Identifying Features on Fundus Photos, OCT, or Fluorescein Angiography to Diagnose Polypoidal Choroidal Vasculopathy Without ICG Angiography

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OBJECTIVE To explore the sensitivity, specificity, and predictive accuracy of potentially diagnostic features from fundus photos, OCT, or fluorescein angiography to diagnose PCV without ICG angiography.

PURPOSE Indocyanine green angiography (ICGA) is a gold standard to diagnose polypoidal choroidal vasculopathy (PCV). However, it adds expense, is invasive, and not always available. This study explores the sensitivity, specificity, and predictive accuracy of potentially diagnostic features on fundus photos (FP), OCT, and fluorescein angiography (FA) to diagnose PCV without ICGA.

METHODS With IRB approval, 124 eyes of 120 subjects presenting from January 2013 to December 2016 with newly-identified serous/serosanguinous maculopathy that had FP, OCT, FA and ICGA before treatment at an eye center in Thailand were enrolled. De-identified images of FP alone, OCT alone, and FA alone were graded by 3 retina specialists masked to ICGA findings for possible features of PCV pre-specified before grading compared with gold standard grading for PCV by 2 other retina specialists with access to FP, OCT, FA and ICGA. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), predictive accuracy from area under the ROC curve (AUC) were determined.

RESULTS The mean age (±SD) was 57.7 (±12.6), 43% were female, and, based on the gold standard of the two retina specialists who had access to FP, OCT, FA, and ICGA 52% had PCV,

36% had central serous chorioretinopathy, and 10% had typical neovascular AMD not considered PCV. Potentially diagnostic features for PCV included the following: 1) FP: notched/hemorrhagic PED (AUC 0.76, 95%CI: 0.69-0.84); 2) OCT: PED notch (AUC 0.88, 95%CI: 0.82-0.93); 3) OCT: sharply peaked PED (AUC 0.84, 95%CI: 0.77-0.90); and 4) OCT: hyperreflective ring (AUC 0.84, 95%CI: 0.77-0.90). When at least 2 of these 4 signs presented, the AUC was 0.93 (95%CI: 0.89-0.98) with 0.95 sensitivity (95%CI: 0.87-0.99), 0.95 specificity (95%CI: 0.82-0.97), 0.92 PPV (95%CI: 0.83-0.97), and 0.95 NPV (95%CI: 0.86-0.99).

CONCLUSION These data suggest potentially diagnostic features on fundus photography and OCT provide high sensitivity and specificity of PCV diagnosis, especially when at least 2 of 4 highly suggestive signs are present, including a notched or PED on FP or OCT, a sharply peaked PED or a hyper-reflective ring on OCT.

Table 1. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy (area under the curve) of multiple potentially diagnostic features from fundus photos, OCT, and fluorescein angiography for polypoidal choroidal vasculopathy in absence of ICG

Major Criteria*	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	AUC (95%CI)
≥1 of 4 Major criteria	0.98 (0.92-1.00)	0.67 (0.53-0.78)	0.76 (0.65-0.85)	0.98 (0.87-1.00)	0.83 (0.76-0.89)
≥2 of 4 Major criteria	**0.95 (0.87-0.99)**	**0.95 (0.82-0.97)**	**0.92 (0.83-0.97)**	**0.95 (0.86-0.99)**	**0.93 (0.89-0.98)**
≥3 of 4 Major criteria	0.84 (0.73-0.92)	0.95 (0.86-0.99)	0.95 (0.85-0.99)	0.85 (0.74-0.93)	0.90 (0.84-0.95)
≥ 4 of 4 Major criteria	0.53 (0.40-0.66)	0.97 (0.88-1.00)	0.94 (0.81-0.99)	0.66 (0.55-0.76)	0.75 (0.68-0.81)
Major + Minor Criteria*					
1 Major + ≥1 Minor	0.03 (0.00-0.11)	0.83 (0.71-0.92)	0.17 (0.02-0.48)	0.45 (0.35-0.54)	0.43 (0.38-0.48)
1 Major + ≥2 Minor	0.03 (0.00-0.11)	1.00 (0.94-1.00)	1.00 (0.16-1.00)	0.49 (0.40-0.58)	0.52 (0.49-0.54)

*Features classified as major criteria in this study were notched/hemorrhagic pigment epithelial detachment (PED) on color fundus photography, sharply peaked PED on optical coherence tomography (OCT), notched PED on OCT, and hyperreflective ring underneath PED on OCT; any other features evaluated in this study and not mentioned above were classified as minor criteria

AUC = area under the receiver operating characteristic curve; 95%CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value

HUMAN RESEARCH Yes: Approved by institutional review board

EVEREST II Study: Evaluation of Indocyanine Green Angiographic Features in Symptomatic Macular Polypoidal Choroidal Vasculopathy Over 24 Months

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OBJECTIVE To determine how the polyp and branching vascular network area changes with treatment in Polypoidal choroidal vasculopathy

PURPOSE To evaluate changes in polyps and the branching vascular network (BVN) in patients with symptomatic macular polypoidal choroidal vasculopathy (PCV).

