Phase 3 in Retina: The Trials to Know


This review will help you understand where several potentially important studies stand.

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Clinical trials now under way or recently completed have the potential to make new therapeutic options available soon for our patients with age-related macular degeneration (AMD) and diabetic eye disease. In this article, we outline recently completed or ongoing phase 3 trials and the data available for brolucizumab (Beovu, Novartis), abicipar pegol (Allergan), faricimab (Roche), and the Port Delivery System (PDS; Genentech).

BROLUCIZUMAB: HAWK AND HARRIER

The completed HAWK and HARRIER studies were parallel randomized, double-masked, multicenter phase 3 trials investigating the efficacy and safety of the anti-VEGF agent brolucizumab in the treatment of wet AMD.[1] HAWK and HARRIER compared brolucizumab with aflibercept (Eylea, Regeneron); they are the only trials comparing these drugs to date.

Researchers gathered data from 408 sites in North, Central, and South America; Europe; Asia; Australia; and Japan. Eligibility criteria required patients to be at least 50 years old, to be treatment-naïve, and to have demonstrated active choroidal neovascularization lesions secondary to AMD affecting the central subfield. Snellen VA equivalent range for inclusion was 20/32 to 20/400.[1]

Study Design

In HAWK, patients were randomly assigned in a 1:1:1 ratio to one of three groups: brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. In HARRIER, patients were randomly assigned in a 1:1 ratio to brolucizumab 6 mg or aflibercept 2 mg.

After three monthly loading doses, patients in the brolucizumab groups received treatment every 12 weeks; there was an option to adjust dosing to every 8 weeks based on masked assessments of disease activity at defined visits. Patients in the aflibercept group received treatment every 8 weeks at the time of study initiation, which is consistent with that drug's US FDA labeling.[2]

HAWK enrolled 1,082 patients and HARRIER 743. Demographics and baseline ocular characteristics were similar across groups in both trials. Both trials had high completion rates. The primary endpoint was noninferiority of mean BCVA change in the brolucizumab groups compared with aflibercept from baseline to week 48. Secondary endpoints included central subfield retinal thickness, retinal fluid (intraretinal and/or subretinal fluid), and disease activity.

Results

Brolucizumab met the primary endpoint of the trial and showed superiority in secondary endpoints.[1]

In HAWK, eyes treated with brolucizumab 3 mg and brolucizumab 6 mg gained 6.1 and 6.6 letters, respectively, compared with 6.8 letters in aflibercept-treated eyes (95% CI for

AT A GLANCE

- The approval of brolucizumab (Beovu, Novartis) gives retina specialists a new option for treating wet AMD.
- The DARPin abicipar pegol (Allergan) and the bispecific antibody faricimab (Roche) are both in phase 3 trials.
- The phase 3 ARCHWAY study of the Port Delivery System (Genentech) for wet AMD is fully enrolled.

treatment difference, -2.5 to 1.3; $P < .001$ for noninferiority; 95% CI for treatment difference, -2.1 to 1.8; $P < .001$ for noninferiority, respectively, for the 3 mg and 6 mg groups). In HARRIER, eyes treated with brolucizumab 6 mg gained 6.9 letters compared with 7.6 letters in aflibercept-treated eyes (95% CI for treatment difference, -2.4 to 1.0; $P < .001$ for noninferiority).[1] Figure 1 displays this data graphically.

The probabilities for maintaining 12-week dosing after loading through week 48 were 49.4% in the 3 mg group (95% CI for Kaplan-Meier estimate, 43.9–54.6%) and 55.6% in the 6 mg group (95% CI, 50.2–60.8%) in HAWK, and 51.0% in the 6 mg group (95% CI , 45.7–56.1%) in HARRIER. In patients who received brolucizumab who did not show disease activity during the initial 12 weeks, the probabilities for remaining on 12-week dosing up to week 48 increased to 80.9% in the 3 mg group (95% CI, 74.5–85.7%) and 85.4% in the 6 mg group (95% CI , 79.9–89.5%) in HAWK and 81.7% in the 6 mg group (95% CI, 75.8–86.3%) in HARRIER.

