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Treating Neovascular Age-Related Macular Degeneration with Beovu®

News Flash

The US Food and Drug Administration (FDA) has approved Beovu intravitreal injection (brolucizumab; Novartis), for the treatment of neovascular AMD in October of 2019. Trials leading to FDA-approval showed that this agent has the ability to offer both greater fluid resolution vs aflibercept (Eylea; Regeneron) and the ability to maintain most wet AMD patients on a 3-month dosing interval immediately after a monthly 3-month loading phase. However, recent reports of intraocular inflammation including occlusive retinal vasculitis have slowed its widespread implementation into clinics.

Patient Challenges with Neovascular AMD

Age-related macular degeneration (AMD) is a chronic, progressive disease and a leading cause of vision loss. Pivotal trials validated intravitreally administered anti-vascular endothelial growth factor therapy for neovascular AMD (nAMD), which has greatly improved patient outcomes. However, with our current armamentarium of bevacizumab (Avastin), ranibizumab 0.8mg (Lucentis), aflibercept (Eylea), the need for frequent clinic and injection visits is a substantial burden to patients and their family members whom often need to accompany patients to office visits.

How Brolucizumab (Beovu) Works

Brolucizumab is an advanced humanized single-chain antibody fragment (scFV, 26 kDa) which is the smallest function unit of an antibody. Compared to prior larger anti-VEGF agents (Lucentis 48 kDa, Eylea 97 kDa, Avastin 150 kDa), brolucizumab allows for delivery of a greater molar dose leading to enhanced tissue penetration, rapid clearance from systemic circulation, and more potent inhibition of and higher affinity to all VEGF-A isoforms. Preclinical data demonstrated a 2.2- and 1.7-fold higher exposure in the retina and retinal pigment epithelium (RPE)/choroid compared to Lucentis, which improves control of intraretinal fluid (IRF), subretinal fluid (SRF), and sub-RPE fluid.

HAWK and HARRIER Trials

The HAWK and HARRIER long-term, multinational clinical trials led to the FDA approval of this medication. In October of 2019, eligibility criteria included patients with treatment-naïve nAMD:

- 50 years or more
- Untreated, active central choroidal neovascularization lesions secondary to AMD
- Choroidal neovascularization lesions comprising >50% of total lesion area on fluorescein angiography
- IRF and/or SRF affecting the central subfield as assessed on spectral-domain OCT
- BCVA between 78 and 23 ETDRS letters (Snellen equivalents, ~20/32 to 20/400)
- No fibrosis or geographic atrophy affecting the central subfield

In these trials, the control arm was injected with aflibercept (Eylea) monthly for 3 doses during the loading phase and then patients were kept on a q8 week dosing schedule. In the treatment arms, eligible patients received either 3 mg brolucizumab or 6 mg brolucizumab monthly (HAWK) or 6 mg brolucizumab only (HARRIER) for 3 doses during the loading phase but were then immediately transitioned to 3-month (q12 week) dosing intervals. If there was persistent disease activity or a decline in vision during the study, patients were transitioned to brolucizumab q8 weeks for the remainder of the study. As the primary endpoint, Beovu demonstrated non-inferiority versus aflibercept in mean change in BCVA at year 1. In both clinical trials, approximately 30% of patients gained at least 15 letters at year 1. At year 1, more than half the patients were maintained on the 3-month dosing interval (56% in HAWK and 51% in HARRIER). If patients had stable vision and were dry on OCT during the first q12 week dose, 80.8-87.1% of patients in HAWK and 82.5% in HARRIER were maintained on a 3-month dosing interval, Figure 1..

