TIME TO DRY ANALYSIS OF BROLUCIZUMAB VERSUS AFLIBERCEPT IN PATIENTS WITH NEOVASCULAR AMD: 96-WEEK DATA FROM THE HAWK & HARRIER TRIALS

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KEY HIGHLIGHTS

- More than 50% of patients on brolucizumab 6 mg were maintained exclusively on a q12w dosing after loading up to Week 48
- The 48- and 96-week 'time to dry' analyses (of ≥2 or ≥3 consecutive fluid free visits) showed that, versus aflibercept:
  - Brolucizumab patients achieved 'first time to fluid free' faster
  - More patients treated with brolucizumab achieved sustained dryness

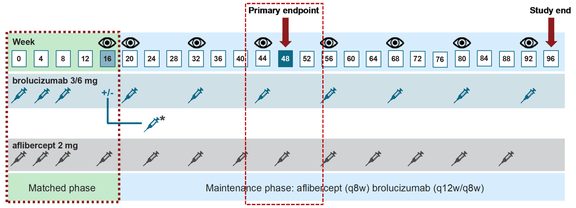
INTRODUCTION

- Neovascular age-related macular degeneration (nAMD) is a common cause of severe and irreversible vision loss and often results in blindness.[1]
- Brolucizumab is a novel single-chain antibody fragment with potent anti-vascular endothelial growth factor attributes.[2]
- The innovative molecular structure and small size of brolucizumab enables concentrated molar dosing and may facilitate effective tissue penetration, for a longer-lasting effect.[2,3]
- Sustained drying of the retina is an indicator of disease control and may be associated with long-term outcomes.[4,5]
- Retreatment decisions are made based on OCT, and sustained dryness is potentially associated with reduced treatment burden.[4–8]
- Here we report a post-hoc analysis of fluid resolution over 96 weeks for HAWK (NCT02307682) and HARRIER (NCT02434328), two Phase III, prospective studies assessing the efficacy and safety of brolucizumab versus aflibercept in 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) 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.
- Time to first sustained dryness was evaluated by the Kaplan-Meier method and a proportional hazard analysis.
- Cumulative incidence was calculated from the Kaplan-Meier analysis and sustained dryness was defined as ≥2 or ≥3 consecutive fluid free (intraretinal fluid [IRF] and subretinal fluid [SRF]) visits.

Figure 1. Study design of HAWK and HARRIER



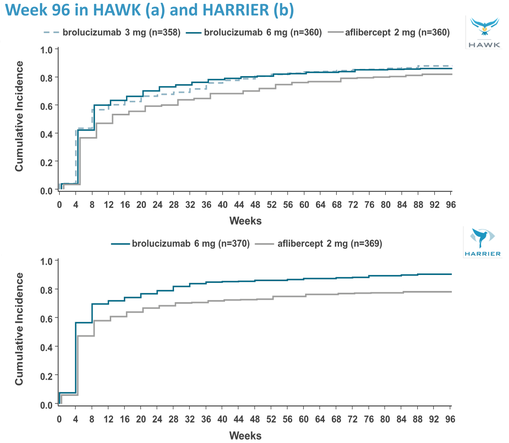
[a]Disease activity assessments were conducted at pre-specified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics. Additional assessments 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

Time to sustained dryness until Week 96

- Superior anatomical outcomes were achieved with brolucizumab 6 mg from baseline to Week 16 and Week 48 and sustained to Week 96 in both HAWK and HARRIER compared to aflibercept.
- Time to sustained dryness (no IRF and SRF) occurred from the matched phase and continued to Week 96 in both HAWK (**Figure 2a**) and HARRIER (**Figure 2b**).

Figure 2. Time to sustained dryness with ≥3 consecutive fluid free visits until Week 96 in HAWK (a) and HARRIER (b)



Full analysis set, LOCF.

- A higher proportion of brolucizumab patients achieved sustained dryness (no IRF or SRF) for both ≥2 (**Table 1**) and ≥ 3 (**Table 2&3**) consecutive clinic visits compared to aflibercept in both HAWK and HARRIER.