Adverse events were similar across groups in both trials. Of note, in HAWK, the incidence of uveitis was 2.2% and of iritis was 2.2% in the brolucizumab 6 mg group compared with 0.3% and 0.0%, respectively, in the aflibercept group; corresponding rates in HARRIER were less than 1.0% in both arms.[1]

In October, the FDA approved brolucizumab for the treatment of wet AMD. The labeling specifies 6 mg (0.05 mL) monthly for three doses followed by one dose of 6 mg (0.05 mL) every 8 to 12 weeks.[3]

It remains to be seen how real-world performance will stack up against the phase 3 clinical trial data and how quickly physicians will adopt use of this anti-VEGF option. The addition of brolucizumab to the retina specialist's armamentarium could reshape the landscape of wet AMD

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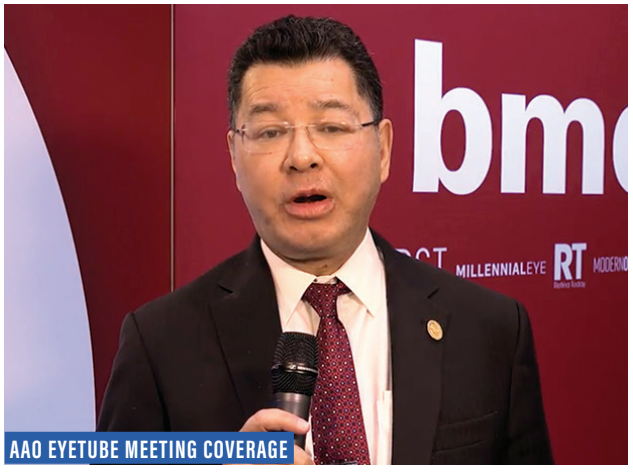

J. Fernando Arevalo, MD, PhD, FACS, discusses HAWK and HARRIER.

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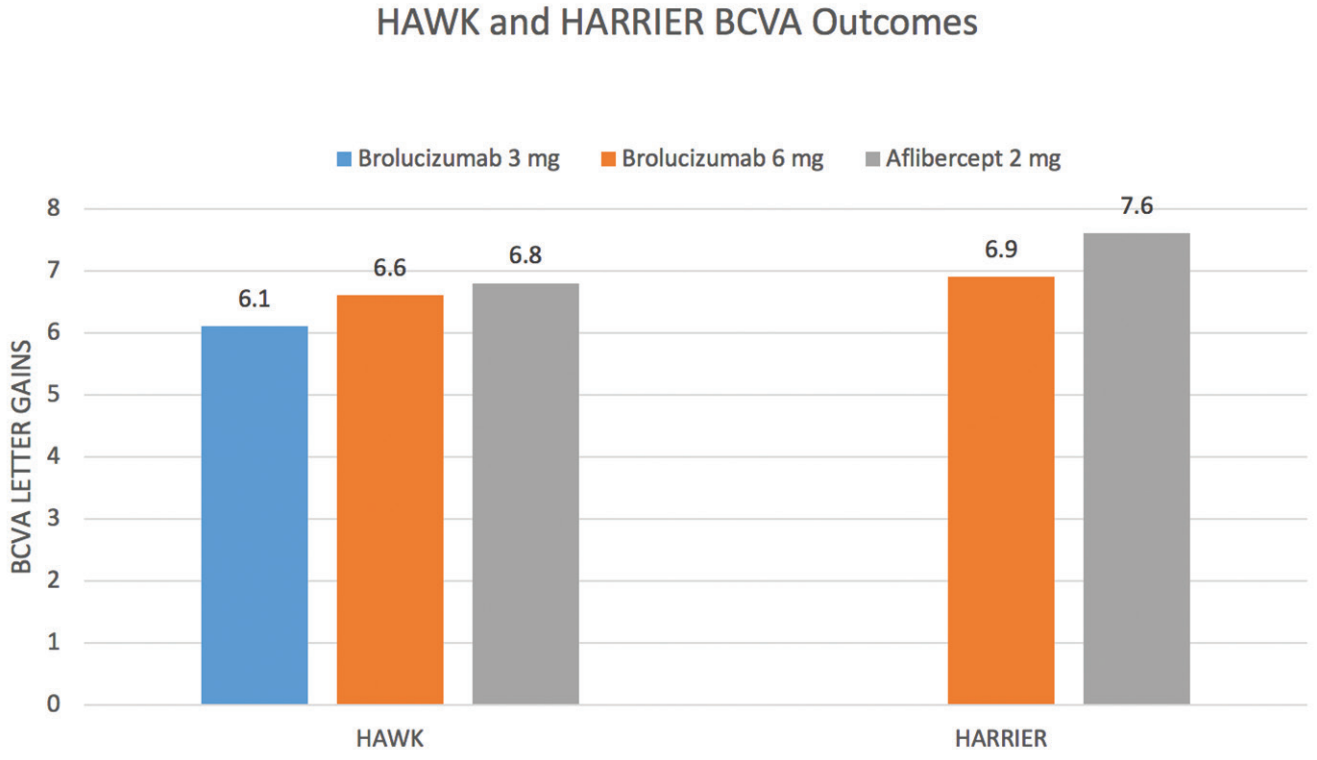

