Brolucizumab q16w/q12w dosing allocation in nAMD: a *post hoc* evaluation of data from HAWK and HARRIER

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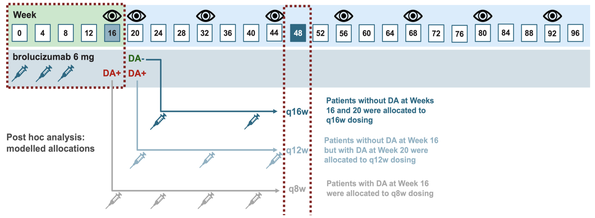
INTRODUCTION

- The Phase III HAWK and HARRIER studies followed an adaptive design post-loading, whereby brolucizumab was dosed in a 12-week dosing interval (q12w) with treatment intervals reduced to 8-week dosing intervals(q8w) if disease activity was observed.[1,2]
- Recent trials of a new anti-vascular endothelial growth factor (VEGF) agent in neovascular age-related macular degeneration (nAMD) used a fixed dosing stratification approach in which, following loading phase, patients were assigned to treatment intervals of q8w, q12w, or 16-week dosing interval (q16w), fixed through Year 1.[3,4]
- Differences between the study designs used in the development trials of brolucizumab and faricimab raises a question regarding the durability potential of brolucizumab if a fixed dosing regimen had been used.
- This *post hoc* analysis evaluates the percentage of brolucizumab 6 mg patients that would be assigned to fixed q16w, q12w, and q8w intervals, had fixed treatment allocation criteria from recent development trials been used.

METHODS

- In the HAWK and HARRIER trials, patients (aged ≥50 years, treatment-naïve, choroidal neovascularization [CNV] lesions secondary to nAMD with presence of subfoveal fluid, best-corrected visual acuity [BCVA] of 78–23 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) were randomised 1:1:1 to brolucizumab 3 mg (HAWK only), brolucizumab 6 mg or aflibercept 2 mg,.[1]
- The first disease activity assessments (DAAs) were conducted at Weeks 16 and 20, following three loading doses (**Figure 1**).
- In this *post hoc* analysis, the following criteria were applied for hypothetical allocation of patients from the brolucizumab 6 mg treatment arms of HAWK or HARRIER to q8w, q12w, and q16w fixed dosing:
  - Patients with DA at Week 16 were allocated to q8w dosing;
  - Patients without DA at Week 16 but with DA at Week 20 were allocated to q12w dosing;
  - Patients without DA at Weeks 16 and 20 were allocated to q16w dosing (**Figure 1**).

Figure 1. HAWK and HARRIER study design & modelled patient allocations to q8w, q12w, and q16w regimens[1]



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 Weeks 16 and 48. DA, disease activity; DAA, disease activity assessment; q8w, 8-week dosing interval; q12w, 12-week dosing interval; q16w, 16-week dosing interval.

Methods for CSFT simulation

- Central subfield thickness (CSFT) outcomes over 1 year were simulated for 350 brolucizumab 6 mg patients allocated to fixed q16w, q12w or q8w dosing regimens and 350 aflibercept 2 mg patients dosed q8w.
- Simulations were performed using a pharmacokinetic/pharmacodynamic (PK/PD) model describing CSFT response to anti-VEGF treatment, developed by fitting CSFT data from several studies of brolucizumab in nAMD.
- PK of all study drugs was described using a one-compartment model with drug-specific half-lives; CSFT was described using a logistic growth model with an added drug effect.
- Individual CSFT profiles were simulated for HAWK and HARRIER with individual parameters sampled from the distributions of the random effects. To obtain confidence intervals (CIs) of simulated mean CSFT, 200 studies were simulated.

RESULTS

Modelled patient allocations in different brolucizumab regimens

- The percentage of patients on a fixed dosing regimen of q12w or longer through year 1 would be 79.1% in HAWK and 77.3% in HARRIER (**Table 1**).

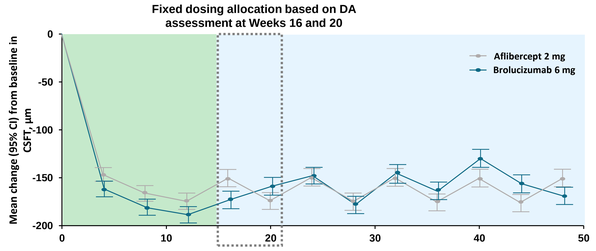
Table 1. Modelled patient allocations to q8w, q12w, and q16w regimens

Regimen allocation at Week 16/20	HAWK Patients, % (n/N)	HARRIER Patients, % (n/N)	Arithmetic mean of HAWK and HARRIER allocations (%)
q8w	20.9 (63/301)	22.7 (73/321)	21.80
q12w	20.6 (62/301)	24.0 (77/321)	22.30
q16w	58.5 (176/301)	53.3 (171/321)	55.90
≥q12w	79.1 (238/301)	77.3 (248/321)	78.14

q8w, 8-week dosing interval; q12w, 12-week dosing interval; q16w, 16-week dosing interval.

Simulated mean reduction in CSFT

Figure 2. Simulated mean reduction in CSFT was similar for brolucizumab 6 mg dosed up to q16w and aflibercept 2 mg dosed at q8w



CI, confidence interval; CSFT, central subfield thickness; DA, disease activity; q8w, 8-week dosing interval; q16w, 16-week dosing interval.

CONCLUSIONS

- In HAWK and HARRIER, a conservative approach was applied to brolucizumab 6 mg dosing with a treatment interval of q12w/q8w and no q16w allocation.
- Applying DA criteria, similar to recent studies, an early fixed allocation to the brolucizumab treatment arm translates to >75% of patients on an interval of q12w or longer and >50% of patients on a q16w interval.
- Using these allocations, the simulated CSFT data show similar outcomes for brolucizumab 6 mg (dosed up to q16w) and aflibercept 2 mg (dosed q8w).

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