METHODS EVEREST II was a 24-month, randomized, multicenter study. 322 patients diagnosed with PCV were randomized 1:1 to ranibizumab (RBZ) and verteporfin photodynamic therapy (vPDT) combination therapy (n=168) or RBZ monotherapy (n=154). Indocyanine green angiography (ICGA) were graded by the central reading center at baseline, Months 3, 6, 12, and 24.

RESULTS At baseline, the number of polyps in both treatment arms was comparable. At Month 12, combination therapy was superior to RBZ monotherapy in achieving complete polyp regression (CPREG; 69.7% vs 33.8%; $p<0.0001$) and this superiority was maintained at 24 months (56.6% vs 26.7%; $p<0.0001$). In the combination arm, the proportions of patients with CPREG were comparable at Months 3, 6, and 12 (71.4%, 71.3% and 69.7%, respectively) with a slight decrease at Month 24 (56.6%). In the monotherapy arm, the proportion increased from 21.7% at Month 3 to 30.4% at Month 6 and 32.6% at Month 12, decreasing slightly at Month 24 (26.7%). The percent reduction in polyp size from baseline was numerically higher in the combination arm than in the monotherapy arm: 65.2% vs 32.8% at Month 12 and 52.3% vs 33.7% at Month 24. Active BVN size increased from baseline in both treatment arms.

CONCLUSION RBZ and vPDT combination therapy was superior to RBZ monotherapy in PCV patients in terms of CPREG and was more effective in reducing polyp size and regulating BVN size over 24 months.

HUMAN RESEARCH Yes: Approved by institutional review board

Dual Targeting VEGF/Ang2 Surrobody in an Experimental Model of Neovascularization

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- Joshua Logan Morgenstern

OBJECTIVE To determine the safety and efficacy of a novel drug to inhibit choroidal neovascularization

PURPOSE Choroidal neovascularization (CNV) is the leading cause of severe vision loss in age-related macular degeneration (AMD). Pro-angiogenic factors such as VEGF and Angiopoietin-2 (Ang2) are elevated in AMD and correlated with disease severity. The aim of this study was to assess and compare the therapeutic efficacy of novel surrobody (surrogate antibody), a bispecific inhibitor of VEGF and ANG2.

METHODS Surrobody was tested prospectively and in a masked fashion in four areas: target binding affinity, biocompatibility, intravitreal half-life, and anti-angiogenesis. First, testing was done for affinity to VEGF and Ang-2 using ELISA and surface plasmon resonance (SPR) spectroscopy. Next, biocompatibility was tested in Brown Norway rats (n =10 eyes) with serial electroretinography and histology. Intraocular half-life was determined by fluorescein labeling in New Zealand White Cross rabbits (n= 6 eyes), taking serial photofluorometer measurements. Finally, inhibition of CNV in a laser induced model using Brown Norway rats (n=20 eyes) was evaluated and compared with aflibercept.

RESULTS Surrobody demonstrated a high affinity for both VEGF and Ang2 on SPR spectrospcopy and ELISA testing, with a dissociation constant of 61.5 pM. The intravitreal half-life as measured by photospectometry was 6.75 days. Biocompatibility testing as measure by serial ERGs and histology demonstrated no adverse effects. In terms of efficacy, CNV area was decreased by 60% and 53% in eyes receiving surrobody and afilbercept treatment, respectively, compared to

the BSS administration (p=0015, one-way ANOVA). Reduction of CNV area in surrobody treated eyes was found to be statistically significant compared to afilbercept (p=.028).

CONCLUSION With a high affinity for both VEGF and Ang2, a longer intravitreal half-life than current therapeutics, good biocompatibility, and demonstrated efficacy against neovascularization, the new surrobody compound may prove to be a useful addition in treating diseases such as exudative macular degeneration and diabetic retinopathy. Further testing is underway.

