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Brolucizumab 12- and 16-Week Fixed Dosing Potential in Neovascular AMD: A post hoc Evaluation of Data from the HAWK and HARRIER Trials

Michael Singer[a] Arshad M. Khanani[b] Armin Wolf[c] Rita Flores[d, e] Jay Chhablani[f] Guruprasad B[g] Andreas Clemens[h, i] Kinfemichael Gedif[g] Xiaoxi Liu[g] Zufar Mulyukov[h] Giuseppe Querques[j, k]

[a]Medical Center of Ophthalmology, University of Texas Health Science Center, San Antonio, TX, USA; [b]Sierra Eye Associates, Reno, NV, USA; [c]Department of Ophthalmology, University of Ulm, Ulm, Germany; [d]Department of Ophthalmology, Centro Hospitalar Universitário de Lisboa Central EPE, Lisbon, Portugal; [e]CEDOC-Chronic Diseases Research Center, Universidade Nova de Lisboa, Lisbon, Portugal; [f]UPMC Eye Center, University of Pittsburgh, Pittsburgh, PA, USA; [g]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [h]Novartis Pharma AG, Basel, Switzerland; [i]Department of Cardiology and Angiology I, Heart Center Freiburg University, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany; [j]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy; [k]Ophthalmology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Keywords
Anti-vascular endothelial growth factor · Brolucizumab · Fixed dosing · Neovascular age-related macular degeneration

Abstract
Introduction: This post hoc analysis applies a fixed dosing stratification approach to patient-level brolucizumab data from the phase III HAWK and HARRIER trials to determine the proportion of patients who would have been assigned to fixed dosing regimens with treatment intervals of 8, 12, or 16 weeks (q8w, q12w, or q16w) based on the presence/absence of disease activity (DA) following the loading phase. The analysis also simulates central subfield thickness (CSFT) data to estimate the anatomical outcomes if the patients had been thus assigned. Of note, the limitations of this analysis include the post hoc nature of the work and the inability to directly compare HAWK and HARRIER with TENAYA and LUCERNE due to the differences in design. ***Design:*** This study was a post hoc modelling analysis of patient-level data. ***Methods:*** Using patient-level data from HAWK and HARRIER, patients (n = 730) were allocated to a fixed q16w, q12w, or q8w regimen based on assessment of DA at weeks 16 and 20. Two definitions of DA were used: DA 1, based on a phase II study of faricimab, and DA 2, a definition derived from common clinical consideration including visual acuity and anatomical changes. CSFT simulations were performed using a pharmacokinetic/pharmacodynamic model describing CSFT response to anti-VEGF treatment. Outcome measures were modelled patient allocation to fixed regimens and mean CSFT reduction. ***Results:*** Using DA definitions 1 and 2, respectively, 78% and 76% of patients in the brolucizumab arm were allocated to a greater than or equal to q12w regimen, and 56% and 52% were allocated to a q16w regimen.

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Karger@karger.com
www.karger.com/oph

Correspondence to:
Giuseppe Querques, querques.giuseppe@hsr.it

Mean reduction in CSFT was similar between the two study drugs with both DA definition assumptions. ***Conclusions:*** This analysis demonstrates the potential durability of action and effectiveness of brolucizumab.

Introduction

Anti-vascular endothelial growth factor (anti-VEGF) therapy is the gold standard treatment for neovascular age-related macular degeneration (nAMD), with proven efficacy in visual and anatomical outcomes in clinical trials [1]. However, treatment burden is a continuing concern in nAMD. While visual outcomes are generally better with more frequent injections, with early pivotal trials of anti-VEGF therapy using a monthly dosing schedule [2, 3], high injection burden in the clinical setting leads to long-term reduced compliance in many patients and subsequent suboptimal visual outcomes [1, 4, 5]. There remains an unmet need for anti-VEGF agents with greater durability, to reduce the burden of treatment through less frequent dosing [5]. The HAWK and HARRIER trials compared the efficacy and safety of the anti-VEGF agents brolucizumab and aflibercept for the treatment of nAMD and were the basis of the approval of brolucizumab 6 mg in this indication in the USA, Europe, and other territories [6, 7].

