

A NOVEL COMPOUND FOR TREATMENT OF WET AMD

Clinical studies are evaluating a new anti-VEGF agent's potential to join current treatment options.

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Age-related macular degeneration (AMD) is a leading cause of visual acuity loss in the United States and other Western nations.¹ The majority of visual acuity loss occurs as a result of choroidal neovascularization (CNV); other causes include geographic atrophy (GA) and neovascular changes with associated subretinal fluid or hemorrhage.¹ Neovascular changes occur when abnormal choroidal vessels violate the blood-retina barrier and penetrate the Bruch membrane.¹

These vessels can leak fluid or hemorrhage, leading to permanent visual acuity loss.¹ Fibrovascular proliferation can also accompany these changes and lead to permanent, irreversible visual acuity loss.¹

The standard of care treatment for wet AMD is anti-VEGF therapy. Aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentech) are two anti-VEGF treatments approved by the US Food and Drug Administration for treatment of neovascular AMD. Typically, the anti-VEGF drug is injected into the vitreous, where it binds to abnormal VEGF proteins and prevents them from stimulating further blood vessel growth and leakage. Although patient response to treatment varies, many require monthly injections. Newer drugs pending approval and alternative delivery methods are being developed with intent to reduce the frequency of injections, prolong the interval of treatment, and thereby improve patients' quality of life and reduce costs.

This article describes a potential new entry into the category of ophthalmic VEGF inhibitors, now being evaluated in a series of clinical trials: brolicizumab (Alcon), a humanized, single-chain antibody fragment inhibitor of VEGF-A.²⁻⁴

BROLUCIZUMAB

In vitro studies showed that brolicizumab (formerly known as RTH258 and ESBA1008) binds to all isoforms of VEGF-A

including VEGF 165, and animal studies found that it was well-tolerated in cynomolgus monkeys with no ocular or systemic toxicity.^{2,4} Brolicizumab is the smallest anti-VEGF molecule tested in humans to date, with a molecular weight of 26 kDa. By comparison, the molecular weights of aflibercept and ranibizumab are 97 kDa and 48 kDa, respectively (Figure 1).^{4,5} The designed ankyrin repeat protein molecule MP0112 (abicipar pegol, Allergan), has an even smaller molecular weight of 34 kDa and inhibits all forms of VEGF.

In animals, brolicizumab was administered safely in doses up to 6000 µg, with less than one-fourth the systemic exposure of other anti-VEGF agents.^{3,5} Its smaller molecular size and high affinity allow exceptional tissue penetration and administration of higher drug concentrations, the combination of which could potentially lead to a longer treatment effect and thereby reduce the treatment frequency and burden for patients.^{3,5,7} Following is an overview of the human trials involving brolicizumab.



AT A GLANCE

- Brolicizumab is a humanized, single-chain antibody fragment inhibitor of VEGF-A.
- In the randomized OSPREY study of treatment-naïve patients with neovascular AMD, those who received brolicizumab tolerated it well. Additionally, the drug was shown to be noninferior to aflibercept.
- In the phase 2 OWL study, a primary efficacy signal was detected, with responder rates of 70% and 80% in the brolicizumab injection arms in stages 1 and 2, respectively, and of 60% in brolicizumab infusion arms in both stages.
- Use of brolicizumab in combination with the Posterior MicroPump may represent a way to reduce the treatment burden for patients and physicians.



Figure 1. With a molecular weight of 26 kDa, brolucizumab is the smallest anti-VEGF molecule tested in humans to date.

CLINICAL TRIAL BREAKDOWN

Brolucizumab was first evaluated in humans in a phase 1/2, 6-month, ascending single-dose, double-masked study that compared the safety and efficacy of brolucizumab versus ranibizumab in 194 treatment-naïve patients with neovascular AMD.⁶⁻¹¹ In the dose-escalation phase, patients were randomly assigned to receive a single intravitreal injection of 0.5 mg, 3.0 mg, or 4.5 mg brolucizumab or 0.5 mg ranibizumab in a 5:2 randomization.⁶⁻¹¹ All doses were well-tolerated, and no drug-related targeted adverse events were reported in study eyes within 1 week of study drug injection.^{6,7}