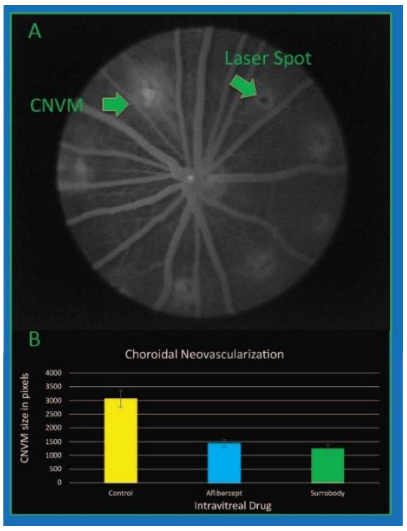

Figure 1: Inhibition of CNVM. A) Fundus photograph depicting CNVM growth after laser induction. B) Surrobody reduced CNV growth by 53%, more inhibition than both control and aflibercept.

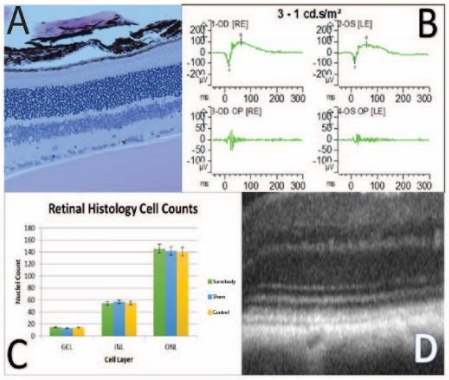

Figure 2: Surrobody Biocompatibility. Two months after intravitreal injection, all eyes demonstrated normal A) histology, B) ERGs, C) cell counts, and D) optical coherence tomography.

HUMAN RESEARCH No: Study does not involve

Extended Q16W Dosing Potential for Faricimab in Neovascular Age-Related Macular Degeneration (nAMD): STAIRWAY Phase 2 Trial

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OBJECTIVE To present key results from the phase 2 STAIRWAY trial showing potential for extended faricimab dosing at q16w and q12w intervals in patients with neovascular age-related macular degeneration (nAMD).

PURPOSE Faricimab, the first bispecific antibody designed for intraocular use, binds and neutralizes both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). Ang-2 signaling can drive vascular destabilization and microvascular inflammation. STAIRWAY (NCT03038880) evaluated extended faricimab dosing at 16- (q16w) and 12-week (q12w) intervals in patients with nAMD.

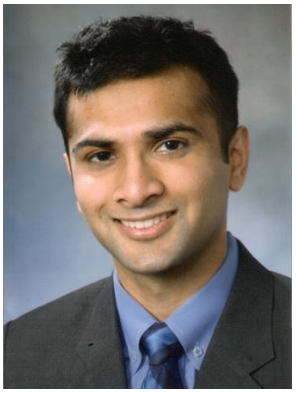
METHODS STAIRWAY was a phase 2, 52-week trial that enrolled 76 patients aged ≥ 50 years with nAMD and new-onset choroidal neovascularization (CNV). Patients were randomized 2:2:1 to intravitreal 6.0 mg faricimab, q16w or q12w after initiation, or 0.5 mg ranibizumab every 4 weeks (q4w). The primary objective was to evaluate efficacy of faricimab administered at q16w and q12w intervals, assessed by best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letter score). Disease assessment was performed at week 24, 12 weeks after last loading dose, and any q16w faricimab–assigned patients with active disease per protocol-specified criteria received q12w treatment through trial end.

RESULTS Baseline demographic and ocular characteristics were well balanced. A disease assessment was performed at week 24 according to prespecified criteria, which included: BCVA, central subfield thickness (CST), presence of new macular hemorrhage, and clinical signs of disease activity that in the investigator's opinion required immediate treatment. At week 24, 65% (36/55) of faricimab-treated patients had no disease activity 12 weeks after their previous injection. Initial BCVA improvements for faricimab-treated patients were fully maintained with q16w and q12w dosing. At week 52, q16w faricimab–, q12w faricimab–, and q4w ranibizumab–treated patients had a mean BCVA change from baseline of 11.4, 10.1, and 9.6 letters, respectively, with 46.4%, 33.3%, and 37.5% of patients, respectively, gaining ≥ 15 letters from baseline. CST and CNV lesion size reductions with q16w and q12w faricimab were comparable with q4w ranibizumab. No new or unexpected safety signals were identified.