Table 1. Cumulative incidence of ≥2 consecutive fluid free (no IRF and SRF) clinic visits

HAWK	Brolucizumab 3 mg (n=358)	Brolucizumab 6 mg (n=360)	Aflibercept 2 mg (n=360)
Week 48			
cIR (%)	**82.9**	**86.5**	**76.5**
HR (95% CI)*	1.21 (1.03, 1.43)	1.39 (1.18, 1.63)	-
***P*-value**	0.0230	0.0001	-
Week 96			
cIR (%)	**90.8**	**90.4**	**84.8**
HR (95% CI)*	1.22 (1.04, 1.43)	1.33 (1.14, 1.56)	-
***P*-value**	0.0130	0.0004	
HARRIER		**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 48			
cIR (%)		**91.5**	**81.4**
HR (95% CI)*		1.35 (1.15, 1.58)	-
***P*-value**		0.0002	
Week 96			
cIR (%)		**94.5**	**85.5**
HR (95% CI)*		1.37 (1.17, 1.60)	
***P*-value**		<0.0001	

Full analysis set, LOCF. Cumulative incidences are Kaplan-Maïer estimates.
Definitions:
- Cumulative incidence rate is the number of new cases up to a specified time divided by number of population that is at risk of the event, calculated from the KM analysis
- Hazard Ratio is the chance of having an event i.e. consecutive fluid-free visits in the brolucizumab arm compared to aflibercept. A higher hazard ratio in the current analysis indicates earlier fluid resolution

Hazard ratio obtained from proportional hazard model. *Broluziumab vs Aflibercept 2mg
Nominal P-value. cIR, cumulative incidence rate; CI, confidence interval; HR, hazard ratio; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.

Table 2. Cumulative incidence of ≥3 consecutive fluid free (no IRF and SRF) clinic visits (HAWK)

HAWK	Brolucizumab 3 mg (n=358)	Brolucizumab 6 mg (n=360)	Aflibercept 2 mg (n=360)
Week 48			
cIR (%)	**77.6**	**79.1**	**68.3**
HR (95% CI)*	1.27 (1.06, 1.51)	1.34 (1.12, 1.59)	-
***P*-value**	0.0080	0.0010	-
Week 96			
cIR (%)	**87.9**	**86.1**	**82.0**
HR (95% CI)*	1.24 (1.05, 1.45)	1.24 (1.06, 1.46)	-
***P*-value**	0.0104	0.0080	-

Full analysis set, LOCF. Cumulative incidences are Kaplan-Maïer estimates.
Hazard ratio obtained from proportional hazard model. *Brolucizumab vs Aflibercept 2mg
Nominal P-value. cIR, cumulative incidence rate; CI, confidence interval; HR, hazard ratio; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.

Table 3. Cumulative incidence of ≥3 consecutive fluid free (no IRF and SRF) clinic visits (HARRIER)

HARRIER	Brolucizumab 6 mg (n=370)	Aflibercept 2 mg (n=369)
Week 48		
cIR (%)	**85.9**	**73.0**
HR (95% CI)*	1.40 (1.19, 1.65)	-
***P*-value**	<0.0001	-
Week 96		
cIR (%)	**91.2**	**78.8**
HR (95% CI)*	1.43 (1.21, 1.67)	-
***P*-value**	<0.0001	-

Full analysis set, LOCF. Cumulative incidences are Kaplan-Maïer estimates.
Hazard ratio obtained from proportional hazard model. *Brolucizumab vs Aflibercept 2mg
Nominal P-value. cIR, cumulative incidence rate; CI, confidence interval; HR, hazard ratio; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.

CONCLUSIONS

- **More patients treated with brolucizumab achieved sustained dryness than those treated with aflibercept in HAWK and HARRIER.**
- **Brolucizumab patients also achieved 'first time to fluid free' faster than aflibercept patients.**

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