At the time of the design of the HAWK and HARRIER studies, 8-weekly maintenance therapy was well established with aflibercept, and 12-weekly maintenance was emerging as the new paradigm for treatment burden reduction. The brolucizumab treatment arms of HAWK and HARRIER followed a conservative, adaptive study design whereby all patients received 3 monthly loading injections followed by dosing every 12 weeks (q12w) unless disease activity (DA) was identified at prespecified DA assessment visits. These visits were at weeks 16, 20, 32, and 44 in HAWK and at these plus additional visits at weeks 28 and 40 in HARRIER. In the event of DA, patients were permanently adjusted to dosing every 8 weeks (q8w), with no option for treatment intervals to be extended later if DA subsided [6, 7].

Following this design, brolucizumab 6 mg provided non-inferior visual acuity outcomes versus aflibercept 2 mg given q8w, and the majority of brolucizumab 6 mg-treated eyes (56% in HAWK and 51% in HARRIER) were maintained on q12w dosing to the primary analysis at week 48 [7]. Significantly greater central subfield thickness (CSFT) reductions from baseline to week 48 were observed with brolucizumab 6 mg versus aflibercept 2 mg in HAWK ($p = 0.001$) and HARRIER ($p < 0.001$).

Faricimab is an experimental monoclonal antibody which targets VEGF-A and angiopoietin-2 [8]. For this new anti-VEGF agent, q12w and q16w dosing allocations were evaluated in the phase III TENAYA and LUCERNE studies. In these studies, faricimab 6 mg was given according to a fixed regimen following four loading doses. Patients were allocated to fixed q8w, q12w, or q16w, based on the presence of DA at week 20 and 24 and the absence of DA at week 24. This regimen was not adjusted based on the presence or absence of DA later in year 1 [9–11]. The differences between the adaptive study design used in the development of brolucizumab and the fixed dosing design used in the faricimab development trials provoke a question regarding the durability potential of brolucizumab if a fixed dosing regimen, similar to TENAYA and LUCERNE, had been used in the HAWK and HARRIER studies.

The aim of this modelling analysis is to apply the fixed dosing stratification approach from the TENAYA and LUCERNE studies to patient-level brolucizumab data from the HAWK and HARRIER trials. This will allow us to determine the proportion of brolucizumab patients who would have been assigned to each of the fixed q16w, q12w, and q8w dosing regimens after the loading phase based on DA assessments at weeks 16 and 20. In addition, simulation of CSFT data will be performed to provide an estimation of the anatomical treatment outcomes that might have been achieved if the patients had been allocated to a fixed regimen with these modelled q8w, q12w, and q16w allocations.

Methods

Study Design

This was a post hoc study of patient-level data, performed in two parts: a patient allocation analysis and a CSFT simulation analysis.

Patient Population

The patient allocation analysis included patient-level data from the brolucizumab 6 mg arms of HAWK (NCT02307682) and HARRIER (NCT02434328), two 2-year, randomized, double-masked, multicentre active-controlled phase III trials conducted at 408 sites in North, Central, and South America; Europe; Asia; Australia; and Japan [7]. These trials were conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline, and other regulations as applicable and were compliant with the Health Insurance Portability and Accountability Act of 1996. All trial participants provided written informed consent, and Independent Ethics Committee/Institu-