CONCLUSION Both BCVA gains and anatomic improvements with q16w and q12w faricimab were comparable with q4w ranibizumab treatment. Combined inhibition of Ang-2 and VEGF with faricimab may extend durability of response and address an important need for patients with nAMD. A global phase 3 program assessing extended interval dosing with faricimab will commence in 2019.

HUMAN RESEARCH Yes: Approved by institutional review board

96-Week Visual and Expanded Anatomical Outcomes of Brolucizumab Versus Aflibercept in Patients With nAMD: Results From HAWK and HARRIER



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- Robin Hamilton, Mr
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OBJECTIVE Comparative assessment of the 96-week outcomes in patients with neovascular age-related macular degeneration (nAMD) treated with brolucizumab or aflibercept.

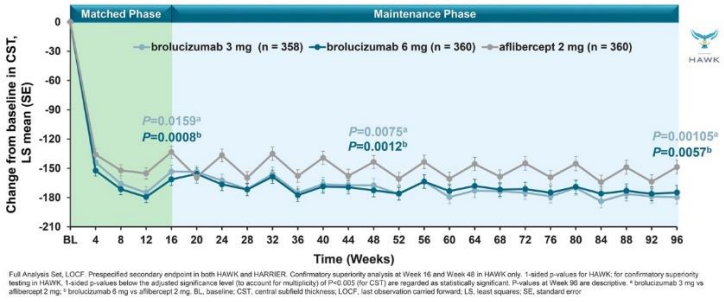
PURPOSE HAWK and HARRIER are two Phase III, prospective studies investigating the efficacy and safety of brolucizumab (Bro) 3 and 6mg compared with aflibercept (Afl) 2mg in patients with nAMD. The present analysis reports the 96-week vision and anatomic outcomes of Bro versus Afl in patients with nAMD.

METHODS Patients (Pts) were randomized 1:1:1 to Bro 3mg (n=358), 6 mg (n=360) or Afl 2mg (n=360) [HAWK], or 1:1 to Bro 6mg (n=370) or Afl 2mg (n=369) [HARRIER]. After three loading doses (baseline, Week (Wk) 4, Wk 8), Bro patients were treated every 12 weeks (q12w), with an option to adjust to 8-week dosing (q8w) during the first q12w treatment interval and at predefined disease activity assessment visits; Afl was dosed in a fixed q8w regimen after the loading dose as per label.

RESULTS Bro was non-inferior to Afl in mean BCVA change at Wk 48 and the visual gains were maintained to Wk 96. Bro achieved superior reductions in CST from baseline to Wk 16 and Wk 48, and these were maintained at Wk 96 (HAWK: P=0.0010 [Bro 3mg vs Afl]; P=0.0057 [Bro 6mg vs Afl] – Fig1); HARRIER: P<0.0001 – Fig2). The proportions of pts with IRF and/or SRF at Wk 96 in HAWK were 31% (P=0.0344) for Bro 3mg, 24% (P=0.0001) for Bro 6mg, and 37% for Afl; and in HARRIER were 24% (P <0.0001) for Bro 6mg and 39% for Afl. The proportions of pts with sub-RPE fluid at Wk 96 in HAWK were 14%, 11% for Bro 3mg, 6mg, and 15% for Afl; and in HARRIER were 17% (P=0.0371) for Bro 6mg and 22% for Afl. The proportions of pts who were fluid-free at Wk 96 were higher for Bro 6mg than Afl in HAWK (71.3% [Bro]; 58.8% [Afl], P=0.0006) and HARRIER (64.8% [Bro]; 52.4% [Afl], P=0.0009). These outcomes were achieved with >75% of Bro 6mg pts who completed Wk 48 on a q12w interval remaining on a q12w interval until Wk 96.

CONCLUSION The superior anatomic outcomes in IRF and/or SRF and CST at Wk 16 and Wk 48 along with the comparable vision gains seen with Bro 6mg versus Afl 2mg at Wk 48, were maintained at Wk 96, with a high proportion of Bro pts maintained on a q12 dosing interval immediately after loading. Pts on Bro achieved better fluid control compared with Afl through Wk 96.