Brolucizumab was then evaluated in a two-part dose-expansion phase. In the first part, patients were randomly assigned, 1:1, to either 4.5 mg brolucizumab or 0.5 mg ranibizumab, and in the second part patients were re-randomized, 5:30:35:9, to receive 0.5 mg, 3.0 mg, or 6.0 mg brolucizumab or 0.5 mg ranibizumab.⁷⁻¹¹ All randomized patients were evaluated for 6 months after

a single intravitreal injection administered at day 1.⁷ This phase 1/2 study met its primary objective by demonstrating noninferiority to ranibizumab in the change of central subfield thickness (CST) from baseline to month 1 after a single intravitreal injection of 4.5 mg or 6.0 mg brolucizumab.⁷⁻¹¹ In the 3.0-mg, 4.5-mg, and 6.0-mg brolucizumab groups, the change in BCVA showed improvement between day 28 and day 42, compared with a worsening trend in BCVA in the ranibizumab group after month 1.^{7,9} The results of this study showed a dose-dependent effect on BCVA and CST and continued to support a good safety profile for brolucizumab.⁷⁻¹¹

OSPREY

The phase 2, randomized, double-masked OSPREY study compared the safety and efficacy of repeated doses of brolucizumab or aflibercept.^{11,12} Treatment-naïve patients with neovascular AMD were randomly assigned, 1:1, to receive 6.0 mg brolucizumab or 2.0 mg aflibercept.^{11,12} The study's objective was to test the noninferiority of brolucizumab to aflibercept at weeks 12 and 16.^{11,12} Data from 89 patients were analyzed, and the results showed that the noninferiority criterion was met and that brolucizumab was well-tolerated.^{11,12}

OWL

Our company, Retina Research Center (RRC), participated in OWL, a phase 2 study evaluating the efficacy of microvolume injections or infusions of brolucizumab versus ranibizumab in treatment-naïve patients with neovascular AMD.^{3,8} Microvolume infusions were administered in the office over a 16-minute period via an external pump connected to a cannula placed in the

TABLE 1. SNAPSHOT OF OWL STUDY

Stage 1				
Cohort	Randomized Group	N	Day 0	Day 28
1	Microvolume brolucizumab injection	10	1.2 mg/10 μ L brolucizumab inj	6.0 mg/50 μ L brolucizumab inj
1	Ranibizumab injection	3	0.5 mg/50 μ L ranibizumab inj	0.5 mg/50 μ L ranibizumab inj
2	Microvolume brolucizumab infusion	10	1.0 mg/8.3 μ L brolucizumab inf	6.0 mg/50 μ L brolucizumab inj
2	Ranibizumab injection	3	0.5 mg/50 μ L ranibizumab inj	0.5 mg/50 μ L ranibizumab inj
Stage 2				
Cohort	Randomized Group	N	Day 0	Day 28
3	Microvolume brolucizumab injection	10	0.6 mg/10 μ L brolucizumab inj	6.0 mg/50 μ L brolucizumab inj
3	Ranibizumab injection	3	0.5 mg/50 μ L ranibizumab inj	0.5 mg/50 μ L ranibizumab inj
4	Microvolume brolucizumab infusion	10	0.5 mg/8.3 μ L brolucizumab inf	6.0 mg/50 μ L brolucizumab inj
4	Ranibizumab injection	3	0.5 mg/50 μ L ranibizumab inj	0.5 mg/50 μ L ranibizumab inj

Abbreviations: inj, injection; inf, infusion



Figure 2: Microvolume infusion pump used in the OWL study (A). First patient treated in the microvolume infusion study (B). Magnified view of cannula placement for microinfusion (C).

patient's eye (Figure 2).³ This study included 52 patients at 15 sites in two stages with a 10:3 randomization of brolocizumab to ranibizumab per each cohort (Table 1). RRC enrolled seven patients in both stages; three with occult CNV and four with classic CNV. We also enrolled and treated the first patient in the infusion arm.

In OWL, the primary efficacy endpoint was defined as percentage of brolocizumab responders who achieved three of four of the following criteria: CST decrease of 80 μm or greater at day 14, CST decrease of 80 μm or greater at

day 28, BCVA improvement of 4 letters or more at day 14, and BCVA improvement of 4 letters or more at day 28.^{3,5,8}

In both stages, a primary efficacy signal was detected, with responder rates of 70% and 80% in the brolocizumab injection arms in stages 1 and 2, respectively, and of 60% in the brolocizumab arms in both stages, compared with 100% and 50% responders in stages 1 and 2, respectively, in the ranibizumab groups.^{3,5,8} No safety issues were noted that would prevent further development of brolocizumab via microvolume delivery.^{3,5,8}