Figure 1. Patients in HAWK and HARRIER demonstrated no statistically significant difference in BCVA gains over the course of the study comparing brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg. This occurred despite more than half of patients receiving brolucizumab 6 mg at 12-week dosing compared with 8-week dosing in the aflibercept arm.

management. For the first time, retina doctors will have an anti-VEGF option indicated for injection as infrequently as every 3 months. The extended durability of this drug may reduce the treatment burden on a patient population that is subject to frequent visits and injections with current options. We look forward to learning more about the drug's use and performance in real-world settings.

ABICIPAR PEGOL: CEDAR, SEQUOIA, AND MAPLE

The SEQUOIA and CEDAR studies were phase 3 multicenter, randomized, controlled trials that compared abicipar to ranibizumab (Lucentis, Genentech) for the treatment of wet AMD.

Abicipar utilizes a novel mechanism—designed ankyrin repeat proteins, or *DARPin technology*—to decrease VEGF levels. Whereas current anti-VEGF therapies are based on antibodies or antibody fragments, DARPin technology mimics antibodies, and compounds can be designed to have high specificity and affinity for a specific target. These proteins are smaller than antibodies, and it is expected that they may have better tissue penetration, high affinity that enables them to be active at lower concentrations, and increased stability leading to a longer lasting effect.

Study Design

CEDAR and SEQUOIA enrolled 1,888 patients with wet AMD. Researchers randomly assigned patients to one of three arms: abicipar 2 mg every 8 weeks after three monthly loading doses; abicipar 2 mg every 12 weeks after two monthly loading doses and a loading dose at week 12, and monthly ranibizumab injections.[4]

The primary endpoint of the study was the proportion of patients with stable vision, which was defined as a loss of less than 15 ETDRS letters, at week 52. Secondary endpoints included mean change from baseline in ETDRS BCVA, mean change from baseline in central retinal thickness, and proportion of patients with at least a 15-letter gain at week 52.

Results

In both studies, the 8-week and 12-week abicipar arms met the prespecified criteria for noninferiority to monthly ranibizumab treatment for the primary endpoint.[5] Initial visual gains for patients in the abicipar arms were maintained throughout week 52.[6]

The overall incidence of treatment-emergent adverse events was comparable among all three treatment groups. However, abicipar-treated patients had a higher risk of developing intraocular inflammation compared with ranibizumab-treated patients. Incidence of intraocular inflammation was similar among the two abicipar treatment arms (15.1% and 15.4% in the abicipar 8-week and 12-week arms, respectively), and was 0.0% in the ranibizumab arm.

MAPLE

MAPLE was a 28-week open-label study that enrolled 123 patients with wet AMD and evaluated the safety of abicipar produced using a modified manufacturing process. In MAPLE, the incidence of intraocular inflammation was 8.9%.[7] This was lower than the rate observed in the abicipar arms in the SEQUOIA and CEDAR studies but higher than the rate observed in the ranibizumab arms in those studies.

A biologics license application for abicipar was submitted to the FDA in September. Action on the filing is expected in 2020.

FARICIMAB: BOULEVARD, YOSEMITE, AND RHINE

Faricimab is a bispecific antibody designed specifically for the treatment of retinal diseases that simultaneously binds to and deactivates angiopoietin-2 (Ang-2) and VEGF-A. By targeting both Ang-2 and VEGF-A, faricimab may achieve sustained efficacy at longer treatment intervals.

BOULEVARD

BOULEVARD was a phase 2 multicenter, randomized, controlled trial comparing faricimab to ranibizumab in patients with diabetic macular edema. Patients who had never received ranibizumab treatment were randomly assigned in a 1:1:1 ratio to intravitreal 6.0 mg faricimab, 1.5 mg faricimab, or 0.3 mg ranibizumab; patients previously treated with an anti-VEGF agent were randomly assigned in a 1:1 ratio to 6.0 mg faricimab or 0.3 mg ranibizumab.[8,9]

Patients received dosed injections monthly for 20 weeks and were observed up to week 36 to assess durability. In the treatment-naïve patients, 6.0 mg faricimab, 1.5 mg faricimab,

and 0.3 mg ranibizumab resulted in mean improvements of 13.9, 11.7, and 10.3 ETDRS letters from baseline, respectively (Figure 2) The 6.0-mg faricimab dose demonstrated a statistically significant gain of 3.6 letters over ranibizumab (P = 0.03). Patients in the faricimab arms demonstrated a dose-dependent reduction in mean central subfield thickness and a longer mean time to retreatment during the observation period compared with ranibizumab.[8,9]

YOSEMITE and RHINE

YOSEMITE and RHINE are phase 3, randomized, controlled trials evaluating the safety and efficacy of faricimab versus aflibercept for the treatment of diabetic macular edema.[10,11] It should be noted that the comparator drug here is different; the phase 2 BOULEVARD trial compared faricimab to ranibizumab.