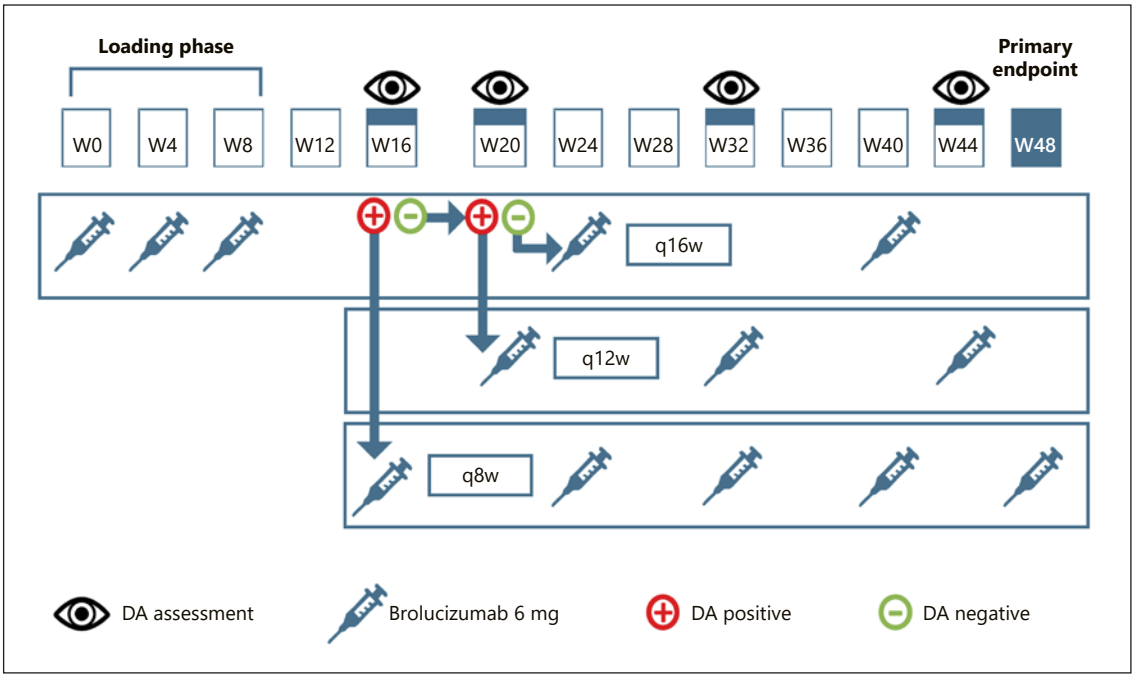

Fig. 1. Allocation of patients to q8w, q12w, and q16w regimens in the modelling analysis. Patients received 3 monthly injections as a loading dose before being evaluated at week 16 and week 20. Based on their DA status at these time points, patients were assigned to a fixed dosing regimen for the remainder of the study. DA, disease activity; q8w, 8-week dosing interval; q12w, 12-week dosing interval, q16w, 16-week dosing interval.

tional Review Board approval was obtained for these trials. A total of 360 patients were included in the full analysis set of the brolucizumab 6 mg arm of HAWK and 370 in the same arm of HARRIER. The CSFT simulation analysis included these data plus patient-level data from the aflibercept arms of the same studies (n = 360 and 369 for HAWK and HARRIER, respectively).

Patient Allocation

In the HAWK and HARRIER studies, DA assessments were conducted at weeks 16 and 20, following the three loading doses at weeks 0, 4, and 8. In the current analysis, HAWK and HARRIER patient-level data from weeks 16 and 20 were used to allocate patients to a fixed q16w, q12w, or q8w dosing regimen based on the presence or absence of DA at these time points (Fig. 1), according to the DA criteria described below. According to these modelled regimens, and as shown in Figure 1, patients allocated to a q8w regimen would receive 8 injections in year 1, those allocated q12w would receive 6, and those allocated 16qw, 5.

Patients who did not meet DA criteria for this analysis at week 16 but who received an injection at that visit based on the HAWK and HARRIER protocol (where DA was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics) were excluded from the analysis. Patients who did not meet DA criteria at week 20 were considered to be a q16w patient for this analysis, whether or not they received an injection.

The patient allocation analysis was performed twice, using two different DA criteria for the assessment at weeks 16 and 20, which corresponds to the assessment 8 weeks after the loading intervals as in TENAYA and LUCERNE (Table 1). DA definition 1 was based on the definition of DA used for allocation of treatment regimen in the phase II study of faricimab in nAMD, STAIRWAY [12], while DA definition 2 was a simpler, clinician-relevant definition of DA.