TABLE 2. PATIENTS ENROLLED IN THE SHRIKE STUDY AT RETINA RESEARCH CENTER

Patient No.	Date of Exit Visit	Date of Standard of Care Treatment in Clinic	Interval From Last Anti-VEGF Treatment in Study to Clinic Retreatment	Previous Treatments
1	11/19/2015	12/17/2015	8 weeks	1 bevacizumab, 8 ranibizumab, 10 aflibercept
2	11/24/2015	11/24/2015	4 weeks	1 bevacizumab, 7 ranibizumab, 15 aflibercept
3	11/24/2015	2/22/2016	17 weeks	1 ranibizumab, 12 aflibercept
4	12/4/2015	No retreatment to date	27+ weeks	3 aflibercept
5	12/15/2015	1/20/2016	9 weeks	3 bevacizumab, 2 aflibercept
6	12/14/2015	4/13/2016	21 weeks	3 ranibizumab, 5 aflibercept
7	12/30/2015	No retreatment to date; fluid present on OCT, VA unchanged; investigating alternative possibilities		10 aflibercept
8	1/25/2016	2/1/2016	5 weeks	4 ranibizumab, 8 aflibercept
9	1/4/2016	2/2/2016	8 weeks	6 aflibercept
10	2/8/2016	3/16/2016	9 weeks	4 ranibizumab, 5 aflibercept
11	2/11/2016	No retreatment to date	18+ weeks	6 aflibercept
12	2/22/2016	4/27/2016	13 weeks	7 ranibizumab, 17 aflibercept

Abbreviations: OCT, optical coherence tomography; VA, visual acuity

“ With the anticipated increased duration of action of brolucizumab combined with the use of a sustained-delivery system, the treatment burden ... should decrease.

SHRIKE

SHRIKE is a 3-month substudy evaluating the safety and pharmacokinetics of brolucizumab. Two US sites (including RRC) and four Japanese sites were selected to participate in SHRIKE. Enrollment is open in Japan and closed in the United States. The aim of the study is to enroll 48 patients to be treated with three intravitreal injections of 3.0 mg or 6.0 mg brolucizumab at day 0, day 28, and day 56 in a 1:1 randomization. Pharmacokinetic samples are to be collected at day 0, 24 hours, 72 hours, and days 7, 14, 21, 28, 57, and 84. BCVA is assessed at screening and at days 0, 3, 7, 14, 21, 28, 57, and 84.

RRC enrolled 12 patients who have all completed the study. All 12 patients had been previously treated with at least one other anti-VEGF agent, and all had been treated with aflibercept prior to entering the study (Table 2). This is the only study to date in which brolucizumab was used in previously treated eyes of patients with neovascular AMD. After the exit visit, all of our patients were followed monthly in clinic, and optical coherence tomography (OCT) was performed at each visit to establish the time interval from last anti-VEGF injection in the study until retreatment became necessary. Of the 12 patients enrolled at RRC, nine (75%) had dry maculas when assessed immediately after the study exit visit. At the time of this report, four of the 12 patients treated at RRC in the study had not required retreatment after exiting the study. Table 2 shows the interval from last study treatment to retreatment in clinic. Our 12 patients did not experience any drug-related adverse events.

At the conclusion of the SHRIKE study, we plan to further analyze data from all 48 enrolled patients to examine the following parameters: unique characteristics of patients with extended intervals between recurrences after study exit, retreatment intervals after three intravitreal injections of brolucizumab as compared with other anti-VEGF agents, BCVA change from baseline to exit as compared with historical visual acuity change with other anti-VEGF agents, and monthly OCT data in brolucizumab-treated patients versus those receiving standard of care treatment.

HAWK

RRC is also involved in the phase 3, 2-year HAWK study comparing the efficacy and safety of brolucizumab and aflibercept in treatment-naïve patients with wet AMD. The study is designed to enroll 990 patients across 320 sites, and enrollment is now closed. Patients are randomly assigned, 1:1:1, to receive 3.0 mg brolucizumab, 6.0 mg brolucizumab, or 2.0 mg aflibercept. All patients will receive three monthly injections and will then be re-randomized to receive injections every 8 or 12 weeks depending on their group assignment and disease activity assessment. All patients will come in monthly for treatment or sham treatment to maintain masking after the re-randomization.

The primary endpoint of HAWK is to confirm that brolucizumab is noninferior to aflibercept in respect to BCVA change from baseline to week 48. Secondary endpoints include number of patients in the brolucizumab arms who are treated every 12 weeks up to week 48, efficacy of brolucizumab compared with aflibercept up to week 96 with regard to BCVA, CST, and CNV area, and safety and tolerability of brolucizumab in relation to aflibercept.