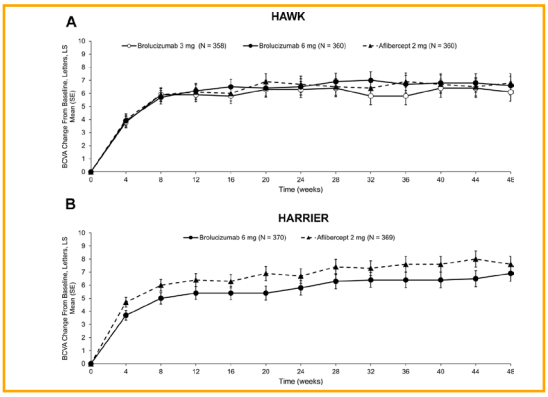
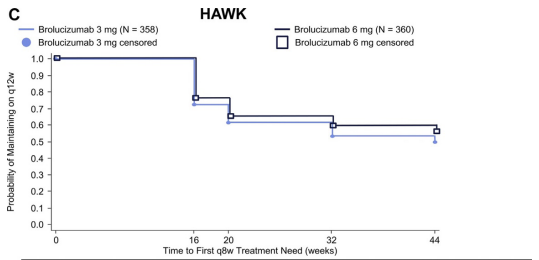
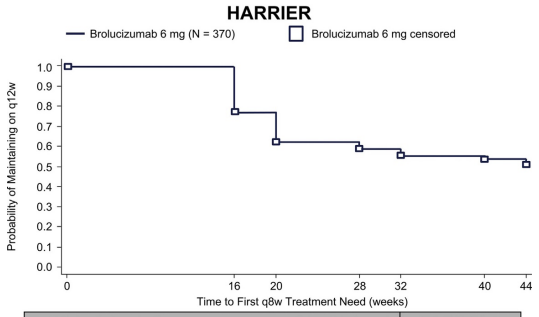


Figure 1:
Best-corrected visual acuity (BCVA) over time in (A) HAWK and (B) HARRIER



Parameter*	Brolucizumab 3 mg	Brolucizumab 6 mg
Positive q12w treatment status at Week 48 (95% CI for Kaplan-Meier estimate), %		
Patients, N	358	360
Efficacy-only approach	50.0 (44.5 to 55.3)	57.5 (52.0 to 62.6)
Efficacy/safety approach	49.4 (43.9 to 54.6)	55.6 (50.2 to 60.8)
Positive q12w treatment status at Week 48 among those with no q8w need during first q12w cycle (95% CI for Kaplan-Meier estimate), %		
Patients, n	208	222
Efficacy-only approach	80.8 (74.5 to 85.7)	87.1 (81.7 to 91.0)
Efficacy/safety approach	80.9 (74.5 to 85.7)	85.4 (79.9 to 89.5)



Parameter*	Brolucizumab 6 mg
Positive q12w treatment status at Week 48 (95% CI for Kaplan-Meier estimate), %	
Patients, N	370
Efficacy-only approach	52.2 (46.8 to 57.3)
Efficacy/safety approach	51.0 (45.7 to 56.1)
Positive q12w treatment status at Week 48 among those with no q8w need during first q12w cycle (95% CI for Kaplan-Meier estimate), %	
Patients, n	221
Efficacy-only approach	82.5 (76.7 to 87.0)
Efficacy/safety approach	81.7 (75.8 to 86.3)†

Figure 1:
(C) Kaplan-Meier analysis of every 12 weeks (q12w) treatment status (or time to require every eight-week dosing)

As secondary outcomes, Beovu also showed greater reduction in central subfield thickness (CST) on OCT as early as week 16 and at year 1, and fewer patients had intraretinal and/or subretinal fluid which are key markers of disease activity, Figure 2.

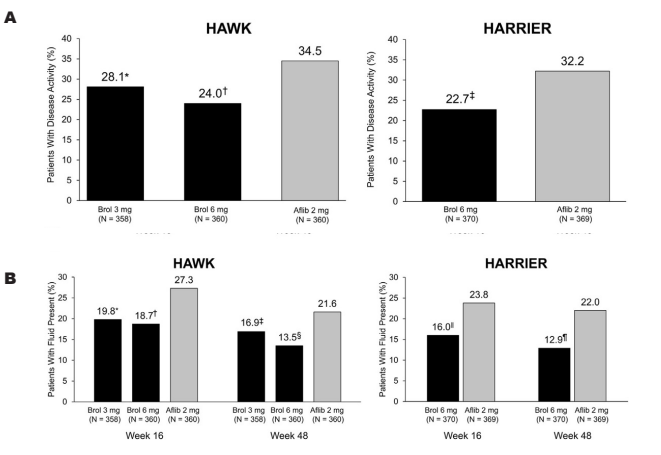


Figure 2:
(A) Disease activity at Week 16. (B) Presence of sub-RPE fluid at Weeks 16 and 48.