CSFT Simulation

Two different scenarios of CSFT outcomes for brolucizumab were simulated over the course of 1 year with patients allocated to the fixed q16w, q12w, or q8w dosing regimens as described above (DA definitions 1 and 2), and CSFT outcomes for aflibercept were simulated over the same time period with patients receiving aflibercept q8w following three loading doses. Simulations were performed using a pharmacokinetic/pharmacodynamic model that describes CSFT response to anti-VEGF treatment. The model was developed by fitting CSFT data from several studies of brolucizumab in nAMD patients: the SEE phase I study of the safety and tolerability of brolucizumab in four ascending doses of 0.5 mg, 3 mg, 4.5 mg, and 6 mg as well as the 0.5-mg ranibizumab comparator arm (194 patients) [13]; the OSPREY phase II study of efficacy of brolucizumab 6 mg versus aflibercept 2 mg (96 patients) [14]; the HAWK phase III 2-year study comparing the efficacy and safety of brolucizumab (3 mg and 6 mg) versus aflibercept 2 mg (1,078 patients); and the HARRIER phase III 2-year study comparing the efficacy and safety of 6-mg brolucizumab versus aflibercept 2 mg (739 patients) [7].

Table 1. DA criteria used in the analysis

	DA criteria
Definition 1	BCVA loss >10 letters from the maximum of the last two visits or
	BCVA loss >5 letters from the average of the last two visits or
	CSFT increase ≥75 μm from minimum of the last two visits or
	CSFT increase ≥50 μm from average of the last two visits
Definition 2	BCVA loss of ≥5 letters or CSFT gain of ≥50 μm compared with 8 weeks prior to the DA assessment (i.e., week 16 was compared with week 8, and week 20 was compared with week 12)

BCVA, best-corrected visual acuity; CSFT, central subfield thickness; DA, disease activity.

Pharmacokinetics of all study drugs were described using a one-compartment model with drug-specific half-lives. The CSFT was described using a logistic growth model with an added drug effect.

During model development, we ensured that the model well described the observed data through a series of goodness-of-fit diagnostic plots, including simulation-based diagnostics such as visual predictive checks which tested that the model reproduces the data in simulations. Through visual predictive check diagnostics, we ensured that not only are mean CSFT data reproduced, but also that 10th and 90th percentiles of the data are reasonably well reproduced in simulations.

Each simulated study comprised 350 patients treated with brolucizumab 6 mg and 350 patients treated with aflibercept 2 mg. The individual CSFT profiles were simulated for the HAWK and HARRIER populations (i.e., baseline CSFT covariate on model parameters) with individual parameters sampled from the distributions of the random effects. The inclusion of baseline CSFT as a model covariate means not only that CSFT baselines are properly simulated in for each virtual patient (sampled from HAWK and HARRIER data), but also that effects of those baselines on any other model parameters (if any) are also captured. To obtain confidence intervals of simulated mean CSFT, we simulated 200 studies.

Simulated patients were assigned to q8w, q12w, and q16w treatment based on CSFT increase from week 12, which is the maximum drug effect time point. Two specific thresholds were selected for CSFT increases from week 12 to week 16 and from week 12 to week 20. At week 16, patients with CSFT increase greater than first threshold were allocated to q8w and treated; the rest continued untreated to week 20. At week 20, the patients not yet assigned to q8w and with CSFT increase greater than the second threshold were allocated to q12w and treated; the rest were allocated to q16w. This initial allocation of treatment intervals was simulated up to week 48. The specific values of the CSFT increase thresholds were selected to match the allocation percentages for the two described DA definitions (Table 2). Mean change from baseline in CSFT was presented as an average of values from weeks 40, 44 and 48, for consistency with the presentation of anatomical endpoints from TENAYA and LUCERNE [11].

Results

Patient Allocation

Table 2 summarizes the results of the patient allocation analysis. Using DA definition 1 to allocate patients to a fixed regimen at weeks 16 and 20, 53% of patients in HARRIER and 59% of patients in HAWK were allocated to a q16w regimen, and 77 and 79%, respectively, were allocated to a greater than or equal to q12w regimen. Similar results were achieved using DA definition 2: 49–56% of patients were allocated to a q16w regimen, and 74–78% were allocated to a greater than or equal to q12w regimen.

