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Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial

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Purpose: To compare the efficacy and safety of brolucizumab with aflibercept to treat neovascular age-related macular degeneration (AMD).

Design: Prospective, randomized, double-masked, multicenter, 2-arm, phase 2 study.

Participants: Eighty-nine treatment-naïve participants, aged ≥50 years, with active choroidal neovascularization secondary to AMD.

Methods: Eligible participants were randomized 1:1 to intravitreal brolucizumab (6 mg/50 μl) or aflibercept (2 mg/50 μl). Both groups received 3 monthly loading doses and were then treated every 8 weeks (q8) with assessment up to week 40. In the brolucizumab group, the final q8 cycle was extended to enable 2 cycles of treatment every 12 weeks (q12; to week 56); participants on aflibercept continued on q8. Unscheduled treatments were allowed at the investigator's discretion.

Main Outcome Measures: The primary and secondary hypotheses were noninferiority (margin: 5 letters at a 1-sided alpha level 0.1) in best-corrected visual acuity (BCVA) change from baseline of brolucizumab versus aflibercept at weeks 12 and 16, respectively. BCVA, central subfield thickness (CSFT), and morphologic features were assessed throughout the study.

Results: The mean BCVA change from baseline (letters) with brolucizumab was noninferior to aflibercept at week 12 (5.75 and 6.89, respectively [80% confidence interval for treatment difference, −4.19 to 1.93]) and week 16 (6.04 and 6.62 [−3.72 to 2.56]), with no notable differences up to week 40. Outcomes exploring disease activity during the q8 treatment cycles suggest greater stability of the brolucizumab participants, supported by receipt of fewer unscheduled treatments versus aflibercept (6 vs. 15) and more stable CSFT reductions. In addition, from post hoc analysis, a greater proportion of brolucizumab-treated eyes had resolved intraretinal and subretinal fluid compared with aflibercept-treated eyes. Approximately 50% of brolucizumab-treated eyes had stable BCVA during the q12 cycles. Brolucizumab and aflibercept adverse events were comparable.

Conclusions: During the matched q8 phase, the BCVA in brolucizumab-treated eyes appeared comparable to aflibercept-treated eyes, with more stable CSFT reductions, receipt of fewer unscheduled treatments, and higher rates of fluid resolution. The brolucizumab safety profile was similar to aflibercept over 56 weeks of treatment. A 12-week treatment cycle for brolucizumab may be viable in a relevant proportion of eyes. *Ophthalmology 2017;■:1−9 © 2017 by the American Academy of Ophthalmology*

Supplementary files is available at www.aaojournal.org.

Therapies targeting vascular endothelial growth factor (VEGF) have substantially improved visual outcomes for patients with neovascular age-related macular degeneration (nAMD).[1,2] Current treatment guidelines recommend anti-VEGF injection as first-line therapy for this disease.[3,4]

Anti-VEGF treatment has enhanced nAMD outcomes, with recommended treatment regimens often requiring frequent intravitreal (IVT) injections and frequent clinical assessment to track patients' response to therapy. The burden of these frequent visits represents a significant challenge for elderly patients, their caregivers, and the treating physicians, and may lead to undertreatment of nAMD.[5] Alternative treatment options, with prolonged intervals between injections, are needed to reduce the treatment burden.

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2) were 2 phase 3, double-masked, multinational, parallel-group, active-controlled clinical trials that were designed to assess the efficacy and safety of aflibercept versus ranibizumab to treat nAMD.[6] During the loading-dose phase (3 monthly injections), all the treatment arms achieved rapid mean improvements in best-corrected visual acuity (BCVA) that were sustained over 52 weeks. The mean visual acuity in the pooled aflibercept 2.0-mg groups (VIEW 1 and VIEW 2) that received maintenance treatment every 8

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weeks (q8) was within 0.3 letters of the ranibizumab group that received dosing every 4 weeks (q4). The VIEW studies supported the regulatory approval of a q8 dosing regimen for aflibercept 2.0 mg for the treatment of nAMD.[6]

Brolucizumab (RTH258, formerly ESBA1008) is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A. It is the smallest of the anti-VEGF antibodies, with a molecular weight of 26 kDa, compared with 115 kDa for aflibercept and 48 kDa for ranibizumab.[7,8] By virtue of its design, it is possible to concentrate brolucizumab up to 120 mg/mL, allowing the administration of 6 mg in a single 50-μL IVT injection. On a molar basis, 6 mg of brolucizumab equals approximately 12 times the 2.0-mg dose of aflibercept and 22 times the 0.5-mg dose of ranibizumab.[8] These attributes may confer potential advantages in the treatment of nAMD. A small molecular weight and high drug concentration gradient between the vitreous and retina may support drug distribution into the retina. Assuming comparable half-life, higher molar doses of drug may be cleared more slowly from the eye, thus prolonging duration of action.