Recent Safety Concerns

Safety Review Committee:

After After FDA approval, the American Society of Retinal Specialists (ASRS) received reports of intraocular inflammation (IOI) including retinal vasculitis and retinal vascular occlusion with Beovu. This prompted Novartis to commission an independent and autonomous Safety Review Committee (SRC) to review the Phase 3 data from the HAWK and HARRIER trials. IOI of any form was identified in 4.6% (50/1088) of study patients vs. 1.1% (8/729) in the aflibercept arm. Of those with IOI from Beovu, 36 subjects had concomitant retinal vasculitis for an overall rate of 3.3% (36/1088). Of these 36 subjects with IOI and vasculitis, 23 subjects had concomitant vascular occlusion for an overall rate of 2.1% (23/1088).

The committee found that the absolute risk of developing IOI of any form and losing 15 or more letters (5 letters equates to 1 line) was similar between Beovu 0.7% (8/1088) and Eylea 0.13% (1/729). Looking specifically at Beovu, the risk of ≥ 3 line vision loss and ≥ 6 line vision loss over 2 years in patients with retinal vasculitis (36/1088) was 22% (8/36) and 14% (5/36), respectively, and in those with occlusive retinal vasculitis (23/1088) was 30% (7/23) and 22% (5/23), respectively. Of note, the SRC identified that the majority of inflammation events presented within the first 6 months of brolucizumab initiation (74%, 37/50) but some events presented between 12-18 months (12%, 6/50).

American Society of Retinal Specialists' Research and Safety in Therapeutics (ReST) Committee:

Meanwhile, the American Society of Retinal Specialists' Research and Safety in Therapeutics (ReST) Committee which is chaired by our very own Paul Hahn MD, PhD performed an analysis specifically citing cases of retinal vasculitis in post FDA approval from October 7, 2019 to April 1, 2020. (Novartis estimates that 70,000 vials had been injected in the United States in 37,000 unique patients through March 27, 2020). Data from 26 eyes of 25 patients with retinal vasculitis after brolucizumab were collected. One patient had bilateral vasculitis. Interestingly, 88% of reported cases occurred in women. All patients had previously been treated with other anti-VEGF agents with a mean number of 39.1 prior injections. No eyes had a history of anti-VEGF-associated inflammation. All adverse events (AEs) arose after 1 (11 eyes, 44%), 2 (11 eyes, 44%) or 3 (4 eyes, 12%) brolucizumab injections in the 5+ months since approval. Symptoms at AE onset included:

- Blurry vision (62%)
- Floaters (46%)
- Pain (31%)
- Redness (19%)
- Scotomas (12%)
- 2 eyes (8%) were asymptomatic

Intraocular inflammation at AE presentation was identified in 24 of 26 eyes (92%). The location of inflammation was:

- Anterior only in 8 eyes (31%)
- Posterior only in 7 eyes (27%)
- Both anterior and posterior in 9 eyes (35%)

Of the 26 eyes with retinal vasculitis, 22 eyes (85%) were reported as having occlusive vasculitis. A spectrum of vasculopathy was seen, ranging from minimal to severe. A range of vascular involvement was identified, including both retinal arteries and veins as well as choroidal vessels. Optic nerve leakage was also noted in many cases. The exact mechanism of this retinochoroidal vasculopathy still remains unclear and arterial vessels were most commonly affected (91% of these eyes). Image analysis identified ischemia in 21 of 24 eyes (88%) which was defined as retinal whitening on photos, non-perfusion on FA, and/or characteristic inner and/or middle retinal hyper-reflectivity and thickening on OCT, Figure 3.