CSFT Simulation

Figures 2 and 3 show simulated CSFT data for brolucizumab and aflibercept in HAWK and HARRIER with brolucizumab 6 mg patients allocated to fixed q16w, q12w, or q8w dosing regimens using DA definition 1 (Fig. 2) and DA definition 2 (Fig. 3) and aflibercept in a fixed q8w regimen, both after 3 loading doses. The mean reduction in CSFT from week 40 to 48 with brolucizumab was −152.39 μm using DA definition 1 and −151.30 μm using DA definition 2. Aflibercept given as a q8w regimen resulted in a mean reduction in CSFT from week 40 to 48 of −158.57 μm.

Discussion

Recent development trials of anti-VEGF therapies in nAMD have used a fixed dosing stratification approach to assign patients to a specific treatment interval for the entire study duration, based on assessment of DA following the loading phase of dosing. This analysis aimed to apply this approach retrospectively to patient-level data for brolucizumab in nAMD, to determine how the study population would have been allocated between regimens if the fixed dosing stratification had been used in the earlier HAWK and HARRIER trials.

In this analysis, two sets of criteria were used to determine DA and allocate patients to a fixed dosing regimen. DA definition 1 is based on the definition of DA used for allocation of treatment regimen in the phase II study of faricimab in nAMD, STAIRWAY [12], and is intended to

Table 2. Modelled patient allocation to q8w, q12w, and q16w regimens

DA criteria	Regimen allocation at week 16/20	HAWK Patients, *n* (%)	HARRIER Patients, *n* (%)	Arithmetic mean of HAWK and HARRIER allocations (%)
Definition 1	q8w	63 (20.9)	73 (22.7)	21.86
	q12w	62 (20.6)	77 (24.0)	22.35
	q16w	176 (58.5)	171 (53.3)	55.79
	≥q12w	238 (79.1)	248 (77.3)	78.14
Definition 2	q8w	64 (21.7)	83 (25.9)	23.90
	q12w	67 (22.7)	80 (25.0)	23.90
	q16w	164 (55.6)	157 (49.1)	52.20
	≥q12w	231 (78.3)	237 (74.1)	76.10

DA criteria definition 1: at least one of (i) BCVA loss >10 letters from the maximum of the last two visits, (ii) BCVA loss >5 letters from the average of the last two visits, (iii) CSFT increase ≥75 µm from minimum of the last two visits, or (iv) CSFT increase ≥50 µm from average of the last two visits. DA definition 2: BCVA loss of ≥5 letters or CSFT gain of ≥50 µm compared with two visits prior to the DA assessment. BCVA, best-corrected visual acuity; CSFT, central subfield thickness; DA, disease activity; q8w, 8-week dosing interval; q12w, 12-week dosing interval, q16w, 16-week dosing interval.

