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# Phase 1 Trial of Anti–Vascular Endothelial Growth Factor/Antiangiopoietin 2 Bispecific Antibody RG7716 for Neovascular Age-Related Macular Degeneration

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***Purpose:*** RG7716 is a novel bispecific antibody that simultaneously binds vascular endothelial growth factor (VEGF) and another key angiogenic factor, angiopoietin 2. A phase 1 study of intravitreal RG7716 was conducted to evaluate single-dose and multiple-dose safety in patients with neovascular age-related macular degeneration (AMD).

***Design:*** Open-label, single and multiple ascending-dose study.

***Participants:*** Twenty-four patients diagnosed with neovascular AMD with best-corrected visual acuity (BCVA) of 20/40 to 20/400 (Snellen equivalent) and refractory subfoveal choroidal neovascularization defined as leakage on fluorescein angiography or fluid on spectral-domain optical coherence tomography despite 3 or more intravitreal anti-VEGF treatments in the preceding 6 months.

***Methods:*** Single intravitreal doses of 0.5 mg, 1.5 mg, 3 mg, and 6 mg RG7716 were administered in stepwise dose-escalation groups, each with 3 patients. In the multiple-dose phase, 6 patients were enrolled and received 3 treatments each of 3 mg and 6 mg RG7716.

***Main Outcome Measures:*** Safety and tolerability, changes in baseline BCVA, and central subfield thickness (CST).

***Results:*** There were no dose-limiting toxicities in either the single-dose or multiple-dose group. Treatment-emergent ocular adverse events were mild. There was a single withdrawal and 1 serious adverse event, both deemed to be unrelated to the study drug by principal investigators. In the combined single-dose groups and in the 6-mg multiple-dose group, BCVA increased from baseline to 28 days after the last dose administration by a median of 7 letters (range, 0–18 letters; n = 11) and 7.5 letters (range, 3–18 letters; n = 6), respectively. The corresponding median reduction from baseline in CST were 42 μm (range, −101 to 10 μm; n = 11) and −117 μm (range, −252 to −7 μm; n = 6), respectively. After multiple 3-mg RG7716 doses, no changes were observed in either BCVA (median, −0.5 letters; range, −9 to 8 letters; n = 6) or CST (median, −9 μm; range, −188 to −1 μm; n = 6).

***Conclusions:*** RG7716 was well tolerated and exhibited an overall favorable safety profile, with evidence of improvements in BCVA and anatomic parameters. These data support further evaluation of RG7716 in phase 2 trials. *Ophthalmology Retina 2017;■:1–12 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

*Supplemental material is available at www.ophthalmologyretina.org.*

The current standard of care (SoC) for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) is anti–vascular endothelial growth factor (VEGF) therapy. Such therapies have markedly improved the management of these patients and have established a new efficacy paradigm of vision stabilization and even vision improvement in many patients. However, anti-VEGF treatments require frequent and long-term administration to maintain vision gains, and some patients may lose their initial vision gains over time, in part because of recurrent leakage from the CNV complex.[1,2] Therefore, alternative therapies that improve outcomes compared with the current SoC are needed.

Angiopoietin 1 and 2 are of key importance in the homeostasis of the vascular compartment: angiopoietin 1 is a strong agonist that stimulates phosphorylation of the Tie2 receptor and angiopoietin 2 is an antagonist that competes with angiopoietin 1 and inhibits Tie2 phosphorylation.[3,4]



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Angiopoietin 1 stabilizes the mature vasculature by promoting recruitment of pericytes and smooth muscle cells and suppressing vascular leakage.[5] High expression of angiopoietin 1 in the retina strongly suppresses VEGF-induced neovascularization and leakage.[5–7] Through inhibition of Tie2, angiopoietin 2 destabilizes the endothelial cell layer, leading to fluid leakage. Angiopoietin 2 also renders the endothelial cell layer more responsive to VEGF and other proangiogenic factors.[8] Not surprisingly, angiopoietin 2 is increased in proangiogenic diseases, including retinal vascular diseases[9,10] such as pathologic retinal neovascularization or CNV.[11–14] Therefore, selective neutralization of both VEGF and angiopoietin 2 may normalize further the pathologic ocular vasculature in comparison with anti-VEGF monotherapy.[10]

RG7716 is a humanized bispecific immunoglobulin G (IgG) 1 monoclonal antibody that simultaneously binds both VEGF and angiopoietin 2 with selective antigen-binding fragments in the same molecule.[10] RG7716 is produced by a proprietary technology (CrossMab) to enforce specific heterodimerization of 2 different antigen-binding domains.[10,15] In the spontaneous CNV mouse model as well as in a nonhuman primate laser-induced CNV model, neutralization of both VEGF-A and angiopoietin 2 reduces vessel leakiness and CNV lesion number more effectively than either agent alone.[10] The anti-inflammatory properties of dual VEGF and angiopoietin 2 neutralization also were demonstrated in an endotoxin-induced uveitis mouse model.[16] These data support the hypothesis that the combination of anti-VEGF and anti-angiopoietin 2 could yield therapeutic benefit in eyes refractory to anti-VEGF monotherapy. Herein we report findings from a phase 1 single and multiple ascending-dose study that was designed to evaluate the preliminary safety of RG7716 when administered intravitreally to patients with neovascular AMD.