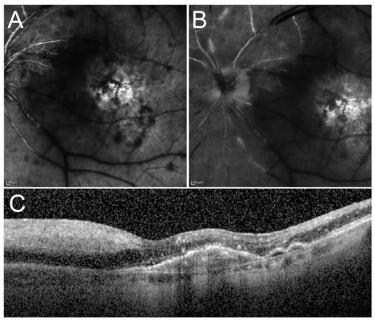


Figure 3:
Figure 3: A 78-year-old man with wet AMD in the left eye and a total of 59 prior anti-VEGF injections was switched to brolucizumab. At the time of his first brolucizumab injection, VA was 20/60. Fourteen days after injection, the patient was seen at an outside clinic with redness and pain and was prescribed topical corticosteroids. Thirty-four days after brolucizumab, he presented to the retina clinic with redness, pain, blurry vision, and floaters. VA was hand motions, and examination revealed 2+ anterior chamber cells, vitritis, occlusive retinal vasculitis, and retinal whitening. Early-phase fluorescein angiography (FA) revealed extensive and diffuse retinal arterial and venous filling defects and hypoperfusion of the choroid in several small multifocal areas (Figure 3A). Late-phase FA images demonstrated slowly resolving choroidal hypoperfusion, persistent arterial and venous filling defects, and focal leakage around arterioles and venules superiorly and inferiorly (Figure 3B). OCT showed hyperreflectivity and thickening of the nasal inner retinal layers, indicating acute retinal ischemia (Figure 3C).

The mean follow-up during the ReST Committee analysis was 53.2 days (range 8-137 days) from the most recent brolucizumab injection, and a mean of 78.0 days (range 21-140 days) from the first brolucizumab injection. Overall, 6 to 7 lines of mean vision loss from baseline (20/243 from 20/52) was recorded at most recent follow-up. Thirteen eyes (50%) lost 3 lines of VA and/or were 20/200 or worse at most recent follow-up.

Treatment approaches were varied, and no trends were identifiable that could predict greater success with any specific approach. Nearly all eyes (24 of 26 eyes, 92%) were treated with topical corticosteroids. Eleven patients (42%) received systemic corticosteroids, 5 eyes (19%) received intravitreal corticosteroid injections, and 4 eyes (15%) had a pars plana vitrectomy. One eye received intravitreal antibiotics, while 2 patients received antiviral medications.

What This Means to Your Patients

For treatment-naïve neovascular AMD patients, brolucizumab can maintain the same visual acuity as Eylea but at a potentially longer treatment interval of q12 week dosing. More than 50% of eyes maintained q12 week dosing throughout the trial. Over 80% of eyes maintained q12 week dosing if patients were dry after 3 loading monthly doses. There was also greater control of intraretinal, subretinal, and sub-RPE fluid. at NJRetina, our internal safety committee is actively monitoring reports and literature about the safety concerns of Beovu and factor these issues in selecting our choice of anti-VEGF therapy for your patients. Many retinal specialists are reserving Beovu for patients with persistent/aggressive disease activity despite frequent injections with other anti-VEGF agents (non-responders).

The ReST Committee recommends a careful evaluation of the anterior and posterior segment for any signs of active inflammation prior to every brolucizumab (or other anti-VEGF) injection. If an intraocular inflammation or a vasculopathy develops, steroids should be started as soon as possible. Since the mechanism of this vasculopathy is unknown, there were no successful treatment trends identified in the initial ReST committee report. As with all therapeutics, the potential benefits need to be balanced with the risk of adverse events on a case by case basis.