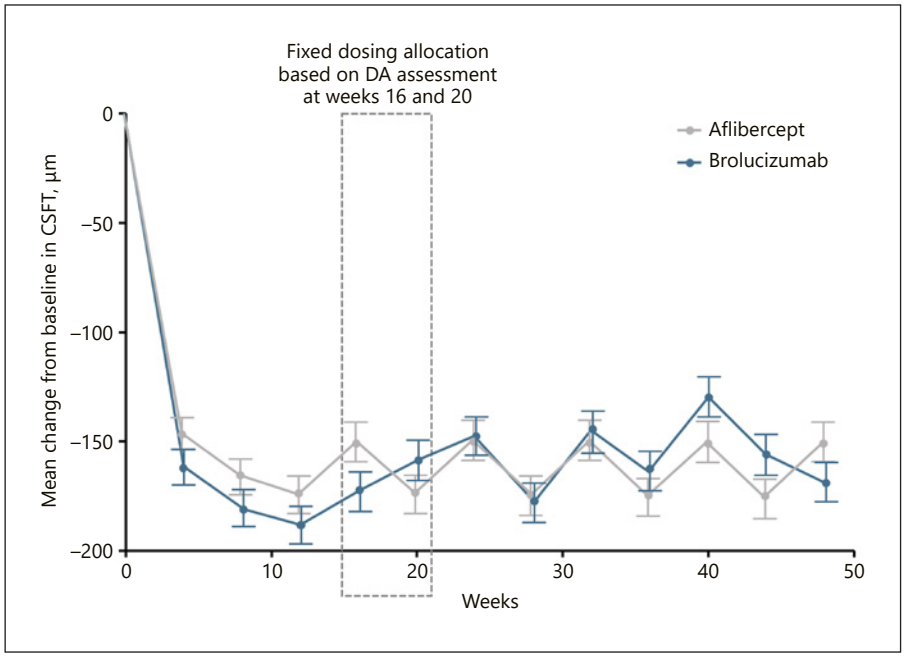

Fig. 2. CSFT simulation over the course of 1 year with brolucizumab 6 mg patients allocated to fixed q16w (56%), q12w (22%), or q8w (22%) dosing regimens using DA definition 1 and aflibercept 2 mg patients allocated to a fixed q8w regimen. Error bars indicate 95% confidence intervals, and the dotted line indicates the time point at which patients were assessed for assignment to fixed dosing intervals. CSFT, central subfield thickness; DA, disease activity.

provide the closest possible approximation of the fixed dosing stratification approach used in the TENAYA and LUCERNE studies. DA definition 2 is intended as a definition of DA which includes visual acuity and anatomical changes and might be considered to be more representative of a typical decision-making process used in clinical practice.

The patient allocation analysis showed that, when assessed for a fixed dosing regimen at weeks 16 and 20, using DA definitions 1 and 2, respectively, 78% and 76% of patients in the brolucizumab arm were allocated to a greater than or equal to q12w regimen, and 56% and 52% were allocated to a q16w regimen. In TENAYA and LUCERNE, 77.8–79.7% of patients in the faricimab arm were allocated to a greater than or equal to q12w regimen

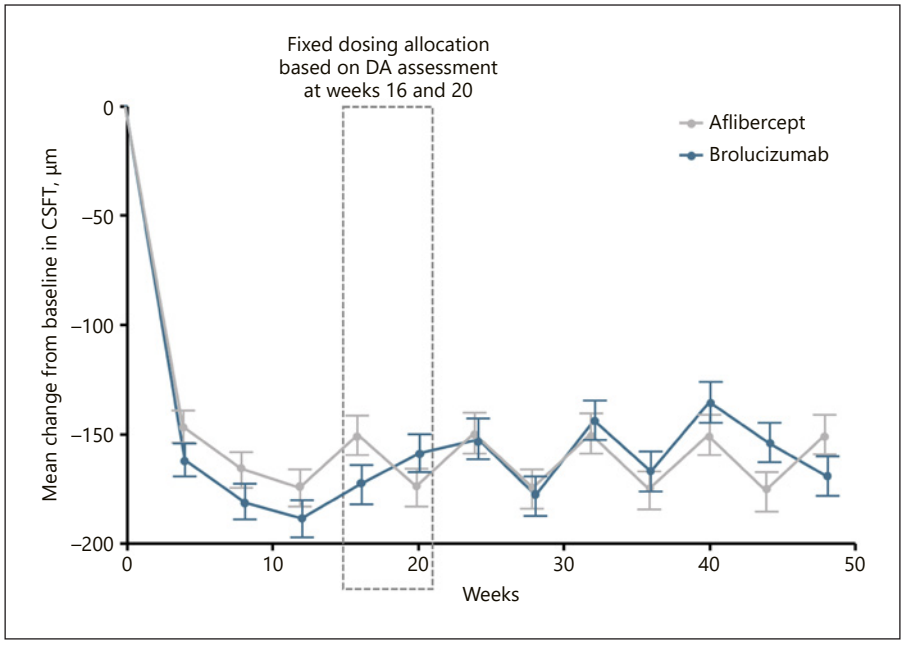

Fig. 3. CSFT simulation over the course of 1 year with brolucizumab 6 mg patients allocated to fixed q16w (52%), q12w (24%), or q8w (24%) dosing regimens using DA definition 2 and aflibercept 2 mg patients allocated to a fixed q8w regimen. Error bars indicate 95% confidence intervals, and the dotted line indicates the time point at which patients were assessed for assignment to fixed dosing intervals. CSFT, central subfield thickness; DA, disease activity.