## Methods

### Ethical Considerations

The study was registered at www.clinicaltrials.gov (identifier, NCT01941082) and was conducted according to the tenets of the Declaration of Helsinki. Institutional review board or ethics committee and health authority approvals were obtained. Written informed consent with a Health Insurance Portability and Accountability Act–compliant statement (United States only) was obtained from each study participant before conducting any protocol-related procedures.

### Study Design

The study was a multicenter (8 sites in the United States and United Kingdom), adaptive, nonrandomized, open-label, sequential single and multiple ascending-dose, parallel group study to investigate safety, tolerability, pharmacokinetics, and pharmacodynamics of RG7716. It was conducted from December 2013 through February 2015. For the single-dose (SD) component, study duration was up to 16 weeks (4 weeks of screening and up to 12 weeks of follow-up), and for the multiple-dose (MD) component, the study duration was up to 24 weeks (4 weeks of screening, 8 weeks of treatment, and 12 weeks of follow-up). The SD component enrolled 4 cohorts (0.5-mg, 1.5-mg, 3-mg, and 6-mg RG7716), each with 3 patients. The MD component enrolled 2 cohorts (3-mg and 6-mg RG7716), each with 6 patients who received a total of 3 administrations at monthly intervals.

### Patient Eligibility and Exclusion Criteria

Eligible patients of either gender had to be 50 years of age or older with a confirmed diagnosis of neovascular AMD; best-corrected visual acuity (BCVA) between 20/40 and 20/400 (Snellen equivalent); evidence of leakage resulting from CNV; evidence of intraretinal fluid, subretinal fluid, subretinal pigment epithelial fluid, or a combination thereof; and 3 or more intravitreal anti-VEGF treatments in the preceding 6 months, with the last intravitreal treatment 4 weeks or more before day 1. Key exclusion criteria were subretinal hemorrhage involving the center of the fovea or occupying more than 50% of the total area of the lesion, CNV resulting from causes other than AMD, retinal pigment epithelial tear involving the macula, significant fibrosis or atrophy involving the fovea, previous photodynamic or laser therapy in the previous 3 months, and previous intravitreal corticosteroid injection or device implantation within the previous 12 months.

### Study Protocol

The primary objective of this study was to assess the safety and tolerability of single and multiple intravitreal doses of RG7716. Secondary outcomes included changes in BCVA, central subfield thickness (CST; based on OCT results), and pharmacokinetics. Baseline measurements included BCVA using the Early Treatment Diabetic Retinopathy Study chart,[17] Pelli-Robson contrast sensitivity, slit-lamp biomicroscopy, spectral-domain OCT, intraocular pressure (IOP), fundus photography, fundus fluorescein angiography, indocyanine green angiography, electrocardiography, and safety laboratory tests. Patients received a single intravitreal administration of RG7716 on day 1 or intravitreal administrations on days 1, 28, and 56 (±2 days each) in the SD and MD components, respectively. In the SD component, follow-up visits were scheduled on days 3 and 7 and at weeks 2, 4, 8, and 12. In the MD component, follow-up visits were scheduled 6±1 days after each drug administration and at 2, 4, 8, and 12 weeks after the last RG7716 administration. At each of the study visits, patients underwent the following assessments: adverse events (AEs), vital signs, eye examination, IOP, BCVA, contrast sensitivity, spectral-domain OCT, collection of pharmacokinetic blood samples, and a query for concomitant medications. Fundus fluorescein angiography and indocyanine green angiography assessments were performed at weeks 4 and 12 in the SD component and at weeks 8, 12, and 20 in the MD component. Aqueous humor samples were collected from a subset of patients (data not reported herein) who consented to this procedure.

In the SD component, a single patient was dosed on day 1 in each cohort, and only after a favorable safety and tolerability assessment on day 3 were the remaining 2 patients dosed (Supplemental Figure, available at www.ophthalmologyretina.org). After all 3 patients in a cohort were dosed, and a minimum of 5 days of safety data were collected, dose escalation could proceed in a different cohort of patients. Dose escalation was guided by the occurrence of drug-related severe sight-threatening events, drug-related ocular dose-limiting toxicity, or AEs, described as (1) intraocular inflammation, uveitis, or vitreitis, defined as a change of 2 units on standard grading scales; (2) sustained elevation of IOP to more than 30 mmHg; or (3) loss of more than 15 letters of visual acuity.

In the MD component, up to 3 patients per week were allowed to start dosing. A decision to proceed with dose escalation to a