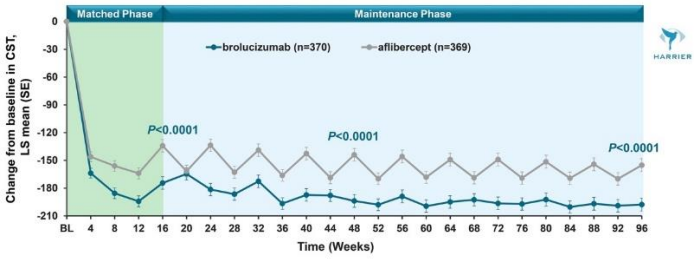
Fig 1. HAWK: Change in CST from baseline to Week 96



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; for confirmatory superiority testing in HAWK, 1-sided p-values below the adjusted significance level (to account for multiplicity) of P<0.003 (for CST) are regarded as statistically significant. P-values at Week 96 are descriptive. [a] brolucizumab 3 mg vs aflibercept 2 mg; [b] brolucizumab 6 mg vs aflibercept 2 mg. BL, baseline; CST, central subfield thickness; LOCF, last observation carried forward; LS, least squares; SE, standard error

Fig 1. HAWK: Change in CST from baseline to Week 96

Fig 2. HARRIER: Change in CST from baseline to Week 96



Full Analysis Set, LOCF. Prespecified secondary endpoint in HARRIER. 1-sided p-values for HARRIER. P-values are descriptive. BL, baseline; CST, central subfield thickness; LOCF, last observation carried forward; LS, least squares; SE, standard error

Fig 2. HARRIER: Change in CST from baseline to Week 96

HUMAN RESEARCH Yes: Approved by institutional review board

Time to Dry Analysis of Brolucizumab Versus Aflibercept in Patients With Neovascular AMD: 96-Week Data From HAWK and HARRIER Trials

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OBJECTIVE To compare the treatment outcomes between brolucizumab and aflibercept with respect to time to achieve sustained dryness through the 96 week in the HAWK and HARRIER studies

PURPOSE HAWK and HARRIER are two phase III, prospective studies investigating the efficacy and safety of brolucizumab in comparison to aflibercept in patients with neovascular age-related macular degeneration (nAMD). The present analysis reports the 96-week treatment outcomes with respect to time to dryness with brolucizumab (Bro) versus aflibercept (Afl) in patients with neovascular AMD.

METHODS Patients (Pts) were randomized 1:1:1 to Bro 3mg (n=358), 6 mg (n=360) or Afl 2mg (n=360) [HAWK], or 1:1 to Bro 6mg (n=370) or Afl 2mg (n=369) [HARRIER]. After three loading doses (baseline, Week (Wk) 4, Wk 8), Bro patients were treated every 12 weeks (q12w), with an option to adjust to 8-week dosing (q8w) during the first q12w treatment interval and at predefined disease activity assessment visits; Afl was dosed in a fixed q8w regimen after the loading dose as per label.

RESULTS In HAWK and HARRIER, Bro was non-inferior to Afl in mean BCVA change from baseline at Wk 48 (primary endpoint) and the visual gains were maintained to Wk 96. The cumulative incidence rate (%) in study eyes with sustained dryness (absence of for ≥ 2 or ≥ 3 consecutive visits) was greater for Bro compared to Afl at Wk 48 [HAWK: ≥ 2/≥ 3 visits (Bro 3mg-82.9/77.1, Bro 6mg-86.4/79.1, Afl-76.4/67.6); HARRIER: ≥ 2/≥ 3 visits (Bro 6mg-91.5/85.9, Afl-81.2/72.7)]. The 50^{th} percentile for sustained dryness was achieved earlier for patients on Bro with most achieving ≥ 2/≥ 3 visits by Wk 8/8 in HAWK and Wk 4/4 in HARRIER compared to Afl (HAWK:≥ 2/≥ 3 visits: Wk 8/12; HARRIER: Wk 8/8]). The 75^{th} percentile was also achieved earlier with Bro compared to Afl (≥ 2/≥ 3 visits: HAWK-[Bro 3mg-Wk 24/40, Bro 6mg-Wk 16/32, Afl-Wk 40/not achieved]; HARRIER: [Bro 6mg-Wk 8/20, Afl-Wk20/not achieved]. The rates of sustained dryness and incidence rates per patient year through 96 Wk will also be presented.

CONCLUSION The comparable vision gains achieved with brolucizumab 6mg versus aflibercept 2mg at Wk 48 were maintained at Wk 96. Patients treated with brolucizumab are more likely to achieve sustained dryness than those treated with aflibercept in HAWK and HARRIER. Brolucizumab also achieved better fluid control faster than aflibercept.

HUMAN RESEARCH Yes: Approved by institutional review board