In each study, more than 900 patients are being randomly assigned to one of three arms: faricimab every 8 weeks, aflibercept every 8 weeks, or a personalized treatment schedule in which patients will be dosed according to the study protocol. The primary endpoint of each study is the change in BCVA from baseline at 1 year. YOSEMITE and RHINE completed enrollment in October.

PORT DELIVERY SYSTEM: LADDER AND ARCHWAY

The PDS is a device designed to provide sustained release of ranibizumab. The device is implanted surgically and can be refilled in an office setting.

LADDER

LADDER was a phase 2, randomized, controlled clinical trial evaluating the efficacy and safety of the PDS in patients with wet AMD. Patients were randomly assigned 3:3:3:2 to receive the PDS filled with ranibizumab 10 mg/mL, 40 mg/mL, 100 mg/mL; or monthly intravitreal ranibizumab 0.5 mg.

The primary endpoint was the time to first required PDS refill, which was determined to be 15 months, 13 months, and 8.7 months in the 100 mg/mL, 40 mg/mL, and 10 mg/mL groups, respectively. A dose response was seen across multiple endpoints in patients with wet AMD. The 100 mg/mL arm showed visual and anatomic outcomes comparable with monthly therapy with ranibizumab 0.5 mg but with a reduced total number of treatments.[12]

ARCHWAY

ARCHWAY is a phase 3, randomized, clinical trial comparing the PDS to intravitreal ranibizumab injection. In the trial, patients will be randomly assigned to receive PDS implantation with refills at fixed 24-week intervals of a special formulation of 100 mg/mL ranibizumab or monthly ranibizumab 0.5 mg therapy. The primary endpoint

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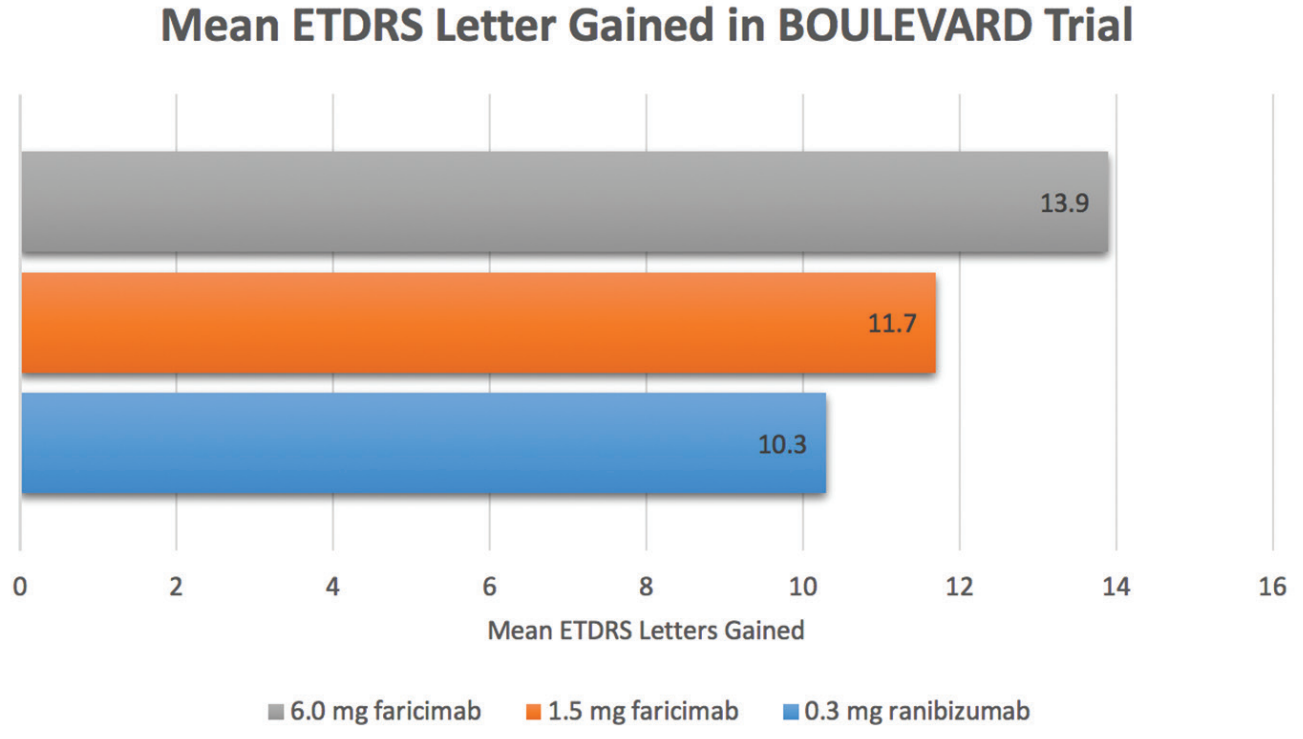

