).
- Similarly, fewer patients receiving brolucizumab had sub-RPE fluid at Weeks 16, 48 and 96 compared to aflibercept.

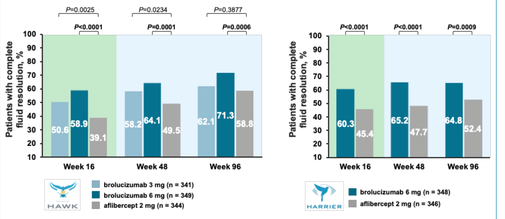
Figure 5. Proportion of patients with IRF and/or SRF



Full Analysis Set, LOCF. Prespecified secondary endpoint in both HAWK and HARRIER. Confirmatory superiority analysis at Week 16 and Week 48 in HAWK only. 1-sided p-values for HAWK and HARRIER. For confirmatory superiority testing in HAWK, 1-sided p-values below the adjusted significance level (to account for multiplicity) of P<0.01 (for IRF and/or SRF) are regarded as statistically significant. 2-sided P-values for both HAWK and HARRIER at Week 96; P-values are descriptive. IRF, intra-retinal fluid; LOCF, last observation carried forward; SRF, sub-retinal fluid.

- In both HAWK and HARRIER, the percentage of patients with complete fluid resolution (absence of SRF, IRF and sub-RPE) was greater with brolucizumab at Weeks 16, 48 and 96 compared to aflibercept (**Figure 6**).

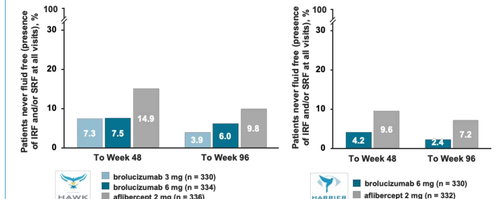
Figure 6. Proportion of patients with complete fluid resolution (absence of SRF, IRF and sub-RPE)*



Full Analysis Set, LOCF. *In patients with at least one fluid present at baseline
P-values are descriptive. IRF, intra-retinal fluid; LOCF, last observation carried forward; RPE, retinal pigment epithelium; SRF, sub-retinal fluid.

- In both HAWK and HARRIER, the percentage of patients never fluid free (presence of IRF and/or SRF at all visits) up to Week 48 and Week 96 were fewer with brolucizumab (both doses) compared to aflibercept 2 mg (**Figure 7**).

Figure 7. Proportion of patients never fluid free (presence of IRF and/or SRF at all visits) up to Week 48 and Week 96



Full Analysis Set, LOCF.
IRF, intra-retinal fluid; LOCF, last observation carried forward; SRF, sub-retinal fluid.

CONCLUSIONS

- **Brolucizumab achieved comparable vision gains and better fluid control with more patients remaining fluid-free at Week 96 compared with aflibercept.**

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