EXTENDED DRUG DELIVERY

The Posterior MicroPump (PMP, Replenish) is a drug delivery device designed to provide flexible pulsology of 2- μ L to 50- μ L doses of a drug and the device can be adjusted as needed. The PMP consists of six subcomponents: electronics contained in a hermetically sealed package responsible for powering and controlling drug dispensing using a closed-loop controlled electrolysis process, a drug reservoir chamber capable of storing up to 50 μ L of drug, a one-way check valve that opens only when the internal pressure exceeds the check valve cracking pressure and prevents reverse leakage, a refill port that can be accessed transconjunctivally, an intraocular cannula, and a flow sensor to directly measure flow. A first-in-human study performed outside the United States demonstrated the safety profile, surgical implantation feasibility, and capabilities of the first-generation PMP in 11 patients with diabetic macular edema.^{5,13} The PMP showed a relevant efficacy signal in microvolume doses that may enable combined treatment with multiple drugs while maintaining standard injection volume.^{5,13} The device shows promise as a drug-delivery mechanism for potential personalized continuous therapy in treating neovascular AMD.

CONCLUSION

So far, our center has used brolucizumab to treat 17 patients with wet AMD. We have been impressed with the drug's efficacy, safety, and durability. With the anticipated increased duration of action of brolucizumab combined with the use of a sustained-delivery system, the treatment burden on patients, their families, physicians, and staff should decrease. This will not only improve patients' quality of life, but also improve the efficiency of their medical care. ■

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1. Bressler NM, Bressler SB. Neovascular (exudative or "wet") age-related macular degeneration. In: Ryan SJ, ed. *Retina*. 5th ed, vol 1. Philadelphia: Saunders, an imprint of Elsevier; 2013:1183-1197.
2. Gaudreault J, Gunde T, Floyd HS, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. *Invest Ophthalmol Vis Sci*. 2012;53(14):3025.
3. Berger BB, Yanni SE, Wenzel A, et al. Efficacy of RTH258 (ESBA1008), an anti-VEGF agent, applied by microvolume injection or infusion in subjects with neovascular AMD. *Invest Ophthalmol Vis Sci*. 2015;56(7):821.
4. Escher D, Schmidt A, Steiner P, et al. Single-chain antibody fragments in ophthalmology. Paper presented at: Euretina Congress; September 17-20, 2015; Nice, France.
5. Berger BB, Weichselberger A, Schmidt W, et al. Microvolume drug delivery: a novel therapeutic strategy for patients with neovascular age-related macular degeneration (nAMD). Paper presented at: Retina Society Annual Meeting; October 7-11, 2015; Paris, France.
6. Weissgerber G, Mallick S, Travesia E, et al. Safety and tolerability of single escalating doses of ESBA1008, a single-chain anti-VEGF antibody fragment, in patients with exudative age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2012;53(14):4641.
7. Holz FG, Dugel PU, Weissgerber G, et al. Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a randomized controlled study [published online ahead of print February 20, 2016]. *Ophthalmology*.
8. Arnold J, Weichselberger A, Weissgerber G, Schmidt W. RTH258, a novel single-chain anti-vascular endothelial growth factor (VEGF) antibody fragment, in patients with neovascular age-related macular degeneration (NAMD): results from phase II studies. Paper presented at: Annual Royal Australian and New Zealand College of Ophthalmologists Scientific Congress 2015; October 31-November 4, 2015; Wellington, New Zealand.
9. Dugel PU. Comparison of anatomic and visual acuity outcomes in neovascular AMD patients treated with ESBA1008 and ranibizumab. Paper presented at: American Academy of Ophthalmology Annual Meeting; October 18-21, 2014; Chicago, IL.
10. Lanzetta P, Wichselberger A, Weissgerber G. Randomized controlled trial assessing safety and preliminary efficacy of RTH258 (ESBA1008), a novel single-chain Fv antibody fragment, in neovascular age-related macular degeneration. Paper presented at: World Congress on Controversies in Ophthalmology; March 26-29, 2015; Sorrento, Italy.
11. Bandello F, Weichselberger A, Weissgerber G, Sallstig P. Safety and efficacy of RTH258, a single-chain anti-vascular endothelial growth factor (VEGF) antibody fragment, in patients with neovascular age-related macular degeneration (NAMD): results from 2 phase II studies. Paper presented at: European School for Advanced Studies in Ophthalmology Retina Academy; October 22-24, 2015; Barcelona, Spain.
12. Singerman LJ, Weichselberger A, Sallstig P. OSPREY trial: randomized, active-controlled, phase II study to evaluate safety and efficacy of RTH258, a humanized single-chain anti-VEGF antibody fragment, in patients with neovascular AMD. Presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2015; Denver, CO.
13. Humayun M, Santos A, Alkimirano JC, et al. Implantable MicroPump for drug delivery in patients with diabetic macular edema. *Transl Vis Sci Technol*. 2014;3(6):5.

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