NJRetina Welcomes Our Newest Physicians

Rishabh Date, MD

Rishabh Date, MD, is a retina specialist and vitreoretinal surgeon at NJRetina. After completing his undergraduate degree at the University of California San Diego where he graduated summa cum laude and was inducted into Phi Beta Kappa Honor Society, he earned his medical degree from UCLA David Geffen School of Medicine. He completed his residency in ophthalmology at Baylor College of Medicine in Houston followed by a two-year fellowship in vitreoretinal diseases and surgery at Vanderbilt University Medical Center in Nashville.

He is board certified by the American Board of Ophthalmology and a member of the American Society of Retina Specialists, Association for Research and Vision in Ophthalmology, and the American Academy of Ophthalmology.

Megan Nichols, MD

Megan Nichols, MD, is a retina specialist and vitreoretinal surgeon at NJRetina. Dr. Nichols earned her medical degree from the Jefferson Medical College of Thomas Jefferson University in Philadelphia followed by a residency in Ophthalmology at University of Virginia. She then completed a fellowship in Vitreoretinal Diseases and Surgery at Beth Israel Lahey Health in greater Boston.

She is board certified by the American Board of Ophthalmology and is a member of the American Society of Retina Specialists.

To learn more about Dr. Date and Dr. Nichols, visit njretina.com.

At the **Forefront** of **Clinical Research**

At the Forefront of Clinical Research NJRetina currently conducts clinical trials at key locations. Our clinical research coordinators who conduct the trials will be happy to discuss the inclusion/ exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

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Joe Martinez - Teaneck: 201-837-7300; 4

Dina Christodoro - Toms River: 732-797-3984

Amy Leviton - Edison: 732-906-1887

Enrolling Studies:

Dry AMD

Teaneck & Edison

A Genetic Screening and Registry Study to Evaluate Long-term Clinical Outcomes and Disease Progression in Subjects with Non-Central Geographic Atrophy (GA) Who Are Carriers of High-Risk Genetic Complement Variants Associated with Dry Age-related Macular Degeneration (AMD) A Prospective Natural History Study to Evaluate Clinical Characteristics and Disease Progression in Subjects with Non-Central Geographic Atrophy (GA) Who Are Carriers of High-Risk Genetic Variants of Complement Factor H (CFH) (Gemini)

Teaneck

Phase II, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (SPIAM)

Teaneck & Toms River

A Phase II, Multi-Center, Randomized, Single-Masked, Sham Injection Controlled Study of the Safety, Tolerability, and Evidence of Activity of Intravitreal Injection of R7171009 in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration (Gallego)

Vauxhall

A Study of Disease Progression in Genetically Defined Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration (Gyroscope)

Wet AMD

Edison and Teaneck

A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of Hight-Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration (Candela)

Soon to Enroll Studies:

Dry AMD:

- A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD) (NGM study) – Teaneck

Wet AMD:

- A Randomized, Double-Masked, Active-Controlled Phase 3 Study of the Efficacy and Safety of High - Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration (Pulsar) – Teaneck and Edison

DME:

- A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High- Dose Aflibercept in Patients with Diabetic Macular Edema (Photon) – Teaneck and Edison
- A Phase III, Multicenter, Randomized, Visual Assessor Masked, Active Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Diabetic Macular Edema (PAGODA) – Teaneck

Diabetic Retinopathy:

- A Phase 2, Randomized, Dose-escalation, Observation-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of RGX-314 Gene Therapy Delivered via One or Two Suprachoroidal Space (SCS) Injections in Participants with Diabetic Retinopathy (DR) Without Center Involved-Diabetic Macular Edema (CI-DME) (ALTITUDE) – Teaneck
- Phase III, Multicenter, Randomized Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Diabetic Retinopathy (PAVILION) – Teaneck

References:

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Hahn, P; Witkin, AJ; Murray TG. Occlusive Retinal Vasculitis Following Intravitreal Brolucizumab: An ASRS Research and Safety in Therapeutics (ReST) Committee Report. ASRS Special Report. Summer 2020 (Online First). https://www.asrs.org/publications/retina- times/details/2929/oclusive-retinal-vasculitis-following-intravitreal-brolucizumab-an-asrs- research-and-safety-in-thera.

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