and 44.9–45.7% to a q16w regimen [11]. In both our analysis and TENAYA and LUCERNE, patients were assigned to a q16w regimen if there were no signs of DA up to and including 12 weeks after the final loading phase injection. If the proportion of patients thus assigned to a q16w regimen is an indicator of durability of action, our analysis provides evidence that the durability of brolucizumab may be at least equivalent to that of faricimab. However, it is of note that in TENAYA and LUCERNE, patients received 4 monthly loading doses prior to allocation, compared with 3 monthly loading doses in HAWK and HARRIER, making our comparison a conservative one.

The increased durability of faricimab compared with earlier anti-VEGF agents has been hypothesized to be an additive effect resulting from the dual inhibition of VEGF-A and angiopoietin-2 [12]. In the case of brolucizumab, it is the agent's smaller molecular size, high stability, and solubility, enabling a high molar dose, that is thought to provide its prolonged duration of treatment effect [13].

This analysis also provides modelling evidence of the anatomic CSFT outcomes with the hypothetical q8w/q12w/q16w allocation using DA assessments. The CSFT simulation showed a greater reduction in CSFT during the loading phase with brolucizumab compared with aflibercept, and a similar mean reduction in CSFT averaged over weeks 40–48. The simulated aflibercept CSFT data showed good similarity to the actual aflibercept CSFT data from HAWK and HARRIER, which gives us confidence that our simulation model is reasonably accurate.

The limitations of this analysis include the post hoc nature of the work, and the inability to directly compare HAWK and HARRIER with TENAYA and LUCERNE due to the differences in design, particularly in the loading dose phase. In addition, the model does not differentiate between different fluid compartments, considering only the overall contribution of all fluids to CSFT.

In conclusion, this modelling analysis demonstrates the potential durability of action and effectiveness of brolucizumab. Despite only receiving 3 loading doses, over three-quarters of patients treated with brolucizumab in HAWK and HARRIER would have been allocated to a greater than or equal to q12w regimen. In addition, under their allocated regimens, it is predicted that patients in the brolucizumab arm of HAWK and HARRIER would have achieved similar CSFT reductions to those treated with aflibercept but with fewer injections.

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Statement of Ethics

The HAWK and HARRIER trials were conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline, and other regulations as applicable and were compliant with the Health Insurance Portability and Accountability Act of 1996. All trial participants provided written informed consent, and Independent Ethics Committee/Institutional Review Board approval was obtained for these trials.

Conflict of Interest Statement

M.S.: consulting fees: Aerie, Allegro, Alimera, Allergan, Eyepoint, Genentech, Kodiak, Novartis, Regeneron, and Santen; speakers bureau: Allergan, Eyepoint, Genentech, Novartis, Regeneron, and Spark; contracted research: Aerie, Allegro, Allergan, Alimera, DRCR, Genentech, Icon, Ionis, Kalvista, Kodiak, Novartis, Opthea, Optos, Regeneron, Santen, Senju, Sydnexis, and Ribomic; and equity: Aviceda, Nanoscope, and Inflammasome. A.M.K.: consulting fees: Adverum, Aerpio, Alcon, Allergan, Dutch Ophthalmic Research Center, Graybug, Gemini Therapeutics, Genentech, Inc., Gyroscope, Kato Pharmaceuticals, Kodiak Sciences Inc., Novartis, Opthea, Oxurion, PolyPhotonix, Recens Medical, and Regenxbio; research support: Adverum, Alkahest, Allergan, Allegro, Gemini Therapeutics, Genentech, Inc., Gyroscope, Iveric Bio, Kodiak Sciences Inc., NGM Pharmaceuticals, Novartis, Opthea, Oxurion, Regenxbio, and Recens Medical; and lecture fees: Allergan, Genentech, and Novartis. A.W.: consulting fees: Alimera, Bayer, Roche, Novartis, Oertli, Optos, and Zeiss and contracted research: Allergan, Alimera, Bayer, Ophthea, Optos, and Roche. R.F.: consulting fee: Allergan, Bayer, Novartis, and Roche. J.C.: consulting fees: Allergan, Biogen, and Salutaris. G.B.: employed by and holds shares in Novartis Pharmaceuticals Corporation. A.C.: employed by and holds shares in Novartis Pharma AG. K.G.: employee: Novartis Pharmaceuticals Corporation. X.L.: employee: Novartis Pharmaceuticals Corporation. Z.M.: employee: Novartis Pharma AG. G.Q.: consulting fees/advisor: Alimera Sciences Inc., Allegro, Allergan, Apellis, Baush & Lomb, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, CenterVue, Heidelberg Engineering, Nevacar, Novartis Pharmaceuticals Corporation, Roche, SIFI, Topcon, Thea, and Zeiss.