Figure 2. In the phase 2 BOULEVARD study, patients who received 6.0 mg faricimab demonstrated a greater mean gain of 13.9 ETDRS letters than those receiving 0.3 mg ranibizumab, who demonstrated a mean letter gain of 10.3 letters. The difference was statistically significant (P = .03).

(Continued from page 20)

of the study is noninferiority to ranibizumab as measured by change in BCVA averaged over weeks 36 and 40.[13]

ARCHWAY is fully enrolled.

CONCLUSION

Retina could be on the brink of a pharmacologic breakthrough not seen since the approval of ranibizumab in 2006. A new wave of available treatments could lead to a welcome shift in the landscape of therapeutic options for retinal disease. With the aging of the population and the increasing rate of diabetes, treatments with longer durations of effect and greater efficacy will be needed to reduce treatment burdens and increase access to care. We are hopeful that exciting breakthroughs may be on the horizon thanks to the number of pharmacotherapies in clinical trials that are nearing or now crossing the finish line of approval and clinical acceptance. ■

1. Dugel PU, Koh A, Ogura Y, et al; HAWK and HARRIER Study Investigators. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration [published online ahead of print April 12, 2019]. *Ophthalmology*.
2. Eylea (aflibercept) injection [package insert]. Tarrytown, New York: Regeneron Pharmaceuticals; July 2014.
3. Beovu (brolucizumab) injection [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals; October 2019.
4. Safety and efficacy of abicipar pegol in patients with neovascular age-related macular degeneration. ClinicalTrials.gov identifier: NCT02462486. https://clinicaltrials.gov/ct2/show/NCT02462486. Accessed October 21, 2019.
5. A safety and efficacy study of abicipar pegol in patients with neovascular age-related macular degeneration (CDER). ClinicalTrials.gov identifier: NCT02462928. https://clinicaltrials.gov/ct2/show/NCT02462928. Accessed October 21, 2019.
6. Khurana R. Abicipar for neovascular age-related macular degeneration: two-year results from CEDAR and SEQUOIA phase 3 clinical trials. Paper presented at: American Academy of Ophthalmology Annual Meeting; October 2019; San Francisco.
7. Allergan and Molecular Partners announce topline safety results from MAPLE study of abicipar pegol [press release]. Dublin, Ireland: Molecular Partners; April 2, 2019.
8. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-a with faricimab in diabetic macular edema. *Ophthalmology*. 2019;126(8):1155-1170.
9. A study of faricimab (RO6867461) in participants with center-involving diabetic macular edema (BOULEVARD). ClinicalTrials.gov identifier: NCT02699450. https://clinicaltrials.gov/ct2/show/NCT02699450. Accessed October 21, 2019.
10. A study to evaluate the efficacy and safety of faricimab (RO6867461) in participants with diabetic macular edema (YOSEMITE). ClinicalTrials.gov identifier: NCT03622580. https://clinicaltrials.gov/ct2/show/NCT03622580. Accessed October 21, 2019.
11. A study to evaluate the efficacy and safety of faricimab (RO6867461) in participants with diabetic macular edema (RHINE). ClinicalTrials.gov identifier: NCT03622593. https://clinicaltrials.gov/ct2/show/NCT03622593. Accessed October 21, 2019.
12. Campochiaro PA, Marcus DM, Awh CC, et al. The port delivery system with ranibizumab for neovascular age-related macular degeneration: results from the randomized phase 2 LADDER clinical trial. *Ophthalmology*. 2019;126(8):1141-1154.
13. A phase III study to evaluate the port delivery system implant with ranibizumab compared with monthly ranibizumab injections in participants with wet age-related macular degeneration (ARCHWAY). ClinicalTrials.gov identifier: NCT03677934. https://clinicaltrials.gov/ct2/show/NCT03677934. Accessed October 21, 2019.

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