In a first-in-human study of participants with nAMD, the 1-month change in central subfield thickness (CSFT) in eyes treated with a single IVT injection of brolucizumab at 4.5- and 6.0-mg doses was noninferior to a single IVT injection of 0.5 mg ranibizumab (noninferiority margin: 40 μm, 1-sided alpha 0.05), and, numerically, the results supported the same conclusion for the 3.0-mg dose. Notably, the median time until another injection was required was 30 days longer for brolucizumab at the 3-mg and 6-mg doses and 15 days longer at the 4.5-mg dose compared with ranibizumab, providing support for a more durable treatment response.[9]

The primary and key secondary objectives of this study were to compare the change in BCVA after 3 monthly injections of brolucizumab treatment (6 mg/50 μl) with that of aflibercept (2 mg/50 μl) at 12 and 16 weeks, respectively. Other secondary objectives were to compare the functional and anatomic outcomes in eyes receiving maintenance treatment with brolucizumab and aflibercept q8 up to week 40, to assess the potential of treatment every 12 weeks (q12) with brolucizumab based on 2 q12 cycles, and to evaluate the relative safety of brolucizumab and aflibercept.

Methods

Study Design

This was a prospective, randomized, double-masked, multicenter, 2-arm, phase 2 study comparing the efficacy and safety of brolucizumab with that of aflibercept in participants with nAMD (ClinicalTrials.gov identifier NCT01796964). The study protocol was approved by all institutional review boards and complied with the ethical standards defined by the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent before participating in the study. Forty-one investigational centers in the United States participated in the study, and the work is compliant with the Health Insurance Portability and Accountability Act of 1996.

Enrolled participants were randomized 1:1 using a web-based interactive response technology system to receive either brolucizumab (Alcon Laboratories Inc., Fort Worth, TX; 6.0 mg/50 μl IVT) or aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY; 2.0 mg/50 μl IVT) treatment. For masking purposes, sham treatment was administered when necessary, as described below.

There were 3 treatment periods over the course of the study (Fig 1). In the first period, loading doses of the study drug were administered at baseline and at weeks 4 and 8, with a corresponding efficacy assessment at week 12. The second period included 4 matching q8 dosing cycles (active treatments, besides week 8, at weeks 16, 24, and 32) for both treatment groups, with a corresponding assessment period up to week 40 (8 weeks after the last q8 dose administration in both treatment arms). During the third period up to week 56, participants in the brolucizumab group received only 1 additional treatment at week 44, extending the final q8 dosing cycle to a q12 dosing cycle, and a second q12 cycle was completed at week 56; participants on aflibercept continued on a q8 cycle, with treatments at weeks 40 and 48. To preserve masking during weeks 40 through 48, both groups had appropriately timed sham injections. The dosing schedule is shown schematically in Figure 1. At study visits when no active treatment was scheduled, the masked investigator could provide an unscheduled treatment with the participant's assigned treatment if the investigator determined it was medically necessary and after confirmation with the sponsor. At visits with potential sham injections, the investigator also had the option to apply an active treatment instead of a scheduled sham treatment based on medical need.

Efficacy assessors (BCVA technicians and photographers), the sponsor, and the monitors who reported, obtained, and reviewed the clinical evaluations were masked. Although the treating physician was masked through the week 36 injection, the application of sham injections could have unmasked the physician who administered injections and who conducted postinjection safety assessments from week 40 onward.

At screening, all participants underwent measurement of BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale in both eyes, as well as a complete bilateral ophthalmic examination that included slit-lamp examination, intraocular pressure (IOP) measurements, and a dilated fundus examination. In addition, color fundus photography (CF), fluorescein angiography (FA), and spectral-domain optical coherence tomography (SD OCT) imaging were obtained for both eyes of all participants (Appendix 1, available at www.aaojournal.org, for details regarding the protocols for ETDRS, IOP, CF, FA, and SD OCT data collection). The SD OCT, CF, and FA images were transferred to the Duke Reading Center for evaluation of study eligibility and analysis of relevant endpoints.

Participants

To be eligible for the study, participants had to be aged ≥50 years or older with untreated active choroidal neovascularization due to age-related macular degeneration in the study eye, with a BCVA between 73 and 23 letters, inclusive. The study eye had to have leakage on FA and subretinal fluid (SRF), intraretinal fluid (IRF), or sub−retinal pigment epithelium fluid on SD OCT, as confirmed by the Duke Reading Center. Exclusion criteria included any active intraocular or periocular infection or inflammation in either eye and previous treatment with an approved or investigational therapy for nAMD other than vitamin supplements in the study eye. The fellow eye could not be treated as a study eye. A detailed description of the inclusion and exclusion criteria is provided in Appendix 2 (available at www.aaojournal.org).

Outcomes

The primary efficacy parameter was BCVA. A certified visual acuity examiner evaluated BCVA in the study eye at all visits and