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Author Contributions

Michael Singer, Arshad M Khanani, Armin Wolf, Rita Flores, Jay Chhablani, and Giuseppe Querques: writing – review and editing; critical appraisal and interpretation of scientific content; and final approval. Guruprasad B, Andreas Clemens, and Kinfemichael Gedif: conceptualization; critical appraisal and interpretation of scientific content; and writing – original draft. Xiaoxi Liu and Zufar Mulyukov: conceptualization, data curation, formal analysis, and validation.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Lanzetta P, Loewenstein A, Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. Graefes Arch Clin Exp Ophthalmol. 2017;255(7):1259–73.

2 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419–31.

3 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432–44.

4 Spooner KL, Mhlanga CT, Hong TH, Broadhead GK, Chang AA. The burden of neovascular age-related macular degeneration: a patient's perspective. Clin Ophthalmol. 2018;12:2483–91.

5 Mones J, Singh RP, Bandello F, Souied E, Liu X, Gale R. Undertreatment of neovascular age-related macular degeneration after 10 years of anti-vascular endothelial growth factor therapy in the real world: the need for a change of mindset. Ophthalmologica. 2020;243(1):1–8.

6 Dugel PU, Singh RP, Koh A, Ogura Y, Weissgerber G, Gedif K, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2021;128(1):89–99.

7 Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2020;127(1):72–84.

8 Regula JT, Lundh von Leithner P, Foxton R, Barathi VA, Cheung CM, Bo Tun SB, et al. Targeting key angiogenic pathways with a bispecific crossMAb optimized for neovascular eye diseases. EMBO Mol Med. 2016;8(11):1265–88.

9 Clinicaltrials.gov. A Study to evaluate the efficacy and safety of faricimab in participants with neovascular age-related macular degeneration (TENAYA). Available from: www.clinicaltrials.gov/ct2/show/NCT03823287 (accessed April 17, 2021.

10 Clinicaltrials.gov. A Study to evaluate the efficacy and safety of faricimab in participants with neovascular age-related macular degeneration (LUCERNE). Available from: www.clinicaltrials.gov/ct2/show/NCT03823300 (accessed April 17, 2021.

11 Roche. Angiogenesis highlights 2021. Roche Analyst Webcast. 2021 Feb 16. Available from: www.roche.com/dam/jcr:1a6c3f66-3d4f-4d07-8eb6-28e81c7e1cc2/en/angiogenesis-2021.pdf (accessed April 17, 2021.
12 Khanani AM, Patel SS, Ferrone PJ, Osborne A, Sahni J, Grzeschik S, et al. Efficacy of every four monthly and quarterly dosing of faricimab versus ranibizumab in neovascular age-related macular degeneration: the STAIRWAY phase 2 randomized clinical trial. JAMA Ophthalmol. 2020;138(9):964–72.
13 Holz FG, Dugel PU, Weissgerber G, Hamilton R, Silva R, Bandello F, et al. Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a Randomized Controlled Study. Ophthalmology. 2016;123(5):1080–9.
14 Dugel PU, Jaffe GJ, Sallstig P, Warburton J, Weichselberger A, Wieland M, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. Ophthalmology. 2017;124(9):1296–304.